TECTA gene function and hearing loss: a review

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Abstract

Hearing loss is considered as the most prevalent impairment worldwide. It is one of the most genetically heterogeneous, which makes molecular diagnosis challenging in most cases. *TECTA* is a modular, non-collagenous protein of the tectorial membrane that plays a more dynamic role in normal hearing. Mutation in *TECTA* cause dominant and recessive forms of non-syndromic hearing loss. The clinical findings suggest stable, moderate-to-severe forms of hereditary hearing loss may be diagnostic of a mutation in *TECTA*. In this review, Directory of Open Access Journals (DOAJ), Pub Med, Google Scholar LISTA (EBSCO), Embase, and Web of Science were searched using relevant search terms to retrieve eligible publications. This paper provides an overview of (1) *TECTA* gene function, (2) the prevalence of *TECTA* related hearing loss, disease symptoms, (3) identification pattern and (4) animal models. It also summarizes how mutations in *TECTA* induced hearing loss with mid-frequency audio profile pattern.

Key words: Hearing loss, Mutation, TECTA gene

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Introduction

Sensory and neurological diseases are one of the largest medical complex problems and (1, 2), hearing loss is the most common neural sensory disorder in human (3, 4). In developing countries one out of 500 neonates are born deaf (5). In 50-60 percent of patients the cause of the disease is deterioration in the function of a single gene (3). 70% of all hereditary hearing loss is non-syndromic and 30% is syndromic (6). Non-syndromic hearing impairment is extremely heterogeneous; 68 autosomal recessive loci (DFNB), 52 autosomal dominant loci (DFNA), 5 involved loci on X chromosome and 2 involved loci on Y chromosome has been reported so far (7). Hearing loss caused by *TECTA* mutations are inherited in two forms of autosomal dominant (DFNA8/12MIM 601543-MIM601842) and autosomal recessive (DFNB21). Mutation in the *TECTA* gene is the cause of 4% of all non-syndromic autosomal dominant hearing loss and has been reported in various kinds of hearing impairments in different populations (8). The most mutations related to DFNB21 have been found in Iran (9). Patients 'audiometric pattern' is flat or U shaped in the mild or mild to severe frequencies (10). Patients' audiograms are considered as the most important tools to identify mutations in the *TECTA* gene (10). In this review article, we aimed at investigating TECTA gene function; the prevalence of *TECT*A related hearing loss, disease symptoms, identification patterns and related animal models.

Materials and Methods

Scientific databases Directory of Open Access Journals (DOAJ), Google Scholar, Pub Med, LISTA (EBSCO), Embase, and Web of Science were searched using relevant search terms to retrieve eligible publications on structure and function, audiometric pattern and inheritance pattern of hearing loss and animal modeling related to the *TECTA* gene.

Result and Discussion

TECTA gene structure and function

Human *TECTA* gene (MIM 602574, Gene ID 7007) has been located at 11q22–q24 and mouse *TECTA* gene is on chromosome 9 (8). Studies have revealed that *TECTA* is highly conserved in zebrafish, mice and humans (11). Alpha tectorin is encoded by the *TECTA* gene and is one of the most important non-collagen parts of the tectorial membrane of the inner ear (12). The *TECTA* gene contains 23 exons and renders a protein of 2155 amino acids (13). Tectorial membrane is a fiber extended to extracellular matrix and is connected to stereocilia clusters of sensory hair cells (Figure 1). Sounds cause the movement of tectorial membrane related cells (14). Stereocilia motions give rise to the transforming of sound waves into neural pulse. Tectorial membrane is highly expressed in the inner ear and is found in three forms of collagenic (alpha-tectorin), non-collagenic (beta-tectorin) and glycoprotein (otogelin). Alpha-tectorin is a large glycoprotein containing several domains including Entactin G1 (ENT) domain, the large area of Zonadhesin (ZA) which includes three factors of von Willebrand factor type C or D (vWFD V1, V2, V3, V4), N-terminal entactin G1-like domain and C-terminal Zona Pellucida and also three trypsins inhibiting cysteine-rich domains (Figure 2) (12, 14). These domains have formed a network by disulfide bonds and in association with beta-tectorin have established the non-collagenic matrix in tectorial membrane (11).

Audiometric pattern in hearing loss associated with *TECTA* deficiency

A large number of mutations associated with hearing loss have been reported so far. Using audiogram pattern is an appropriate step to select the presumably mutated genes. To reduce costs and save time, surveying audio profile of the deafness families is an effective step to screen families for linkage analysis. Studies have revealed that any mutation in *TECTA* gene which inactivates the gene products is associated with non-syndromic autosomal recessive hearing loss. Autosomal recessive mutations in *TECTA* gene lead to a moderate to severe deafness and display an audiogram pattern in a flat or U shape at all frequencies. Fortunately, this pattern helps to identify *TECTA* gene as the cause of some kinds of hearing loss. While all missense mutations in *TECTA* gene cause autosomal dominant type of hearing loss, depending on the involved domain harboring the mutation, clinical manifestations are different (10). Mutations in the ZP domain cause a dominant negative phenotype giving rise to a disrupted connection between different tectorin polypeptides, so deteriorate tectorial membrane structure. Any defect in this membrane results in a reduction in the quality of sounds transferred to stereociliary fibers of hair cells and eventually cause hearing loss (15). Another hypothesis explains that any instability of alpha tectorin mRNA or its destruction lead to decreased protein levels in tectorial membrane (7). Mutation in ZP domain causes non-progressive prelingual deafness at mild frequency, while any mutation in ZA domain results in progressive hearing loss at the high frequency range in childhood (16). Researchers have demonstrated that there is a significant relationship between mutations in ZP and mild hearing loss and also ZA and Progressive high frequency hearing impairment (17). Furthermore, mutation in Entactin-G1-like domain at the first repeat of vWFD and also at TIL2 repeats in ZP and ZA domain cause high-frequency hearing loss. Even the site of the mutation can affect hearing loss stability, so missense mutations occurring at cysteine repeats of ZA and ZP domain cause progressive post lingual hearing loss (18). These mutations decay disulfide bonds and destabilize the cellular matrix structure, while the rest of the mutations occurring at the other amino acids in this region cause stable hearing loss.

Deafness related to *TECTA* involved loci

Non syndromic autosomal recessive hearing loss associated with DFNB21

The first time in 1999, DFNB21 has been reported in a Lebanese family with Severe-to-Profound prelingual deafness by Mustapha et al. This mutation has been located at the donor splice site in intron 9 and results in a stop codon at 972 positions rendering a truncated protein. This variant has not been observed in 101 healthy subjects (19). In 2003, in two Iranian and Pakistani families with Severe-to-Profound sensory neural hearing loss, respectively an insertion mutation (649insC (602574.0006)) and a deletion mutation (6037delG (602574.0007)) have been reported (20). In 2007, linkage analysis using D11S1299, D11S1998 and D11S4464 markers surveying 45 GJB2 negative deaf families displayed linkage to the *TECTA* gene. Sequencing of the *TECTA* gene revealed a frame shift mutation (266delT, p.122X), a missense mutation (5211C>A, p.Y1737X) and a 9.6kb deletion in exon 10 and intron 8 and 9 (10). One year later, a 16bp deletion in exon 21 in the Iran population was reported (21). In 2012, the first compound heterozygote from a Korean population was reported using next generation sequencing approach. This missense mutation has been located in exon 15 and insertion has occurred at the donor splice site. The father and mother of this family were heterozygotes for a missense mutation and a splice site mutation respectively. Moreover, these mutations have not been observed in 120 healthy people (17). In 2016, surveying 50 Iranian families with Arab ethnicity, the last identified mutation in the *TECTA* gene was reported (22). This nonsense mutation lead to translation of a truncated protein containing 245 amino acids and was not observed in healthy volunteers (22)(Table 1).

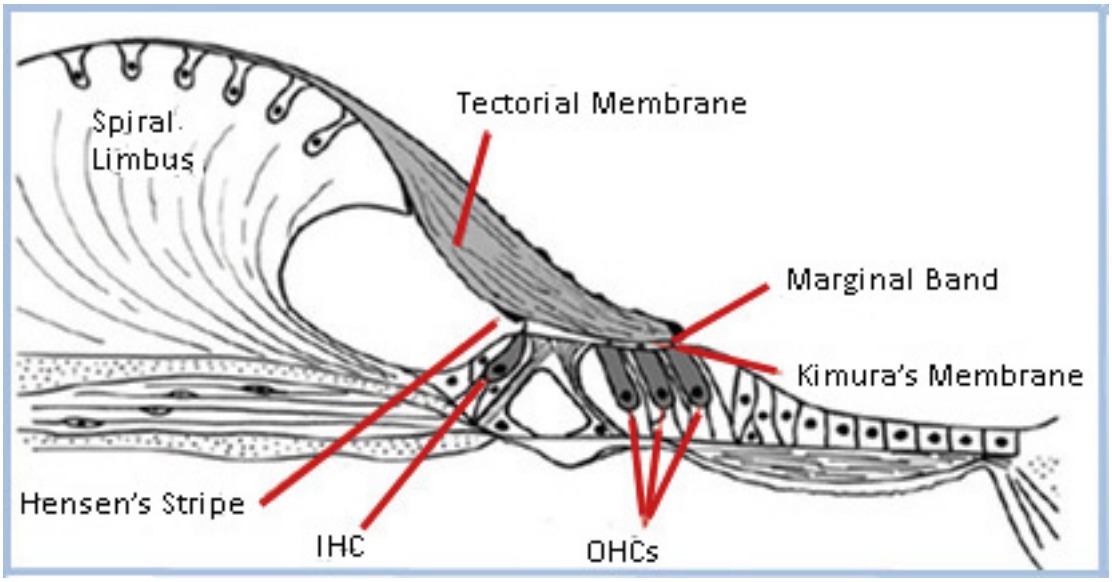

Figure 1: Organ of Corti structure and TECTA. The structure of the organ of corti Schematic picture in the basal area of the cochlea in the human ear. TM is connected to the outer hair-cells Stereocilia via Kimura membrane, hair-cell Stereociliavia Hensen fibers and also spiral limbus (11).

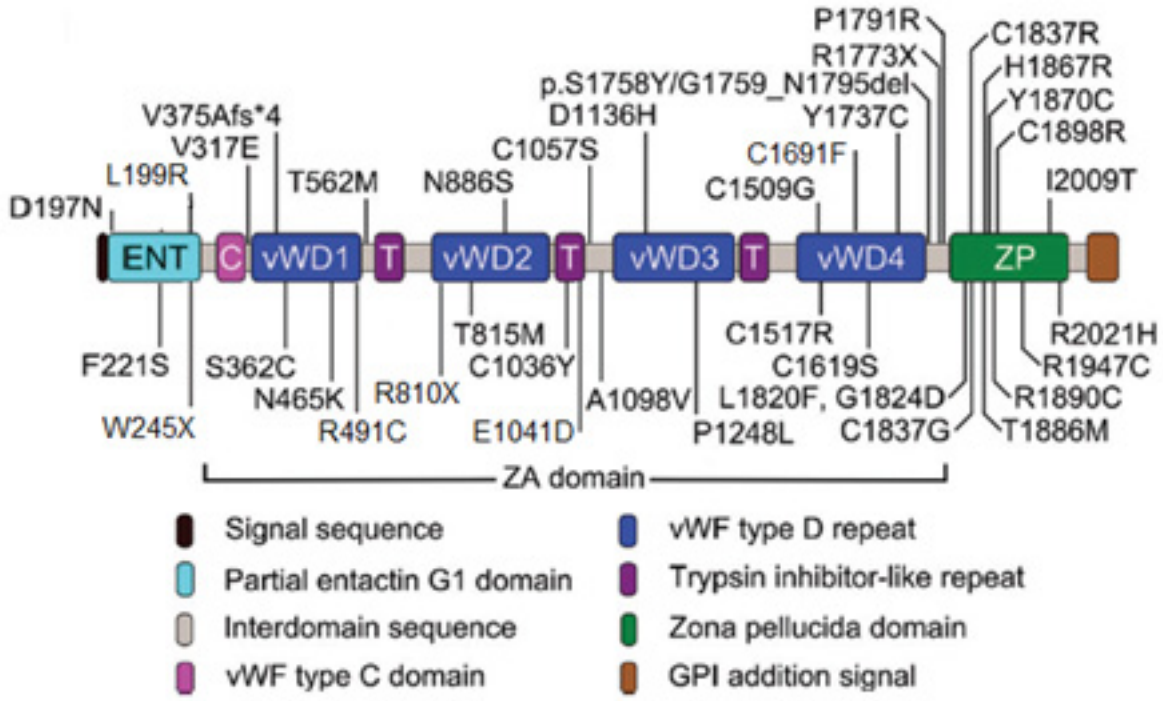

Figure 2: The structures of TECTA domains and the position of missense mutations causing hearing loss. Mutation in Entactin-G1 domain, vWFD, vWFD2 and TIL2 repeats of ZA and ZP cause to mild-frequency hearing loss, while mutation in other parts of ZA domain results in high-frequency hearing impairment.

Autosomal dominant non-syndromic hearing loss

A study accomplished in 1998 for the first time reported that two Australian and Belgian families displayed linkage to DFNB8 and DFNB12 loci at the long arm of chromosome 9, where the *TECTA* gene has been located (7). A compound heterozygous missense mutation (c.5725C>T and c.5738G>A) in the distance between 12bp located at exon 17 in a Belgium pedigree was reported in 18 patients while 40 healthy controls lacked the mutation. c.5876A>G mutation in exon 18 was reported in an Australian family while the mutation was not observed in 100 Australian and Belgian healthy people. These three mutations have been located in the ZP domain and cause prelingual hearing loss (7). In 1999 investigating a French pedigree of mild, moderate and progressive hearing loss showed linkage disequilibrium to DFNA12. *TECTA* gene sequencing revealed a missense mutation (c.4857G>C) changing cysteine 1916 into serine (C1916S) giving rise to the removing of cysteine in CGLC motif of D4vWfin zonadhesin/vonWillebrand domain (23). CGLC motifs in D1 and D2 repeats catalyzes the polymerization of disolphide bonds in VWF and are involved in the formation of non-collagenic tectorial membrane matrix. This mutation changes the properties of sound mechanical transfer in

Table 1: Reported mutations in TECTA gene (DFNB21) and their audiogram pattern

Exon	Mutation	Protein change	Protein domain	Frequency	Time of onset	Frequencies most affected	Ethnicity	Reference
3	c.266delT	p.Leu89Arg*34	ENT	Moderate to Severe	Prelingual	Mild	Iran	(10,36)
4	c.596delT	p.Leu199Argfs*7	ENT	Profound	Prelingual	Mid	Japan	(32, 36)
5	649insC	-	ENT	-	Prelingual	Mild	Iran	(20)
5	c.651dup C	p.Asn218GlnFS*31	ENT	-	Prelingual	All frequencies	Iran	(20)
5	c.734G>A	p.W245*	ENT	-	Prelingual	All frequencies	Iran	(22)
5	IVS9 + 1 G > A	p.248X *	ENT	-	Prelingual	All frequencies	Lebanon	(19)
5	c.654_657delTTTC	p.Phe219Serfs*12	ENT	Moderate to Profound	Prelingual	-	England	(33)
6	c.990C > A	p.Tyr330*	ZA (vWFD1)	Severe	Prelingual	-	China	(33,36)
7	c.1471C > T	p.Arg491Cys	ZA (vWFD1)	Profound	Prelingual	Mid	Japan	(32,36)
9	c.2428C > T	p.Arg810*	ZA (vWFD2)	-	Prelingual	-	England	(34)
9	c.2592C > A	p.Asn864Lys	ZA (vWFD2)	Moderate to Profound	Prelingual	-	England	(33)
9	c.2941+1 G	-	ZA	-	Prelingual	All frequencies	Iran	(10)
9-10	9.6 Kb	del	ZA	Prelingual	-	Mild	Iran	(35)
10	c.3123G > C	p.Glu1041Asp	ZA	-	Prelingual	-	England	(34)
11	c.4055G > A	p.Cys1352Tyr	ZA	Moderate to Profound	Prelingual	-	England	(33)
11	c.3903C > A	p.Cys1301*	ZA (vWFD3)	Moderate	Prelingual	-	Iran	(10)
14	c.4857C > A	p.Cys1619*	ZA (vWFD4)	Profound	Prelingual	-	Palestine	(20)
15	c.5072G > T	p.Cys1691Phe	ZA (vWFD4)	Moderate to Severe	Prelingual	-	Korea	(34,37)
15	c.5211 C>A	p.Tyr1737*	ZA		Prelingual	Mild	Iran	(10)
Intron 15	c.5272 + 1G > A	-	ZA	Moderate to Severe	-	All	Algeria	(36)
15	c.5210A>G	p.Y1737C	ZA	-	Prelingual	Mild	Iran	(37)
Intron 20	c.6162+3insT	-	ZA (vWFD4)	-	Prelingual	Moderately	Korea	(37)
20	c.6037delG	p.2018X*	ZP	-	Prelingual	All frequencies	Pakistan	(20)
21	c. 6203-6218 del	p.lys 2068Arg*38	ZP	-	Prelingual	All frequencies	Iran	(21)

Table 2: reported mutations in TECTA gene (DFNA8/12) and their audiogram pattern

Exon	Mutation	Protein change	Protein domain	Frequency	Time of onset	Frequencies most affected	Ethnicity	Reference
3	c.257– 262delinsGCT	p. Ser 86Cys p. Pro88del	ENT	High	Postlingual	Stable	China	(26)
4	A>c.589G	p.Asp197Asn	ENT	Mid	Prelingual	Stable	USA	(26)
5	C>c.632T	p.Phe211Ser	ENT	Mid	Prelingual	Stable	Spain	(17)
6	A>c.950T	p.Val317Glu	ZA (none)	High	Postlingual	Unknown	Korea	(26)
6	T>c.1084A	p.Ser362Cys	ZA (VWFD1)	Mid	Postlingual	Unknown	USA	(26)
6	c.1124delT	p.Val375Alafs*4	ZA (VWFD1)	Mid	Postlingual	Unknown	Spain	(26)
7	G>c.1395T	p.Asn465Lys	ZA (VWFD1)	Mid	Postlingual	Progressive	Belgium	(26)
7	T>c.1685C	p.Thr562Met	ZA (none)	Mid	Postlingual	Unknown	USA	(26)
9	T>c.2444C	p.Thr815Met	ZA (VWFD2)	Mid	Prelingual	Unknown	USA	(26)
9	G>c.2657A	p.Asn886Ser	ZA (VWFD2)	High	Prelingual	Progressive	Europe	(26)
10	A>c.3107G	p.Cys1036Tyr	ZA (TIL2)	Mid	Postlingual	Stable	Spain	(26)
10	A>c.3169T	p.Cys1057Ser	ZA (none)	High	Postlingual	Progressive	Sweden	(26)
10	T>c.3293C	p.Ala1098Val	ZA (none)	High	Postlingual	Unknown	Spain	(26)
10	C>c.3406G	p.Asp1136His	ZA (VWFD3)	High	Postlingual	Unknown	Spain	(26)
11	T>c.3743C	p.Pro1248Leu	ZA (VWFD3)	High	Prelingual	Unknown	Spain	(26)
13	G>c.4525T	p.Cys1509Gly	ZA (VWFD4)	High	Unknown	Progressive	Turkey	(26)
13	C>c.4549T	p.Cys1517Arg	ZA (VWFD4)	High	Postlingual	Progressive	Spain	(26)
14	C>c.4856G	p.Cys1619Ser	ZA (VWFD4)	High	Postlingual	Progressive	France	(26)
16	A>c.5331G	p.Leu1777Leu	ZA (none)	Mid	Prelingual	Stable	Germany	(26)
16	G>c.5372C	p.Pro1791Arg	ZA (none)	Mid	Prelingual	Unknown	USA	(26)
Intron18	c.5383+2T.G	-	ZA (none)	Mid	Prelingual	Stable	Europe	(26)
Intron18	c.5383+5del GTGA	-	ZA (none)	High	Prelingual	Progressive	Belgium	(26)
17	T>c.5458C	p.Leu1820Phe	ZP	Mid	Postlingual	Stable	Belgium	(7)
17	A>c.5471G	p.Gly1824Asp	ZP	Mid	Postlingual	Stable	Belgium	(7)
17	G>c.5509T	p.Cys1837Gly	ZP	Mid	Postlingual	Progressive	Spain	(38)
17	G>c.5509T	p.Cys1837Gly	ZP	-	Postlingual	Progressive	Spain	(26)
17	C>c.5509T	p.Cys1837Arg	ZP	-	Postlingual	Progressive	USA	(26)
18	c.5597C>T	p.Thr1866Met	ZP	-	Postlingual	Stable	Korea	(26)
18	c.5597C>T	p.Thr1866Met	ZP	-	Postlingual	Progressive	Spain, USA	(26)
18	c.5600A>G	p.His1867Arg	ZP	-	Postlingual	Progressive	Spain	(26)
18	c.5609A>G	p.Tyrl870Cys	ZP	-	Prelingual	Stable	Australia	(7)
18	c.5668C>T	p.Arg1890Cys	ZP	-	Prelingual	Stable	Germany	(16)
18	c.5668C>T	p.Arg1890Cys	ZP	-	Prelingual	Stable	USA	(26)
18	c.5692T>C	p.Cys1898Arg	ZP	-	Postlingual	Unknown	USA	(26)
19	c.5839C>T	p.Arg1947Cys	ZP	-	Postlingual	Unknown	USA	(26)
20	c.6026T>C	p.Ile2009Thr	ZP	-	Postlingual	Stable	Japan	(26)
20	c.6062G>A	p.Arg2021His	ZP	-	Prelingual	Stable	Japan	(39)

tectorial membrane via disturbing the proper polypeptide cross-linking, resulting in hearing loss in patients (23).

Parallel to this study, C1057S mutation in one domain of zonadhesin/Von Willebrand was reported in a population of Sweden. C1057S mutation attenuates sound transmission by changing polypeptide cross linking, resulting in deafness (8). In 2001 and 2002 two missense mutations in exon 17 and 20 were reported in the Spanish (24) and Japanese (8) pedigrees respectively and from 2004-2013 in the USA (10), Turkey (18), Germany (25), Korea (26) and China, some mutations were reported which have been described in detail in Table 2.

The biggest cohort study focusing on DFNA8/12 was accomplished in 2011. In this study 835 American deaf families (autosomal dominant non-syndromic hearing loss) were investigated. According to audiometric data, 73 pedigrees that had deafness at low and high frequency were selected. Their audiograms were screened by Audio Gene software (http://audiogene.eng.uiowa.edu/) which contains a databank including 1926 audiograms from 17 known loci involved in ADNSHL. Based on the audiogram pattern, the software predicts which locus is involved in hearing loss (26, 27). In the next phase of the study, 372 Spanish deaf were surveyed. Audio gene prediction introduced 64 families with possibility of DFNA8/12 involvement that *TECTA* gene sequencing indicated that only 9 families carried the mutation, also 14 mutations were reported in the Spanish population (26). In 2014, in China a 9bp deletion was reported (28). In Table 2, all of the autosomal dominant mutations have been represented in detail.

Mouse Models for Human Hearing Impairment

Tecta$^{\Delta ENT/\Delta ENT}$ mouse models have been developed by Exon Skipping, so 96 amino acids were removed from N-terminal of entactin G1 in alpha-tectorine. During the first days of the embryonic period, examining the mouse model demonstrated that the greater epithelial ridge of *TECTA* was very little growth and also was not detectable by western blot analysis. Even three weeks after the birth *TECTA* expression was negligible, while tectorial membrane in Tecta$^{+/+}$ and *Tecta*$^{+/DENT}$ mice was normal and TM had been connected to Spiral limbus fully. But in the mouse model, TM had been separated from spiral limbus and the organ of corti and also had no beta tectorial membrane and otogelin as the collagenic part of tectorial membrane (29). Otoconia membrane has been reduced in the models compared to heterozygotes or normal group. The mouse model was not able to do rotational movements and also there were explicit defects in their movements and behavior. In these mice, there were not any appropriate matrix filaments and sheets, but outer and inner hair cells were normal and had positioned at the right place. The results indicated that mutated alpha tectorin protein is produced and secreted in these mice but is not able to organize the matrix and is ruined rapidly (29). The next mouse model was the mice with mutation in *Tecta*^{Y1870C}.

In ZP domain, this mutation was reported in 1998 in an Australian family with prelingual hair impairment at moderate to severe frequency. In these transgenic mice, TM matrix structure was disturbed and ZA domain thickness was decreased, although these changes had no major effect on the main role of tectorial membrane according to the data obtained from the evaluating of sensitivity and frequency of cochlea mechanical response to sounds. The nervous threshold was evaluated; nervous regulation was extended resulting in a major decrease in the peak of nervous regulation curve (30). *Tecta*$^{C1509G/+}$ mouse model harbored a missense mutation in the ZA domain which had caused a progressive mild to moderate hearing impairment in a Turkish family. Structural phenotype is more subtle, hearing response threshold of brain stem at -40 frequencies was 25dB throughout the hearing range and hearing loss occurs mostly at mild level (10-35 KHz) (31). In a study published in 2014, a three mouse model including *Tecta*$^{L1820F, G1824D/+}$ in ZP domain which had caused deafness at mild frequency in a Belgium family, *Tecta*$^{C1837G/+}$ in ZA domain and which had caused progressive hearing loss at mild frequency in a Spanish family and *Tecta*$^{C1619S/+}$ in ZA domain which had caused progressive hearing loss at high frequency in a French family, were investigated. Mutations in ZA and ZP domain give rise to distinct and different changes in TM structure (28). Changes in TM is similar to the changes when *Tecta*^{Y1870C} mutation occurs and includes reduction in limbus region, the lack of striated sheet matrix, disturbance in the organization of collagenic fiber in the Sulcal region and finally the lamination of Kimura membrane. Defects in tectorial membrane in *Tecta*$^{C1619S/+}$ mouse model is completely different from models harboring mutations in ZP domain and is similar to *Tecta*$^{C1509G/+}$ mouse model. These defects include destroying marginal band; a major reduction in Covernet (upper layer of TM is covered by this fiber canal) and finally changes in fiber network profile give rise to the reduction in hair cells connection (11). In the case of mutations in ZP domain, the threshold of brain stem hearing response (in the range of 8-40 KHz) increased by 30-40 dB, while mice carrying mutations in ZA domain displayed a 20-30 dB increase, although TM phenotype is stable and there is no evidence implying gradual deterioration of hearing structure or function (11). Regarding the data obtained from these five DFNA8/12 related mouse models, genotype-phenotype correlation related to ZP and ZA domain can be clearly observed, so this clue can be used in the prediction of the involved domains in hearing impairment according to the hearing phenotype.

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References

1. Asgharzade S, Rabiei Z, Rafieian-Kopaei M. Effects of Matricaria chamomilla extract on motor coordination impairment induced by scopolamine in rats. Asian Pacific Journal of Tropical Biomedicine. 2015;5(10):829-33.
2. Rabiei Z, Asgharzade S, Bigdeli M. Medicinal herbs effective in the treatment of the Alzheimer's disease. Journal of Babol University of Medical Sciences. 2015;16(15):51-9.
3. Hashemzadeh Chaleshtori M, Simpson MA, Farrokhi E, Dolati M, Hoghooghi Rad L, Amani Geshnigani S, et al. Novel mutations in the pejvakin gene are associated with autosomal recessive non-syndromic hearing loss in Iranian families. Clinical genetics. 2007;72(3):261-3.
4. Asgharzade S, Reiisi S, Tabatabaiefar MA, Chaleshtori MH. Screening of Myo7A Mutations in Iranian Patients with Autosomal Recessive Hearing Loss from West of Iran. Iranian journal of public health. 2017;46(1):76.
5. ASGHARZADE S, CHALESHTORI MH, Tabatabifar M, Reisi S, Modaressi MH. MUTATION IN SECOND EXON OF MYO15A GENE CAUSE OF NONSYNDROMIC HEARING LOSS AND ITS ASSOCIATION IN THE ARAB POPULATION IN IRAN. Genetika. 2016;48(2):587-96.
6. Sadeghi A, Sanati MH, Alasti F, Hashemzadeh Chaleshtori M, Ataei M. Mutation analysis of connexin 26 gene and del (GJB6-D13S1830) in patients with hereditary deafness from two provinces in Iran. Iran J Biotechnol. 2005;3(4):255-8.
7. Verhoeven K, Van Laer L, Kirschhofer K, Legan PK, Hughes DC, Schatteman I, et al. Mutations in the human α-tectorin gene cause autosomal dominant non-syndromic hearing impairment. Nature genetics. 1998;19(1):60-2.
8. Balciuniene J, Dahl N, Jalonen P, Verhoeven K, Van Camp G, Borg E, et al. Alpha-tectorin involvement in hearing disabilities: one gene-two phenotypes. Human genetics. 1999;105(3):211-6.
9. Khosrofar M, Pourreza MR, Asgharzadeh S, Tahmasebi P, Ali Asgari E, Ghasemikhah R, et al. Genetic Linkage Analysis of the DFNB21 Locus in Autosomal Recessive Hearing Loss in large families from Khuzestan Province. Arak Medical University Journal. 2017;20(3):31-8.
10. Meyer NC, Alasti F, Nishimura CJ, Imanirad P, Kahrizi K, Riazalhosseini Y, et al. Identification of three novel TECTA mutations in Iranian families with autosomal recessive nonsyndromic hearing impairment at the DFNB21 locus. American Journal of Medical Genetics Part A. 2007;143(14):1623-9.
11. Legan PK, Goodyear RJ, Morín M, Mencia A, Pollard H, Olavarrieta L, et al. Three deaf mice: mouse models for TECTA-based human hereditary deafness reveal domain-specific structural phenotypes in the tectorial membrane. Human molecular genetics. 2013;23(10):2551-68.
12. Maeda Y, Fukushima K, Kasai N, Maeta M, Nishizaki K. Quantification of TECTA and DFNA5 expression in the developing mouse cochlea. Neuroreport. 2001;12(15):3223-6.
13. Richardson G, Forge A, Kros C, Fleming J, Brown S, Steel K. Myosin VIIA is required for aminoglycoside accumulation in cochlear hair cells. Journal of Neuroscience. 1997;17(24):9506-19.
14. Richardson GP, de Monvel JB, Petit C. How the genetics of deafness illuminates auditory physiology. Annual review of physiology. 2011;73:311-34.
15. Hashemzadeh-Chaleshtori M, Saidijam M, Jami M-S, Ghasemi-Dehkordi P. MicroRNA-183 Family in Inner Ear: Hair Cell Development and Deafness. Journal of audiology & otology. 2016;20(3):131-8.
16. Plantinga RF, de Brouwer AP, Huygen PL, Kunst HP, Kremer H, Cremers CW. A novel TECTA mutation in a Dutch DFNA8/12 family confirms genotype–phenotype correlation. Journal of the Association for Research in Otolaryngology. 2006;7(2):173-81.
17. Sagong B, Baek JI, Bok J, Lee KY, Kim UK. Identification of a nonsense mutation in the STRC gene in a Korean family with moderate hearing loss. Int J Pediatr Otorhinolaryngol. 2016;80:78-81.
18. Pfister M, Thiele H, Van Camp G, Fransen E, Apaydin F, Aydin Ö, et al. A genotype-phenotype correlation with gender-effect for hearing impairment caused by TECTA mutations. Cellular Physiology and Biochemistry. 2004;14(4-6):369-76.
19. Mustapha M, Weil D, Chardenoux S, Elias S, El-Zir E, Beckmann JS, et al. An α-tectorin gene defect causes a newly identified autosomal recessive form of sensorineural pre-lingual non-syndromic deafness, DFNB21. Human molecular genetics. 1999;8(3):409-12.
20. Naz S, Alasti F, Mowjoodi A, Riazuddin S, Sanati M, Friedman T, et al. Distinctive audiometric profile associated with DFNB21 alleles of TECTA. Journal of medical genetics. 2003;40(5):360-3.
21. Alasti F, Sanati MH, Behrouzifard AH, Sadeghi A, De Brouwer AP, Kremer H, et al. A novel TECTA mutation confirms the recognizable phenotype among autosomal recessive hearing impairment families. International journal of pediatric otorhinolaryngology. 2008;72(2):249-55.
22. Asgharzade S, Tabatabaiefar MA, Modarressi MH, Ghahremani MH, Reiisi S, Tahmasebi P, et al. A novel TECTA mutation causes ARNSHL. International Journal of Pediatric Otorhinolaryngology. 2017;92:88-93.
23. Alloisio N, Morle L, Bozon M, Godet J, Verhoeven K, Van Camp G, et al. Mutation in the zonadhesin-like domain of α-tectorin associated with autosomal dominant non-syndromic hearing loss. European Journal of Human Genetics. 1999;7(2):255-8.
24. Moreno-Pelayo MA, del Castillo I, Villamar M, Romero L, Hernández-Calvín FJ, Herraiz C, et al. A cysteine substitution in the zona pellucida domain of α-tectorin results in autosomal dominant, postlingual, progressive, mid frequency hearing loss in a Spanish family. Journal of medical genetics. 2001;38(5):e13-e.
25. Collin RW, de Heer A-MR, Oostrik J, Pauw R-J, Plantinga RF, Huygen PL, et al. Mid-frequency DFNA8/12 hearing loss caused by a synonymous TECTA mutation that affects an exonic splice enhancer. European journal of human genetics. 2008;16(12).
26. Hildebrand MS, Morín M, Meyer NC, Mayo F, Modamio-Hoybjor S, Mencía A, et al. DFNA8/12 caused by TECTA mutations is the most identified subtype of nonsyndromic autosomal dominant hearing loss. Human mutation. 2011;32(7):825-34.

26. Hildebrand MS, Morín M, Meyer NC, Mayo F, Modamio-Hoybjor S, Mencía A, et al. DFNA8/12 caused by TECTA mutations is the most identified subtype of nonsyndromic autosomal dominant hearing loss. Human mutation. 2011;32(7):825-34.
27. Hildebrand MS, Tack D, McMordie SJ, Deluca A, Hur IA, Nishimura C, et al. Audioprofile-directed screening identifies novel mutations in KCNQ4 causing hearing loss at the DFNA2 locus. Genetics in Medicine. 2008;10(11):797-804.
28. Su Y, Tang W-X, Gao X, Yu F, Dai Z-Y, Zhao J-D, et al. A novel mutation in the TECTA gene in a Chinese family with autosomal dominant nonsyndromic hearing loss. PloS one. 2014;9(2):e89240.
29. Legan PK, Lukashkina VA, Goodyear RJ, Kössl M, Russell IJ, Richardson GP. A targeted deletion in α-tectorin reveals that the tectorial membrane is required for the gain and timing of cochlear feedback. Neuron. 2000;28(1):273-85.
30. Legan PK, Lukashkina VA, Goodyear RJ, Lukashkin AN, Verhoeven K, Van Camp G, et al. A deafness mutation isolates a second role for the tectorial membrane in hearing. Nature neuroscience. 2005;8(8):1035-42.
31. Xia A, Gao SS, Yuan T, Osborn A, Bress A, Pfister M, et al. Deficient forward transduction and enhanced reverse transduction in the alpha tectorin C1509G human hearing loss mutation. Disease models & mechanisms. 2010;3(3-4):209-23.
32. Miyagawa M, Nishio SY, Hattori M, Moteki H, Kobayashi Y, Sato H, et al. Mutations in the MYO15A gene are a significant cause of nonsyndromic hearing loss: massively parallel DNA sequencing-based analysis. Ann Otol Rhinol Laryngol. 2015;124 Suppl 1:158S-68S.
33. Hutchin T, Coy N, Conlon H, Telford E, Bromelow K, Blaydon D, et al. Assessment of the genetic causes of recessive childhood non-syndromic deafness in the UK–implications for genetic testing. Clinical genetics. 2005;68(6):506-12.
34. King DA, Fitzgerald TW, Miller R, Canham N, Clayton-Smith J, Johnson D, et al. A novel method for detecting uniparental disomy from trio genotypes identifies a significant excess in children with developmental disorders. Genome research. 2014;24(4):673-87.
35. Li Z, Guo Y, Lu Y, Li J, Jin Z, Li H, et al. Identification of a novel TECTA mutation in a Chinese DFNA8/12 family with prelingual progressive sensorineural hearing impairment. PloS one. 2013;8(7):e70134.
36. Behlouli A, Bonnet C, Abdi S, Hasbellaoui M, Boudjenah F, Hardelin J-P, et al. A novel biallelic splice site mutation of TECTA causes moderate to severe hearing impairment in an Algerian family. International Journal of Pediatric Otorhinolaryngology. 2016;87:28-33.
37. Diaz-Horta O, Duman D, Foster II J, Sırmacı A, Gonzalez M, Mahdieh N, et al. Whole-exome sequencing efficiently detects rare mutations in autosomal recessive nonsyndromic hearing loss. PloS one. 2012;7(11): e50628.
38. Alford RL. Nonsyndromic hereditary hearing loss. Medical Genetics in the Clinical Practice of ORL. 70: Karger Publishers; 2011. p. 37-42.
39. Iwasaki S, Harada D, Usami S-i, Nagura M, Takeshita T, Hoshino T. Association of clinical features with mutation of TECTA in a family with autosomal dominant hearing loss. Archives of Otolaryngology–Head & Neck Surgery. 2002;128(8):913-7.