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REVIEW ARTICLE **OPEN ACCESS**

Tip links and Top Connector Proteins in Stereocilia: a pursuit in hearing loss

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ABSTRACT
Hearing depends on the functioning of sensitive micromachinary of the inner ear cochlea. The sound vibrations received in the cochlea is amplified through stereocilia of the hair cells gated by the tip links. Proteins anchoring to the tip link to the cytoskeleton in the stereociliary links to cadherin 23 and protocadherin 15 are the part of the regulatory process that forms the actin core and the transduction apparatus. The tip links and lateral links are maintaining optimal bundle cohesion and stiffness for transduction. The loss of cross-links of the outer hair cells resulting in disarrangement of the stereociliary bundles are the result of Noise Induction leads to permanent sensorineural hearing loss. This review summarizes about the structure, function and composition of stereociliary linkages of the links and how they are relevant to human hearing impairment.
***Keywords**: Ankle link, Lateral links, Noise induced hearing loss, Shaft link, Stereocilia, Tip links*

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INTRODUCTION

Noise induced hearing loss (NIHL) is defined as hearing impairment due to an exposure of high decibel sound. The normal range of sound is about less than 80dB and the highest level is 150dB. Exposure to loud sound can result in temporary or permanent hearing loss. Noise induce hearing loss is one of the most frequently occurring occupational disease as noise factor is presumed as a most prevalent and common perilous in the worksites. The workers in different industries are exposed to hazardous sound level in workplace; by continuous exposure to loud sound over an extended period of time such as noise generated in mines, manufacturing and fabrication units of industries. Around 30 million adults in the United States are exposed to loud sound level at workplace. Among these 30 million people, one in four will acquired a permanent hearing loss as a result of their occupation [1]. Hearing is the process by which the ear transforms sound vibration into nerve impulses that are transferred to the brain by auditory nerve. Exposure to loud sounds causes injury to sensitive structure in the inner ear hair cells and auditory nerve.

The auditory system is composed of three components: Outer, Middle and Inner ear, which work together to transform sounds from the environment to brain. The inner ear is complex structure, sound waves enter the outer ear and pass through a narrow passage called ear canal which leads to the ear drum. The ear drum can vibrate and these vibrations pass to the middle ear via ossicular chain consists of three tiny bones are malleus, incus and stapes. Malleus link to the tympanic membrane, stapes inserts into the oval window in the inner ear and the incus is in between the malleus and stapes. The vibrations are transferred through ossicular chain into inner ear via stapes. The vibration enters in the inner ear of cochlea and converts sound waves into neural signal. The inner ear consist cochlea and vestibular system responsible for hearing and equilibrium. Cochlea is a snail like structure which is filled with fluid contains perilymph and endolymph in three chambers which are scala tympani, scala media and scala vestibule. Two outer chambers filled with perilymph fluid, third centred chamber i.e. cochlear duct secrets

endolymph fluid which is rich in potassium ions. Cochlear duct contain basilar membrane sits upon organ of corti. The organ of corti consist of sensory cells of auditory system that is hair cells to be found on apical surface of basilar membrane [2]. The sensory epithelium of the cochlea, organ of corti consists of two types of hair cells Outer Hair Cells (OHCs) and Inner Hair Cells (IHCs) based on morphological and physiological characteristics which is responsible for hearing. IHCs are actual sensory cells that pass on information via cochlear nerve fibres to the brainstem auditory nuclei. IHCs contain tallest cilium i.e. Kinocilium is an apical modified architecture of primary cilium. In contrast, OHCs which are capable with electromotility constitute the cochlear amplifiers that contribute to the detection of weak sound induce vibrations. The mammalian stereocilia hair bundles of OHCs are set in three rows of graded height and are tightly interconnected. Sound induces vibration in organ of corti leads to oscillate endolymph fluid present in basilar membrane moves up and down. The stereocilias are contact with tectorial membrane, the bundles of hair cells get deflect and trigger opening of mechanically gated ion channels in stereocilia and hair cells get depolarized as depicted in Figure 1 (A,B,C). Influx of potassium ions in stereocilial hair cells provides potential to vibration and motion into electrical current, which in turn alters the cross-membrane potential and is crucial for hearing. An actin-base stereocilium is organized on apical surface of auditory hair cells in increasing height Figure 1(D). stereocilia are microvillar like projections supported by actin bundles. The tips of the stereocilia from the shorter rows are connected to the sides of the adjacent taller stereocilia by tip links as depicted in the Figure 2. Tip links are thought to be essential element of the mechanoelectrical transduction (MET) tool in sensory hair cells of the inner ear [3]. Tip links are the extracellular filaments that connect stereocilia to each other or to the Kinocilium on the hair cells of the inner ear [4].Inside cochlea the structure of organ of corti consists of tectorial membrane organized on top of stereociliary bundles.

Different types of cochlear proteins present in the inner ear stereocilia, plays individual role significantly. Some associated cochlear proteins such as myosin 1b, whirlin, harmonin, espin, connexin26, cadherin23, protocadherin 15 etc are involved in diverse function in which the stereocilin is one of the concerned proteins in hearing disabilities is focused in this review. Stereocilin is one of the connector protein, encodes by the STRC gene, located on 15q21-q22 in homo sapiens, localizes to horizontal top connectors in mature hair cells, plays a major role in hearing mechanism found to be MW 193 kDa, consist of 1809 amino acids [5-7].Changes in this protein are known to cause bilateral, non-progressive, sensorineural hearing loss. Dysfunction of stereocilin in hearing involves all frequencies, in the range of 125-1000Hz, but it's severe in the higher frequencies [8].

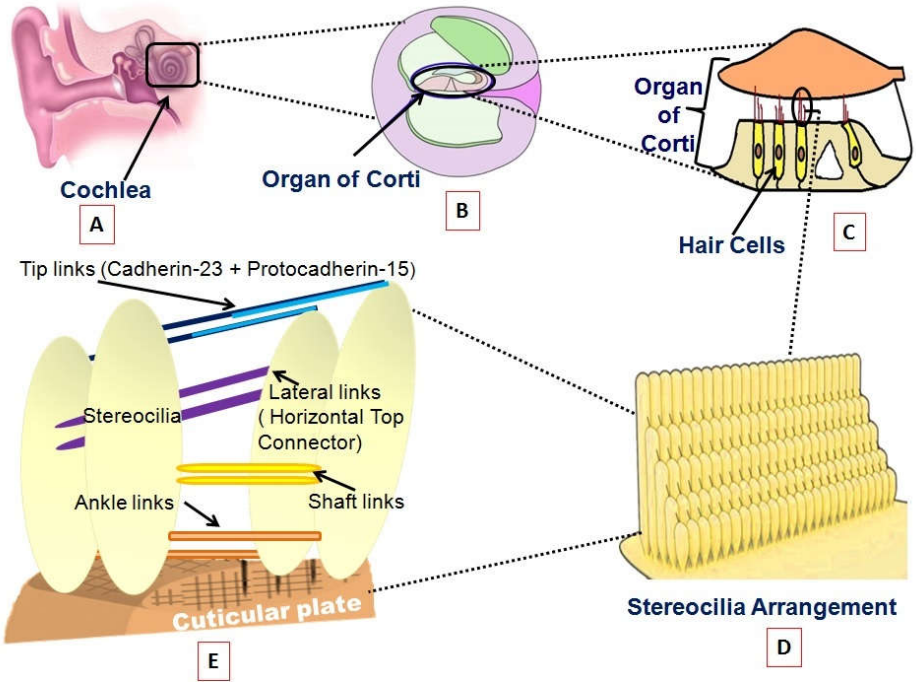

Figure 1: Schematic representation and location of cross linkers in stereocilia A) inner ear cochlea B) Middle ear scala media, organ of corti C) Enlarged structure of corti showing the hair cells D) Arrangement of stereocilia from tallest to the shorter on the cuticular plate E) The four stereociliary cross linkers , the tip links are present on top of stereocilia links the taller stereocilia to the shorter in a row, Horizontal top linkers (lateral links)pairs adjacent stereocilia just beneath the tip links, Shaft link expand part or length of all stereocilia, Ankle links attach to the stereocilia at bases.

The stereocilia are microvillar like projections supported by bundles of actin binding filaments. Stereocilia contains the channels that convert vibration and motion into electric current, which in turn alters the cross membrane potential, and is fundamental for hearing [9]. Stereocilia are connected adjacently with each other with the help of cross linkers Figure 1(D). These cross linkers are the extracellular filaments help in anchoring the stereocilia together. Four different types of cross linkers have been identified in both hair cells (OHC & IHC) which are Tip Link, ankle link, shaft link and horizontal top connector as depicted in the Figure 1(E).Tip link, looks a single filament as the number of links at the tip diminishes to one main tip link, connecting shorter to taller steriocilia in a row, present on the top of the steriocilia [10]. Ankle link attach the stereocilia at their bases, shaft link expand part or all of the length of the stereocilia, and horizontal top linkers pairs adjacent stereocilia just beneath the tip links as depicted in Figure 1(E).

Tip links are extracellular filaments attached to hair cells gated by mechanotransduction channels in steriocilia were studied in different animal model like guinea pigs, turtle and bullfrog along with human beings. In these models the concentration of Ca2+ and the length of tip links are being identified whether these are dependent on the Ca2+ concentration or not and also worked out for type of category of the tip links. The exact distribution of tip links varies into different population depends on species and location of the hair cell. Morphological studies by Kachar, Tsuprun and Santi suggested that the tip link is not a single strand but it is composed of two spirally wound helical strands, which unwound near the top of the link, amongst them one is thinner auxiliary link [11-12]. Similar findings were observed by the Furness and Hackney, who demonstrated bifurcated strands of tip links in the vertebrates. Evidences confirmed that members of the cadherin superfamily that is homodimer of Cadherin 23 (CDH23) forms the upper part of the tip link and homodimer protocadherin 15 (PCDH15) forms the lower part [13-14]. It is hypothesized that CDH23 has a short intracellular transmembrane domain and an ectodomain composed of 27 cadherin repeats. PCDH15 has transmembrane cytoplasmic domains with an ectodomain with 11 cadherin repeats with Ca2+-binding motif. The terminal regions of CDH23 and PCDH15 interact with each other by means of a Ca2+-sensitive binding site. The model is also supported by observations that CDH23 forms dimmers, which can partially unwind into two separate branches at one end in a lower Ca2+ levels. Kazmierczak predicted on the basis of biochemical data that increasing Ca2+ levels can decrease the length of the tip link. Accordingly the dimension of the forked part of the tip link was analyzed under different Ca2+ conditions [15-18]. The proteins, myosin VIIa, myosin 1c, Ankyrin, membrane-associated guanylate kinase MAGI1, and harmonin-b are involved in anchoring the tip link to the cytoskeleton in the stereociliary links to CDH23, suggesting that these proteins are part of the regulatory process that forms the actin core and the transduction apparatus [19]. Calmodulin enriched sites are attached with proteinaceous components like myosin to the tip link for moving with actin core.

Horizontal top connectors (lateral Links, side links) and shafts links are connected adjacent to stereocilia and were arranged with hexagonal symmetry. The horizontal top connectors are mediator of a sliding adhesion. Subsequently, all transduction channels of a hair cell are mechanically parallel, an arrangement that may develop amplification in the inner ear.

Stereocilin are the superhelical lectins binds to extracellular glycoprotein are the member of the mesothelin superfamily. It was first detected in mice linked for human deafness at DFNB16 locus. It was detected in association with horizontal top connectors also known as lateral links that joins adjacent stereocilia within the sensory hair cells and kinocilium which maintains optimal bundle cohesion and stiffness for transduction [20]. The function of the horizontal linker is more likely to be in holding the stereocilia bundles. Lateral links probably knot the stereocilia together to permit the bundle to act as a unity, increasing its stiffness and prevent it from incline in uncertain conditions. These observations strengthen that loss of top connectors substantially affects cochlear non-linearity. Scientist has worked for the memory of the antibodies against stereocilin present in the top connectors in the stereocilin-knockout mouse. The observations noted by Verpy et al were in the lines of Takumida et al. of showing stiffness till postnatal 9 days and complete dissociation of tip links after 15 day showing no link with steriocilia together [21]. Also it has been reported that the top connectors may function to decrease the sticky pull on the bundle [22]. The lateral links contribute to transduction more openly remains to be discovered, although there is some confirmation that the mechanoelectrical transduction (MET) channels might be associated with horizontal connections or top connectors below the tips of shorter stereocilia. There studies suggest that stereocilin occur to be appropriate in forming the top connectors and in their absence, the bundle cannot maintain the normal shape. This in turn affects the ability of the hair cell to sustain intact tip links. The apical surface of stereocilia, the process of mechanotransduction involves displacement of the bundles, modulates opening of MET channels. Deflection of stereocilia in the direction of tallest row depolarizes the sensory cells by influxation of k+ ions enter the cell. Depolarization in turn

open voltage gated calcium channel in the hair cell membrane and resultant Ca2+influx causes greater release of neurotransmitter which releases from the basal end of the cell and convey the signal through auditory nerve to the brain. During transduction process lateral links that is horizontally directed links connecting the rows of stereocilia this link is involved in sensory transduction. Deflection in the direction towards the shortest row close to the channels and reduces the flow of ions, resulting in hyperpolarisation of the cell depicted in Figure 2(A, B).

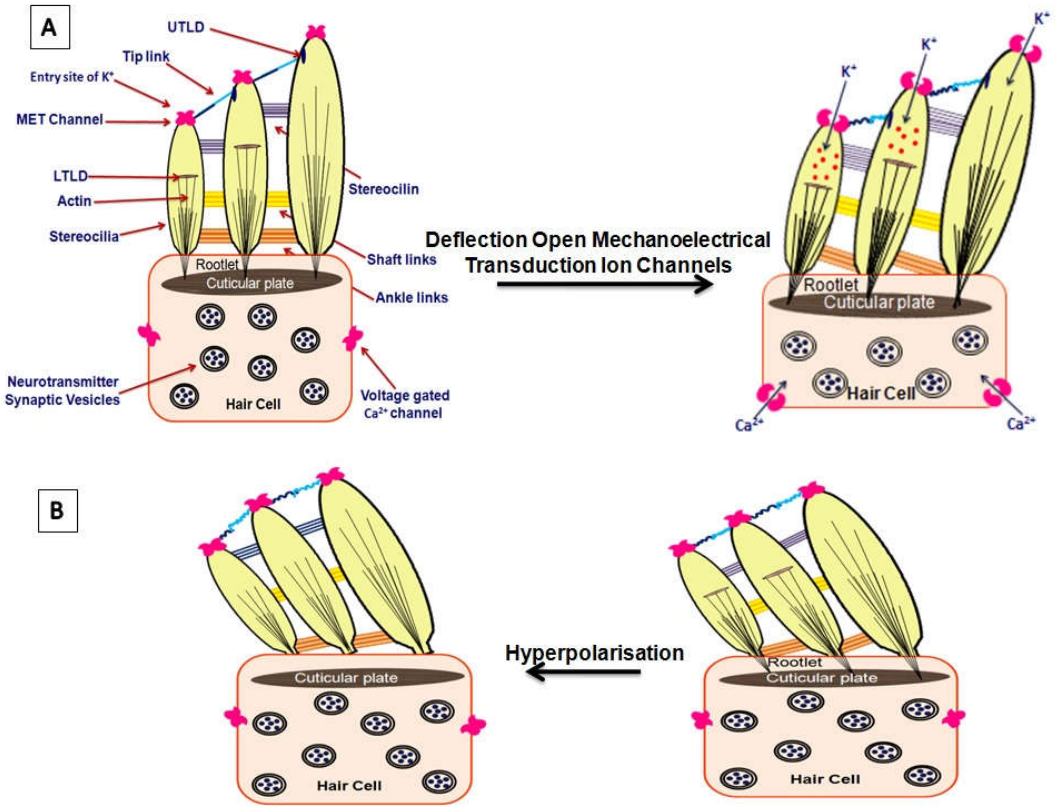

Figure 2 (A, B): Mechanism of deflection of stereocilia with depolarization and hyperpolarization, which depend on the MET channels and cross linkers working togethe, when deflection occurs from tallest to shorter stereocilia. tip link pulls, the MET channels opens and the Influxation of k+ and ca+ ions cause the neurotransmitter to transfer the signal to the brain.

It is thought that during deflection the stereocilin is absent or reduce hence the stereocilia get splay out and the signal is not pass to brain in the nonsyndromic hearing loss. The fluctuation of stereociliary bundles significantly reduces, thus causing reduced inflow of potassium ions into the cells. The STRC gene mutation leads to nonsyndromic hearing loss called DFNB16.

The shaft links are differ according to frequency of regions as the protein tyrosine phosphatase receptor type Q (PTPRQ) plays a major role in connectivity of steriocilia, absence of this PTPRQ forced lateral links to get elongated [23].

These Protein-protein interactions required to form the ankle links, known to be important for stereocilia link formation and a candidate member of the ankle link complex. Ankle links are localized to the base of the stereocilia, and are necessary for normal hearing function. Transmembrane proteins usherin, vezatin and the submembrane protein whirlin are linked by myosin VIIa found in the ankle regions with very large G-protein-coupled receptor play a major role in hair cells development24. The another transient receptor potential mucolipin 3 (TRPML3), the TRP ion channel protein family plays a role in lateral link formation. The genes GPR98 and USH2A are critical for ankle link formation and, when get mutated, resulted in deafness.

Table 1: Mutational studies in cochlear hair cell and stereocilin gene in different models.

Author & Year of Publication	Title	Model	Study Design	Conclusion
Verpy E,*et. al*. [25]	Mutations in a new gene encoding a protein of the hair bundle cause non syndromic deafness at theDFNB16 locus	Mouse	Mutation in L2E3 gene was studied by representational difference analysis (RDA) to generate three subtracted mouse inner ear cDNA libraries from cochlea. Genomic analysis was used for ortholog STRC (stereocilin gene) with the coding sequence linked to the DFNB16 locus. Stereocilin was also detected in inner ear by immunofluorescence.	In mouse inner ear, stereocilin is expressed only in the sensory hair cells and is associated with the mechanoreceptor of sound stimulation
Borum Sagong, *et. al*. [26]	Identification of a nonsense mutation in the STRC gene in Korean family with moderate hearing loss.	Human	Bioinformatics platform was used for filtering and detecting variations within (c.650G > A in TRIOBP and c.4057C > T in STRC) sequence to identify the causative mutation in GJB2 and SLC26A4 gene.	p.Q1353X variation in the STRC gene is the causative mutation for hearing loss suggests that application of targeted sequencing will be valuable for the diagnosis of heterogeneous disorders.
Palvina Plavova, *et. al*. [27]	STRC deletion is a frequent cause of slight to moderate congenital hearing impairment in the Czech Republic	Human	Molecular epidemiology of hearing loss in patients without GJB2 mutations were identified by Sequence capture technology, next-generation sequencing, and multiplex ligation-dependent probe amplification (MLPA) technique. Coverage of STRC was screened in Integrative Genomics Viewer software.	Mutated gene GJB2, STRC, TMPRSS3, USH2A, PCDH15, LOXHD1, MYO15A, MYO6A, KCNQ4, and SIX1 and X-linked POU3F4 were identified in hearing loss.
Vona B. *et. al*. [28] (2015)	DFNB16 is a frequent cause of congenital hearing impairment: implementation of STRC mutation analysis in routine diagnostics	Human	GJB2/GJB6 mutations were identified homozygous and heterozygous deletions with STRC region by microarray and/or quantitative polymerase chain reaction (qPCR) analysis. Sanger sequencing method used to detect smaller mutations in pseudogene exclusion.	Beside GJB2 /GJB6 (DFNB1), STRC biallelic mutations significantly contribute to non syndromic hearing loss in children at higher frequencies.
Luca Jovine, *et. al*. [29]	Sequence similarity between stereocilin and otoancorin points to a unified mechanism for mechanotransduction in the mammalian inner ear	Mouse	A gene encoding the putative Fugu fish homologue of stereocilin was identified by BLAST with mouse stereocilin. GENSCAN analysis of the genomic DNA was combined by stereocilin sequences to yield Fugu stereocilin homologue. STRC mutations start of the alignment with mesothelin were identified by non-syndromal sensorineural deafness linked to locus DFNB16.	Mechanotransduction of stereocilin and otoancorin responsible for the attachment to both sensory and nonsensory cells of the inner ear.
Frykholm C1, *et. al*. [30]	Stereocilin gene variants associated with episodic vertigo: expansion of the DFNB16 phenotype	Human	Hearing loss and episodic vertigo were identified in two brothers and their first cousin by pathological vestibular test along with exome sequencing and SNP array analysis. The DNA variants identified in this study are accessible in the dbSNP.	Stereocilin in the vestibular organ expand the phenotype associated with DFNB16 provides an additional mechanism for episodic vertigo.

Lauren J. Francey, *et. al*. [31]	Genome-Wide SNP Genotyping Identifies the Stereocilin (STRC) Gene as a Major Contributor to Pediatric Bilateral Sensorineural Hearing Impairment	Human	Study analyzed a total of 669 probands with NBSNHI ranging in severity from a mild to profound hearing loss for CNVs using three different Illumina genome-wide SNP genotyping array platforms and Sanger sequencing.	STRC may be a common contributor to NBSNHI among GJB2 mutation negative probands, especially in those with mild to moderate hearing impairment.
Verpy E, *et. al*. [32]	Stereocilin-deficient mice reveal the origin of cochlear waveform distortions	Mice	Stereocilin knockout mice (Strc2/2) were produced using the Cre–lox system. Recordings of cochlear microphonics, compound action potentials and otoacoustic emissions were studied in the mice. The morphology of the cochlear sensory epithelia was studied in Strc1/1 and Strc2/2 mice using SEM. Finally, immunolocalization of stereocilin were studied in mouse stereocilin sequence (AF375593). The distribution of stereocilin was analyzed using confocal immunofluorescence microscopy, scanning and transmission immunoelectron microscopy	Cochlear waveform distortions is a deflection-dependent hair bundle stiffness resulting from constraints imposed by the horizontal top connectors, and not from the intrinsic nonlinear behaviour of the mechanoelectrical transducer channel.
Verpy E, *et. al*. [33]	Stereocilin Connects Outer Hair Cell Stereocilia to One Another and to the Tectorial Membrane	Mice	In this study the distribution of stereocilin in the developing and mature mouse inner ear hair cells were analyzed through the consequences of its absence in stereocilin null (Strc $^{-/-}$) mice model suffers from hearing loss. Stereocilin was also detected in association with two cell surface specific to outer hair cells (OHCs) in the mature cochlea by immunofluorescence and immunogold electron microscopy. It was also detected around the kinocilium of vestibular hair cells and immature OHCs.	Stereocilin is essential for the formation of horizontal top connectors which maintains the cohesiveness of the mature OHC hair bundle is required for tip-link turnover.

CONCLUSION

This critical appraisal of connecters is an important to understand how protein-protein interactions are vital for regulatory processes of transduction of the signals to brain via this micromachinary of the inner ear. This review is focused on molecular composition, concentrating primarily on top connectors and lateral links along with important role of steriocilin in stiffness of the hair cells. The stereociliary connections of the tip links and lateral links are maintaining optimal bundle cohesion and stiffness for transduction of signals. It was noted that, to learn permanent sensorineural hearing loss the information on the connection between the channels of hearing, tip link and top connectors is not known till date, so it is very important to study this area at molecular level.

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REFERENCES

1. Noise-Induced Hearing Loss: NIDCD Fact Sheet: Website; Available on: http://www.nih.gov/nidcd.
2. Ekdale EG (2016) Form and function of the mammalian inner ear. J Anat PubMed., 228(2):324-37.
3. Jain RK., Pingle SK., Tumane RG., Thakkar LR., Jawade AA., Barapatre A., Trivedi M. (2018). Cochlear Proteins Associated with Noise-induced Hearing Loss: An Update. Indian J Occup Environ Med., May-Aug;22(2):60-73.
4. Pickles JO., Comis SD., Osborne MP. (1984). Cross-links between stereocilia in the guinea pig organ of Corti, and their possible relation to sensory transduction. Hearing Res Aug;15(2):103-12.
5. Verpy E., Leibovici M., Michalski N., Goodyear RJ., Houdon C., Weil D., Richardson GP., Petit C. (2011). Stereocilin connects outer hair cell stereocilia to one another and to the tectorial membrane. J Comp Neurol., Feb 1;519(2):194-210.
6. Stereocillin protein gene: Website; Available on: https://www.uniprot.org/uniprot/Q7RTU9
7. Zheng J., Shen W., He DZ., Long KB., Madison LD., Dallos P. (2000). Prestin is the motor protein of cochlear outer hair cells. Nature, May 11,149-55.
8. Flock A., Cheung HC. (1977). Actin filaments in sensory hairs of inner ear receptor cells. J Cell Biol., Nov; 75 (2 Pt 1):339-43.
9. Hakizimana P., Brownell WE., Jacob S., Fridberger A. (2012). Sound-induced length changes in outer hair cell stereocilia. Nat Commun., 3:1094.
10. Goodyear RJ., Marcotti W., Kros CJ., Richardson GP. (2005). Development and properties of stereociliary link types in hair cells of the mouse cochlea. J Comp Neurol., Apr 25, 485:75-85.
11. Kachar B., Parakkal M., Kurc M., Zhao Y., Gillespie PG. (2013). High-resolution structure of hair-cell tip links. Proc Natl Acad Sci.USA., Nov 21;97(24):13336-41.
12. Tsuprun V., Santi P. (2000). Helical structure of hair cell stereocilia tip links in the chinchilla cochlea. J Assoc Res Otolaryngol., Nov;1(3):224-31.
13. Söllner C., Rauch J., Siemens J., Geisler R., Schuster C., Müller U., Nicolson T. (2004). Mutations in cadherin 23 affect tip links in zebrafish sensory hair cells. Tübingen 2000 Screen Consortium; Nature. 29;428(6986):955-9.
14. Ahmed M., Goodyear R., Riazuddin S., Lagziel A., Legan K., Behra M., Burgess M., Lilley S., Wilcox R., Riazuddin S., Griffith J., Frolenkov I., Belyantseva A., Richardson P., Friedman B. (2006). The tip-link antigen, a protein associated with the transduction complex of sensory hair cells, is protocadherin-15. J Neurosci., Jun 28;26(26):7022-34.
15. Kazmierczak P., Sakaguchi H., Tokita J., Wilson-Kubalek M., Milligan A., Müller U., Kachar B. (2007). Cadherin 23 and protocadherin 15 interact to form tip link filaments in sensory hair cells. Nature, Sep 6;449(7158):87-91.
16. Sotomayor M., Corey P., Schulten K. (2005). In search of the hair-cell gating spring elastic properties of ankyrin and cadherin repeats. Structure, Apr;13(4):669-82.
17. Sotomayor M., Weihofen A., Gaudet R., Corey P. (2010). Structural determinants of cadherin-23 function in hearing and deafness. Neuron, Apr 15;66(1):85-100.
18. Elledge M., Kazmierczak P., Clark P., Joseph S., Kolatkar A., Kuhn P., Müller U. (2010). Structure of the N terminus of cadherin 23 reveals a new adhesion mechanism for a subset of cadherin superfamily members. Proc Natl Acad Sci USA, Jun 8;107(23):10708-12.
19. Mburu P., Kikkawa Y., Townsend S., Romero R., Yonekawa H., Brown SD. (2006). Whirlin complexes with p55 at the stereocilia tip during hair cell development. Proc Natl Acad Sci USA, Jul 18;103(29):10973-8.
20. Karavitaki D., Corey P. (2010). Sliding adhesio n confers coherent motion to hair cell stereocilia and parallel gating to transduction channels. J Neurosci., Jul 7;30(27):9051-63.
21. Takumida M., Wersäll J., Bagger-Sjöbäck D. (1988). Stereociliary glycocalyx and interconnections in the guinea pig vestibular organs. Acta Otolaryngol, Jul-Aug;106(1-2):130-9.
22. Andrei S., Kozlov J., Baumgart T., Risler C., Versteegh., Hudspeth A. (2011). Forces between clustered stereocilia minimize friction in the ear on a subnanometre scale. Nature, May 22;474(7351):376-9.
23. Goodyear RJ., Jones SM., Sharifi L., Forge A., Richardson GP. (2012). Hair bundle defects mand loss of function in the vestibular end organs of mice lackingthereceptor-like inositol lipid phosphatase PTPRQ. J Neurosci., Feb 22;32(8):2762-72.
24. McGee J., Goodyear J., McMillan R., Stauffer A., Holt R., Locke G., Birch G., Legan K., White C., Walsh J., Richardson P. (2006). The very largeprotein-coupled receptor VLGR1: a component of the ankle link complex required forthe normal development of auditory hair bundles. J Neurosci., June 14;26(24):6543-6553.
25. Verpy E., Masmoudi S., Zwaenepoel I., Leibovici M., Hutchin TP., Del Castillo I., Nouaille S., Blanchard S., Lainé S., Popot JL., Moreno F., Mueller RF., Petit C. (2001). Mutations in a new gene encoding a protein of the hair bundle cause non-syndromic deafness at the DFNB16 locus. Nat Genet., Nov;29(3):345-9.
26. Sagong B., Baek JI., Bok J., Lee KY., Kim UK. (2016). Identification of a nonsense mutation in the STRC gene in a Korean family with moderate hearing loss. Int J Pediatr Otorhinolaryngol, Jan;80:78-81.
27. Plevova P., Paprskarova M., Tvrda P., Turska P., Slavkovsky R., Mrazkova E. (2017). STRC Deletion is a Frequent Cause of Slight to Moderate Congenital Hearing Impairment in the Czech Republic. Otol Neurotol. Dec;38(10):e393-e400.

28. Vona B., Hofrichter MA., Neuner C., Schröder J., Gehrig A., Hennermann JB., Kraus F., Shehata-Dieler W., Klopocki E., Nanda I., Haaf T. (2014-15). DFNB16 is a frequent cause of congenital hearing impairment: implementation of STRC mutation analysis in routine diagnostics. Clin Genet. Jan 21; 87(1):49-55.
29. Jovine L., Park J., Wassarman PM. (2002). Sequence similarity between stereocilin and otoancorin points to a unified mechanism for mechanotransduction in the mammalian inner ear. BMC Cell Biol., Nov 25;3:28.
30. Frykholm C., Klar J., Tomanovic T., Ameur A., Dahl N. (2018). Stereocilin gene variants associated with episodic vertigo: expansion of the DFNB16 phenotype. Eur J Hum Genet., Dec;26(12):1871-1874.
31. Francey LJ., Conlin LK., Kadesch HE., Clark D., Berrodin D., Sun Y., Glessner J., Hakonarson H., Jalas C., Landau C., Spinner NB., Kenna M., Sagi M., Rehm HL., Krantz ID. (2012). Genome-wide SNP genotyping identifies the Stereocilin(STRC) gene as a major contributor to pediatric bilateral sensorineural hearing impairment. Am J MedGenet A., Feb;158A(2):298-308.
32. Verpy E., Weil D., Leibovici M., Goodyear RJ., Hamard G., Houdon C., Lefèvre GM., Hardelin JP., Richardson GP., Avan P., Petit C. (2008). Stereocilin-deficient mice reveal the origin of cochlear waveform distortions. Nature, Nov 13;456(7219):255-8.
33. Verpy E., Leibovici M., Michalski N., Goodyear RJ., Houdon C., Weil D., Richardson GP., Petit C. (2011). Stereocilin connects outer hair cell stereocilia to one another and to the tectorial membrane. J Comp Neurol., Feb 1;519(2):194-210.

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