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REVIEW ARTICLE **OPEN ACCESS**

Upper tip-link density Intermicrovillar protein: a linkage of stereocilia in hearing

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ABSTRACT
Noise in any form is a preventable cause of hearing loss in societies causing an inner ear structural damage, which involve in detection of sound through deflection of mechanosesnsory stereocilia. Stereocilia consists of large set of proteins involved in transduction of signals to sensory hair cells. The stereociliary scaffolding protein, harmonin, SANS and myosin7a, a tripartite complex play a key role in transduction of sound signals with protein-protein interactions that activate the large complexes responsible for hearing. From this tripartite complex, a Harmonin bridges cadherin 23 to cytoskeletal actin core of the stereocilium which is essential for the developmental differentiation of stereocilia. Harmonin is also associated with the tip link proteins for intermolecular association of stereociliary actin filaments for transduction of sound. Defects in this protein cause prelingual and moderate-to-severe degree of hearing loss. Our cram is mainly focusing on the mechanisum of the harmonin in hearing to gear up identification of disease in early stages.
Keywords: *Cytoskeletal actin, Harmonin, Myosin7a, Prelingual deafness, SANS, Stereocilia, Tripartite complex, USH1C*

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INTRODUCTION

Unwanted sound (Noise) is created during daily routine and environmental activity; it causes detrimental health hazards to human being. High levels of noise remain a problem in all regions of the world. Noise greater than 85dB were experience during gunfire, explosive, machinery, power tools, jet engine, musical instruments, aviation, heavy traffic which may cause Noise Induced Hearing Loss (NIHL) [1]. Continuous and intense noise exposure may change inner ear structure that leads to NIHL. It becomes more complex while dealing with work environment due to its intensity, exposure time, and other risk factors.

According to World Health Organization (WHO), 278 million people have reported for disability of hearing impairment (2005). United States of America stated that, about 30 million workers were exposed to hazardous noise (NIOSH, 1998). In Germany, 4-5 million people (12–15% of the workforce) were exposed to high noise levels (WHO, 2001). Deafness in Southeast Asia ranges from 4.6% to 8.8% and in India, 63 million people (6.3%) suffer from significant auditory loss) [2]. Accordingly, Occupational safety health Administration (OSHA), National Institute of Occupational safety and health (NIOSH) have given permissible exposure limit (PEL) for an 8 hour/day is 85dB and 90 dB respectively for all workers. The conditions are improved in developed countries with the introduction of protective measures) [3]..The average noise level data suggested that developing countries are scarce due to industrialization which is not always accompanied by protection) [4]. Regular exposures to noisy sounds for prolonged period possess a serious risk of irreversible hearing loss) [5]..

Sound induced vibration travel to outer, middle and inner ear and bombarded at tympanic membrane. It connects with chain of three tiny bones namely malleus, incus, and stapes that amplify and transmit a sound wave to inner ear. Cochlea is the part of the inner ear. It consists of scala media, suspended from osseous spiral lamina within the bony labyrinth scala media. The bony labyrinth divided into two fluid filled compartment, the apical scala vestibule and basal scala tympani. The scala media contain organ of corti which is responsible for transmitting sound impulses to the fibers of cochlear nerves. Scala media is an endolymph filled cavity inside the cochlea, located in between the tympanic duct and the vestibular

duct, separated by the basilar membrane and Reissner's membrane (the vestibular membrane) respectively. The basilar membrane supports the sensory structure of the organ of corti. It encloses sensory cell, support cell and gelatinous tectorial membrane. The apical surface of hair cell and their support cell form a regular tightly joined planar mosaic and form reticular lamina. The boundary between endolymph and perilymph are formed by reticular lamina in which stiff junctions prevent mixing of the two fluids. The stereocilia are in endolymph, however the hair cell bodies are in perilymph. During transduction Potassium ions flowing through the hair cells are recycled back to the scala media via the supporting cells and the stria vascularis) [6].. The inner hair cells are closer to modulus line up into single continuous row are able for mechanotransduction, the transformation of mechanical force into an electrical signal, which is the basic principle of hearing) [7].. Three to five rows of the outer hair cells of stereocilia are located at the apex region of basilar membrane. Outer hair cells of stereocilia are arranged in V or W pattern, with the wide part of the "W" facing the tunnel of Corti. The sensory hair cell of the auditory organ alters sound energy i.e. mechanical energy into electrical impulses through Mechanoelectrical-transduction (MET) channels) [8]..The mechanosensitive ion channels involved in this process are located at the tip of the stereocilia are linked by tip-link, connect the top of a lower Stereocilia, where the MET channel is localized, to the side of an adjacent upper one; and are thought to contribute to resting tension and regulate adaptation) [9]. This review is focused on the molecular mechanism of cytoskeletal binding of upper and lower tip link density proteins with an intermicrovillar connection necessary for hearing acuity.

Tiplinks

Tip link are four-stranded link that couple with the tip of one stereocilium to the adjacent taller stereocilium of cell to cell adhesion complex. The recent studies were shown that in mature hair cell, tips links initially interact with CDH23 and PCDH15) [10]. which is composed of Protocadherin 15 (PCDH15) dimers matures into a heterodimer of PCDH15 and Cadherin 23 (CDH23) homodimers localized to the lower and upper tip link density to adjacent stereocilia respectively) [11]. Where each tip link is a symmetric protein complex containing CDH23 to connect the upper part of stereocilia and PCDH15 connect to lower part of stereocilia) [10]. The tip links ends are anchored at electron-dense plaques on the membranes of stereocilia referred as the upper tip-link density (UTLD) and the lower tip-link density (LTLD) proteins. Tip links play important role in hearing transduction, since they are coupled with mechanoelectrical-transduction (MET) channels [12-14]. Sound induced deflection of stereocilia which can cause tension to tip links can open the mechanoelectric channels) [8] as depicted in the figure 1.

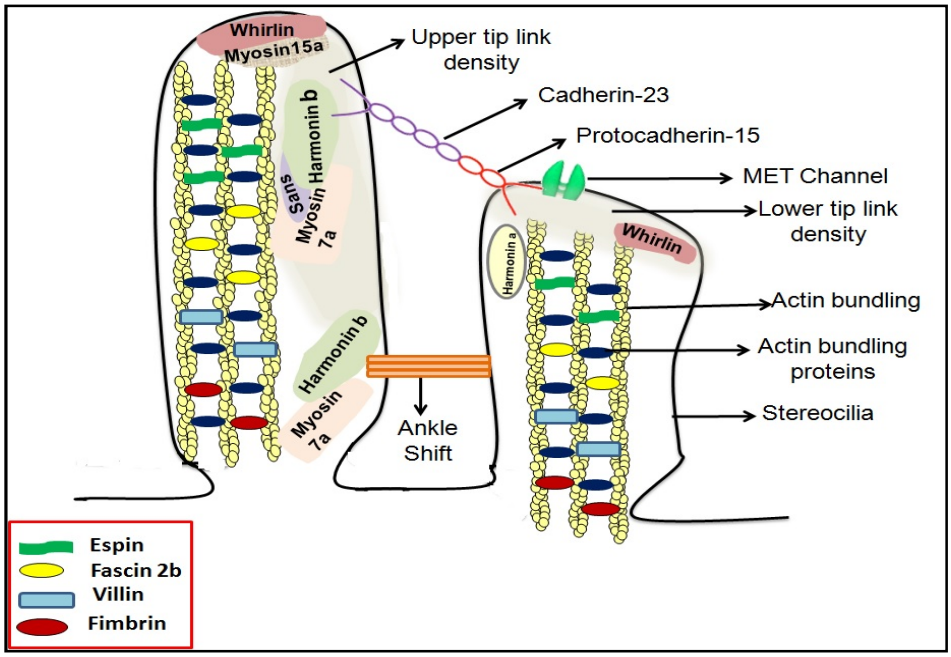

Figure 1: In this diagram it shows the connectivity between the two stereocilia in which tiplinks (cadherin 23 and protocatherin 15) are coupled together with tripartite complex i.e. Harmonin, SANS and Myosin7a in stereocilia connected with actin bundles for communication of signal transduction from upper tip link density (UTLD) to lower tiplink density (LTLD). The actin bundles which are essential component of stereociliary length required necessary proteins like Espin, Fasin, Vilin and fimbrin for proper functioning of hearing acuity.

Pickles *et al* studied the lower and upper density termination points by TEM showing variety of proteins present at lower end of the tip link having whirlin, a submembranous molecular complex protein, controls and coordinates polymerization of actin in stereocilia of hair cells) [15]. Whirlin deficient mouse studied by Mburu *et al* and Holme *et al* showed whirling behavior with deafness gene DFNB31) [16]. The actin binding, inhibitory proteins of actin polymerization are Myosin XVa, myosin VIIa, twinfilin and an actin regulating protein, EPS8 are also present at lower patch of tip link [17,18]. The upper density patch is enriched with scaffold protein with ankyrin repeats (ANKS4B), are SANS, along with myosin 1c, myosin 7a, [19,20]. and harmonin-b, which found during early development of the hair cell. These UTLD and LTLD are also rich with calmodulin, a multifunctional intermediate calcium-binding and unbinding messenger protein [20]. Stereocilia is anchored to actin through interaction of their cytoplasmic domains with tripartite complexes of harmonin, SANS and Myosin7a [19].

Among these tripartite molecules, primarily harmonin plays important role in maintaining harmony of the hair cells which is key molecule in establishing a relation of two adjacent stereocilia by linkages of tip link. Harmonin is concentrated at UTLDs where CDH23 molecules inserted into the stereociliary membrane. Harmonin is encoded by USH1C gene in human. It also plays a critical role in the development and maintenance of cochlear hair cells. It has three isoforms i.e. harmonin-a, b & c. Harmonin c is shorter than a and b [21]. The position of the harnmonin c is not clear till date in literature. Harmonin a is present at the lower stereocilia as depicted in figure 2a. [22].

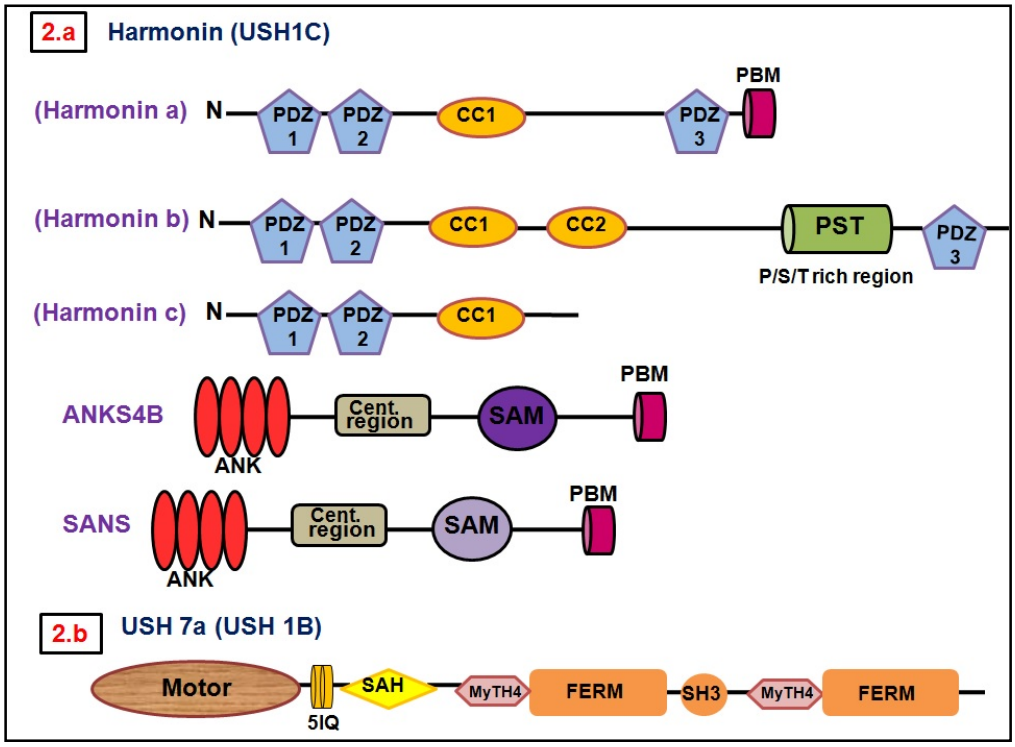

Figure:2 The given diagram shows the Harmonin isoforms structure in detail (Harmonin a, Harmonin b, Harmonin c,) longest isoform is grouped in harmonin-b which contains three PDZ domains along with one additional coiled coil regions (CC1,CC2) compared to harmonin a and c. Structurally harmonin-b encloses three PDZ domain i.e. (postsynaptic density protein, Drosophila dice large tumor suppressor, Zonnula occlundend-1protein) two coiled-coil (CC1,CC2) and one PST domains (a domain rich in proline, serine and threonine). USH 7a is showing two FERM domain with SAH and SH_3(2a, 2b)

A **coiled coil** proteins_is a motif_ having alpha-helices are coiled together like strands involved in important biological functions of regulation of gene expression. One of the coiled coil protein is a Tropomyosin, that binds to seven consecutive actin subunits along with the pitch helix of actin filaments. Once tropomyosin bound with actin core, they start polymerization at end-to-end and constantly stabilizes F-actin and regulates various acting-binding proteins including myosin which is the member of cargo transporting class-7-15 which are frequently found at sensory hair cells of stereocilia. [23,24].

SANS is another supportive putative scaffolding protein which encodes a gene USH1G. SANS, which binds to harmonin and myosin-7a in vitro , and possibly to the intracellular domains of cadherin-23 and protocadherin-15, is located at the lower tip-link insertion point in the developing hair bundle and at the

upper tip-link insertion point in the mature hair bundle. It contains a series of four ankyrin repeats and a sterile α-motif (SAM) domain, with an intervening 95-aa central region (CENT) and a C-terminal PDZ domain-binding consensus motif [25]. depicted in figure 2a. Boëda B, *et al*. and Bahloul A, *et al* suggested that USH1 protein cooperates in hair bundle development and predicted that harmonin-b anchors to the stereocilial actin filament by transient fibrous lateral links in which myosin 7a creates tension on these links, but the role of SANS is still unknown. SANS is directly interacts in vitro with both the myosin 7a tail and harmonin, hence SANS is not been detected within the hair bundle.

The third motor protein molecule of the tripartate assembly is Myosin7a, maintains the necessary mechanical tension across the cadherin links for the cytoskeletal attachment of the tip links along with regulation of stereociliary growth. Mutations in the genes of MYO7A responsible for intracellular movement, elongation of stereocilia, along with defects in hair bundle morphology. Prosser *et al* have confirmed the importance of myosin in regulation of the F-actin rearward flow which increases the actin treadmilling, from this it is being opined that MYO7A may be help in regulation of proteins for restriction of actin formation.**Error! Bookmark not defined.** According to Batiste Boeda *et al,* harmonin-b interacts directly with myosin 7a, which is absent from the disorganized hair bundles of myosin7a mutant mice, suggesting that myosin 7a conveys messages to harmonin-b along with the actin core of the developing stereocilia also it was proposed that the shaping of the hair bundle relies on a functional unit composed of myosin 7a, harmonin-b, and cadherin 23 that is essential to ensure the cohesion of the stereocilia depicted in figure 3.

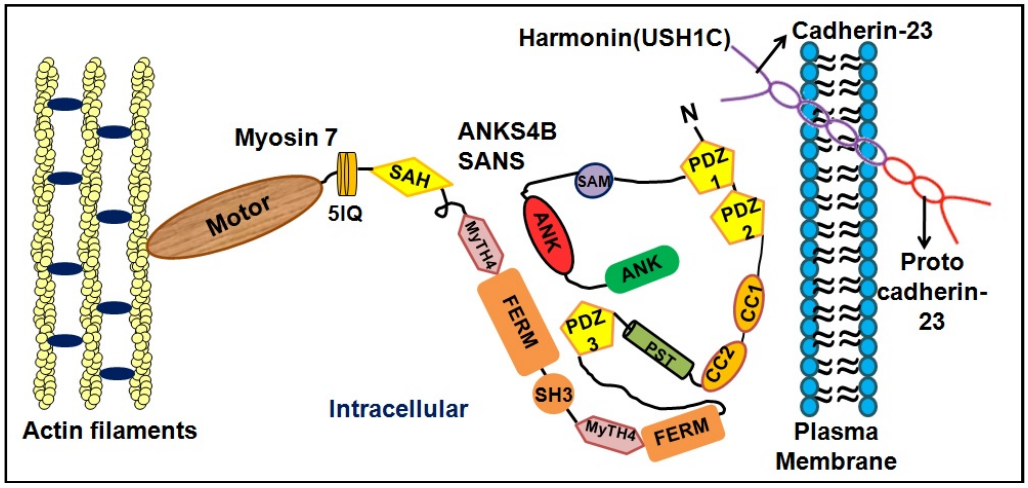

Figure 3: The above diagram shows detail mechanism of the Harmonin to the actin fiament and plasma membrane. The adherence in between the tripartite complex Harmonin, SANS and Myosin7a the stereocilia and the plasma membrane associated tip links (cadherin 23 and protocatherin 15). The tip link cadherin 23 holds the N-terminal PDZ domain and on the other hand the motar protein Myosin7a hold by the actin filaments, the proper holding or arrangement of the proteins in this junction is very crucial for transduction of sound signals with protein-protein interactions which activates the large complex of proteins.

Harmonin is very importantly playing its central role in maintaining the transduction of signals with specific protein-protein interactions that activate the assembly of large protein complexes. Not astonishingly, disrupting of these interactions may play a role in human diseases. Mutations in USH1C gene of harmonin, protein in PDZ domain, are responsible for Usher syndrome type 1C, an autosomal recessive disorder distinguished by congenital sensorineural deafness, vestibular dysfunction and delayed onset retinitis pigmentosa (RP) eventually leading to blindness. Study of the gene liable for Usher syndrome has been especially informative for our understanding of hair bundle development. There are five USH1 genes that codify known products: myosin VIIA (MYO7A), the two cell-cell adhesion cadherin proteins cadherin-23 (CDH23) and protocadherin-15 (PCDH15), and the scaffold proteins harmonin (USH1C) and SANS (USH1G). [26].

Usher syndrome (USH) is divided into three types. Usher type I (USH1) is the most severe form and is characterized by severe to profound congenital deafness, vestibular areflexia, and prepubertal onset of progressive RP. Type II (USH2) displays moderate to severe hearing loss, absence of vestibular dysfunction, and later onset of retinal degeneration. Type III (USH3) shows progressive postlingual hearing loss, variable onset of RP, and variable vestibular response. From this review it is firm that networking of harmonin with PDZ-domain, SANS, and motor protein myosin has vital role in interactions

of inter stereocilia, which maintains the structural integrity of supramolecular signaling uptake for disease free human kind.

Table 1: Detailed information about the harmonin and related proteins with different study model

	First author	Title of Paper	Tested model	Study design	Conclusion
1	B.Boëda *et al.*[27]	Myosin VIIa, harmonin and cadherin 23, three Usher I gene products that cooperate to shape the sensory hair cell bundle	mouse and rat	Mouse and rat model were used to study harmonin which directly interacts with cadherin 23. Further, two polyclonal antibodies directed against the harmonin PST domain were generated to find this interaction. Mouse vestibule, harmonin b was investigated from E13 and restricted to the emerging stereocilia of the hair cells. Harmonin b induces a resistance of actin filament to latrunculin A and cytochalasin D were studied in vitro model. Later, Harmonin b was co-localizes with hEcad±cad23 in co-transfected HeLa cells.	The shaping of the hair bundle relies on a functional unit composed of myosin VIIa, harmonin b and cadherin 23 that is essential to ensure the cohesion of the stereocilia.
2	Jan Reiners *et al,* [28]	Scaffold protein harmonin (USH1C) provides molecular links between Usher syndrome type 1 and type 2	Mice or Wistar rats	In vitro and in vivo models were used to test possible interactions between the USH2 proteins and NBC3 and harmonin. Further, glutathione S-transferase (GST), USH2 proteins and NBC3 were investigated to bind with harmonin isoform a1. His-tagged harmonin was pulled down from three GST-fused cytoplasmic tail fragments of USH2A, VLGR1b and NBC3 to confirm these interactions in vivo model. USH2A isoform b, VLGR1b and NBC3 consistently co-immunoprecipitated with harmonin a1 were determined by immunoprecipitation(IP) assays. Finally results were further verified in yeast two-hybrid interaction assays.	Molecular linkage were identified between the pathophysiology in USH1 and USH2 in a mutual 'interactome' related to the common phenotype in USH.

3	Grillet N *et al* [29]	Harmonin Mutations Cause Mechanotransduction Defects in Cochlear Hair Cells	Mice	To determine the subcellular distribution of harmonin in hair cells, antibody (H3) raise against the PDZ3 domain of Harmonin and Hair Cells which is present in harmonin-a and -b splice variants. Harmonin-PDZ2AAA/AAA Mice Are Deaf and Show Defects in Hair Bundle Morphology were studied. Further, dfcr Mice Are Deaf but Show No Defects in Hair Bundle Morphology was also investigated. Hair Bundles in the Cochlea of dfcr Mice Lack UTLDs but Contain Tip Links, analysis of Mechanotransduction currents in OHCs from dfcr Mice and adaptation in OHCs from dfcr Mice were also analyzed.	Harmonin is a UTLD component and contributes to establishing the sensitivity of Mechanotransduction channels to displacement.
4	Yu IM, Planelles-Herrero *et al* [30]	Myosin 7 and its adaptors link cadherins to actin	human Myo7a and Myo7b genes	The harmonin-a PDZ3c/Myo7b MF2 interaction was determined by crystal structures of Myo7b MF2 and of PDZ3c/Myo7b MF2 complex at 2.44 and 1.88 Å resolution analysis.	Myo7/harmonin-a/SANS:ANKS4B tripartite complexes that link cadherins to the actin-rich core in stereocilia and microvilli.
5	Crawley SW *et al* [31]	ANKS4B is essential for intermicrovillar adhesion complex formation	CACO-2BBE, COS7, and HEK293FT cells	ANKS4B targets to the BB using the ANKR domain. Localization of endogenous ANKS4B in intestinal and kidney tissue sections from USH1C knockout (KO) mice were studied. ANKS4B, USH1C and MYO7B could form a stable tripartite complex were investigated in vitro model. ANKS4B interacts with multiple IMAC components was also determined.	It was revealed ankyrin repeat and sterile α motif domain containing 4B (ANKS4B) localizes to the tips of adherent brush border microvilli and is essential for intermicrovillar adhesion.
6	Yan J *et al* [32]	The structure of the harmonin/sans complex reveals an unexpected interaction mode	coding sequence of harmonin NPDZ1	In this study, harmonin N-terminal domain and PDZ1 form a structural and functional supramodule that	The synergistic PDZ1/SAM and PDZ1/carboxyl PDZ binding-motif interactions, between harmonin and Sans, lock the two scaffold proteins into a highly stable complex. Mutations in

		of the two Usher syndrome proteins		binds to Sans with high affinity were determined. Mutations of harmonin and Sans in USH1 patients was disrupt the formation of the harmonin/Sans complex was helpful in determining the impact of USH1C and USH1G mutations in USH1 patients.	harmonin and Sans was found in USH1 patients are shown to destabilize the complex formation of the two proteins.
7	Johnston AM *et al* [33]	Harp (harmonin-interacting, ankyrin repeat-containing protein), a novel protein that interacts with harmonin in epithelial tissues	Adult mouse kidney MATCHMAKER library was transfer	PDZ domain of harmonin interacts with Harp using a yeast two-hybrid assay. This interaction was confirmed in mammalian cells which was mediated by the three C-terminal amino acids of harp. Harp is expressed in harmonin and co-localization of native harp and harmonin was demonstrated by confocal microscopy in pancreatic duct epithelium and in a pancreatic beta-cell line. Human harp maps to chromosome 16, and its mouse homologue to chromosome 7. GST fusion protein purification, bacterial expression constructs encoding GST, GST-PDZ1, GST-PDZ2 and GST-PDZ3 of harmonin were used to transform competent E. coli. immunoprecipitation of FLAG fusion proteins, cells was performed. A mouse multiple tissue Northern blot (Clontech) was probed with a 32P-labelled cDNA probe corresponding to full-length harp.	The functional domain structures of harp and harmonin, their interaction under native conditions and their co-localization suggest they constitute a scaffolding complex to facilitate signal transduction in epithelia.
8	Verpy E,Leibovici M *et al* [34]	A defect in harmonin, a PDZ domain-containing protein expressed in the inner ear sensory hair cells, underlies	Mouse	Identification of the *Ush1c* transcripts in the mouse inner ear. gene (*USH1C*), encoding a PDZ-domain–containing protein, harmonin, in a subtracted mouse	The detection of the 238-239insC mutation in 6 unrelated patients indicates that subtype C of USH1 is not rare and mutation may be the most frequent in USH1C.

		Usher syndrome type 1C		cDNA library derived from inner ear sensory areas. In patients we found a splice-site mutation, a frameshift mutation and the expansion of an intronic variable number of tandem repeat (VNTR) were identified in population of Acadian descendants from Louisiana and in a Lebanese family. It was also determined in the mouse inner ear, only the sensory hair cells express harmonin. Immunohistofluorescence analysis was performed using the purified MBP-D6 polyclonal antibody14 raised against the human AIE-75 protein. Performed nucleotide sequence analyses using the Genetics Computer Group Package	
9	Aparisi MJ *et al* [35]	Novel mutations in the USH1C gene in Usher syndrome patients	Human	To identify mutations of *USH1C* gene in the Spanish population were screened by direct sequence NM_153676.2 for exons 1–14 and 16–28, and with the consensus sequence NM_005709.2 for exon 15, using the BLAST program. . Further, computational analysis of splicing variants and missense variants were investigated computational analysis with the programs SIFT, PolyPhen, and Pmut to infer the pathologic effect of these variants	A non-sense mutation (p.C224X) and a frame-shift mutation (p.D124TfsX7) mutations in *USH1C* are responsible for 1.5% of USH1 disease in patients of Spanish.

CONCLUSION

High level of noise remains a problem in all regions of the world. As large set of proteins are responsible for hearing loss as suggested by scientists and estimating that, assembly of tripartite complex i.e harmonin, sans and myosin7a is important for maintaining the transduction signal of sensory hair cells with the protein-protein interactions and very crucial for hearing. The PDZ domain scaffolding protein harmonin which holds Sans and myosin7a if this anchoring is not properly done the complex is unable to performed the proper transduction mechanism, which is very important part of hearing acuity.

The other hypothetical insight of the review is on early diagnosis of mutational changes in the first trimester of the pregnancy along with early therapeutic gear up in developmental stages of the infant, which will be helpful for the early diagnosis of disease.

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