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Usher Syndrome: Genes, Proteins, Models, Molecular Mechanisms, and Therapies

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1. Introduction

Usher syndrome (USH) is an autosomal recessive genetic disease, characterized by both deafness and blindness. It was first described by Albrecht von Grafe, a German ophthalmologist, in 1858 (von Graefe, 1858) and then named after Charles Usher, a British ophthalmologist, who reported the inheritance of this disease on the basis of 69 cases in 1914 (Usher, 1914). USH is clinically heterogeneous and is categorized into three types, according to the severity of its hearing and vestibular symptoms (Smith et al., 1994; Petit, 2001). Type I (USH1) patients have congenital severe to profound deafness as well as vestibular dysfunction; Patients with USH2 exhibit congenital moderate degree of hearing loss and normal vestibular function; and those with USH3 display progressive hearing impairment and occasional vestibular dysfunction. The vision problem of all three types is manifested as retinitis pigmentosa (Hartong et al., 2006; Sadeghi et al., 2006; Fishman et al., 2007; Sandberg et al., 2008; Malm et al., 2011), showing early night and peripheral vision loss and eventual central vision loss.

USH is the most common genetic cause of combined blindness and deafness, occurring in about 1 in 23,000 people worldwide (Boughman et al., 1983; Keats and Corey, 1999; Hartong et al., 2006). It represents 50% of the blindness-deafness cases, 5% of all congenital deafness and 18% of retinitis pigmentosa (Millan et al., 2011). In Europe, USH1, USH2 and USH3 generally account for 25-44%, 56-75%, and 2% of all USH cases, respectively (Grondahl, 1987; Hope et al., 1997; Rosenberg et al., 1997; Spandau and Rohrschneider, 2002). Due to the regional founder effect, USH3 is much more common in Birmingham and Finland (Pakarinen et al., 1995; Hope et al., 1997). To date, there is no cure for this disease. USH patients mainly rely on early diagnosis and early education to adapt themselves to their dual sensory loss.

2. USH genes

USH is genetically diverse besides its clinical heterogeneity. Currently, eleven loci have been identified (Hereditary hearing loss homepage and Hmani-Aifa et al., 2009), and nine genes on these loci are known. Among these genes, five are involved in USH1, three in USH2 and one in USH3 (Reiners et al., 2006; Williams, 2008; Millan et al., 2011). Although the functions of some USH genes are relatively clear now in the inner ear (see section 6), extensive work is still necessary to elucidate the functions of USH genes in both the inner ear and the retina.

2.1 USH1 genes

In the past 20 years, seven loci have been assigned to USH1. They are *USH1B-H*. *USH1A* was first localized on 14a32.1 from a study in nine USH1 families in the Poitou-Charentes region of France, and was recently withdrawn due to the discovery that most of these families in fact carry mutations on the *USH1B* locus (Gerber et al., 2006). The genes underlying *USH1B*, *USH1C*, *USH1D*, *USH1F*, and *USH1G* have been identified as *MYO7A* (myosin VIIa) (Weil et al., 1995), *USH1C* (harmonin) (Bitner-Glindzicz et al., 2000; Verpy et al., 2000), *CDH23* (cadherin 23) (Bolz et al., 2001; Bork et al., 2001), *PCDH15* (protocadherin 15) (Ahmed et al., 2001; Alagramam et al., 2001b), and *USH1G* (SANS) (Weil et al., 2003), respectively. Among them, *MYO7A*, *USH1C*, *CDH23* and *PCDH15* are also the causative genes for nonsyndromic deafness, *DFNB2*/*DFNA11* (Liu et al., 1997; Weil et al., 1997), *DFNB18* (Ahmed et al., 2002), *DFNB12* (Bork et al., 2001), and *DFNB23* (Ahmed et al., 2003), respectively. The *USH1E* and *USH1H* loci were mapped to chromosome 21q21 and 15q22-23 (Chaib et al., 1997; Ahmed et al., 2009). However, the genes at these loci have not yet been pinpointed.

MYO7A is the most prevalent gene causing USH1 (Astuto et al., 2000). It encodes an unconventional actin-based motor protein with the conserved motor domain and five IQ motifs (Figure 1A). These domains are responsible for binding to actin, ATP, and myosin light chain. Therefore, MYO7A may move its cargos along the actin filaments using the energy generated from the hydrolysis of ATP. However, the motor domain of MYO7A shows a strong affinity to ADP and, thus, stays bound to actin filament for a long time (Heissler and Manstein, 2011). In this case, MYO7A may be involved in generating tensions between two proteins or cellular structures. The tail of MYO7A has a series of protein-protein interaction domains, including a single α-helix (SAH), a coiled-coil domain (CC), two myosin tail homology 4 domains (MyTH4), two band 4.1, ezrin, radixin, moesin domains (FERM), and a src homology 3 domain (SH3) (Figure 1A). These domains are thought to be engaged in binding to cargos and/or anchoring to proteins.

Harmonin (also known as AIE-75 or PDZ-73) is expressed in many different tissues (Kobayashi et al., 1999; Scanlan et al., 1999). Nine transcripts have so far been discovered (Verpy et al., 2000; Reiners et al., 2003). They are categorized into three groups, isoforms a, b and c (Figure 1B). All these isoforms have multiple PDZ (postsynaptic density 95; discs large; zonula occludens-1) domains and at least one CC domain. The CC domain is reported to participate in harmonin dimerization (Adato et al., 2005b), and the PDZ domain is well known to interact with PDZ-binding motifs (PBMs) in other proteins (Sheng and Sala, 2001). Isoform b specifically has a proline, serine and threonine-rich (PST) domain. This domain has been demonstrated to bind and bundle actin filaments (Boeda et al., 2002). In summary, harmonin may organize a multi-protein complex and attach this complex to actin filaments.

CDH23 and PCDH15 both have multiple transcripts and are grouped into isoforms a, b and c for CDH23 (Lagziel et al., 2005; Lagziel et al., 2009) and isoforms CD1, CD2, CD3 and SI for PCDH 15 (Ahmed et al., 2006) (Figures 1C and 1D). As the distant members of the classical cadherin superfamily, the proteins of these two genes have various repeats of extracellular cadherin (EC) domains in their extracellular regions. Accordingly, it has been proposed and supported by many studies in hair cells (see below) that the two proteins function in cell adhesion through their homophilic and heterophilic interactions. The two proteins probably anchor to the intracellular structures through the PBMs in their cytoplasmic regions (Figures 1C and 1D).

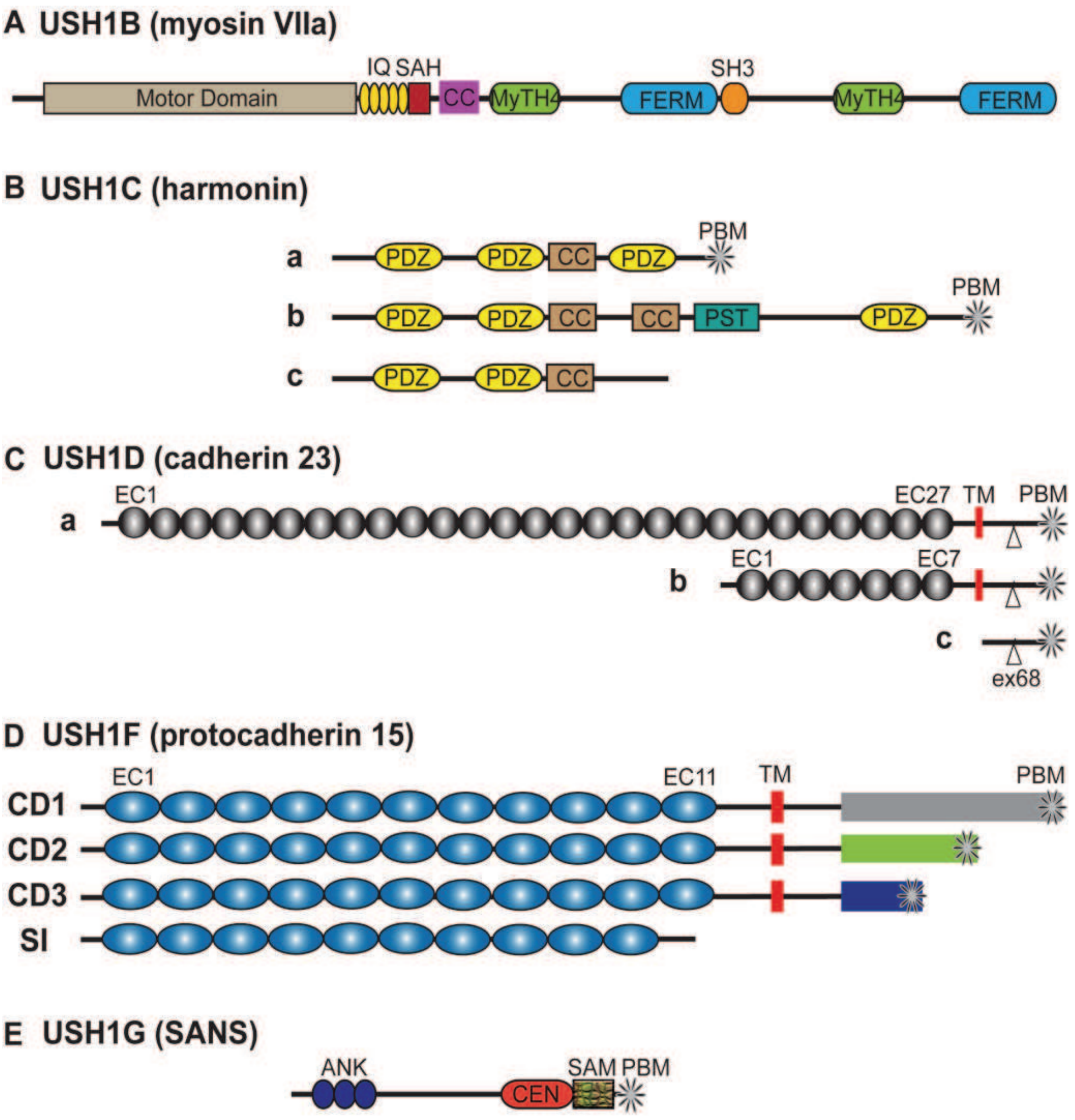

Fig. 1. Domain structures of USH1 proteins

Mutations in SANS are rare in USH1 patients. Some mutations, such as c.1373 A>T and c.163_164 + 13del15, cause the clinical symptoms close to USH2 (Kalay et al., 2005; Bashir et al., 2011). The protein of this gene consists of several putative protein-protein interaction domains, including three ankyrin –like (ANK) repeats, a central (CEN) domain, a sterile alpha motif (SAM) and a PBM (Figure 1E). Therefore, like harmonin, SANS is believed to be a putative scaffold protein.

2.2 USH2 genes

Four USH2 loci were originally defined, *USH2A-D*. The genes responsible for *USH2A*, *USH2C*, and *USH2D* are *USH2A* (usherin) (Eudy et al., 1998), *GPR98* (G Protein-coupled Receptor 98) (Weston et al., 2004), and *WHRN* (whirlin) (Ebermann et al., 2006), respectively. The gene for *USH2B* was once considered to be *NBC3* (sodium bicarbonate cotransporter)

(Bok et al., 2003). However, further study of the consanguineous Tunisian family carrying the *USH2B* locus demonstrates that mixed mutations in the *GPR98* and *PDE6B* genes are responsible for the disease manifestation in the family and, thus, the *USH2B* locus was withdrawn (Hmani-Aifa et al., 2009). Moreover, a novel USH2 locus has recently been localized on the chromosome 15q, though the underlying gene has not been identified so far (Ben Rebeh et al., 2008). ʻ

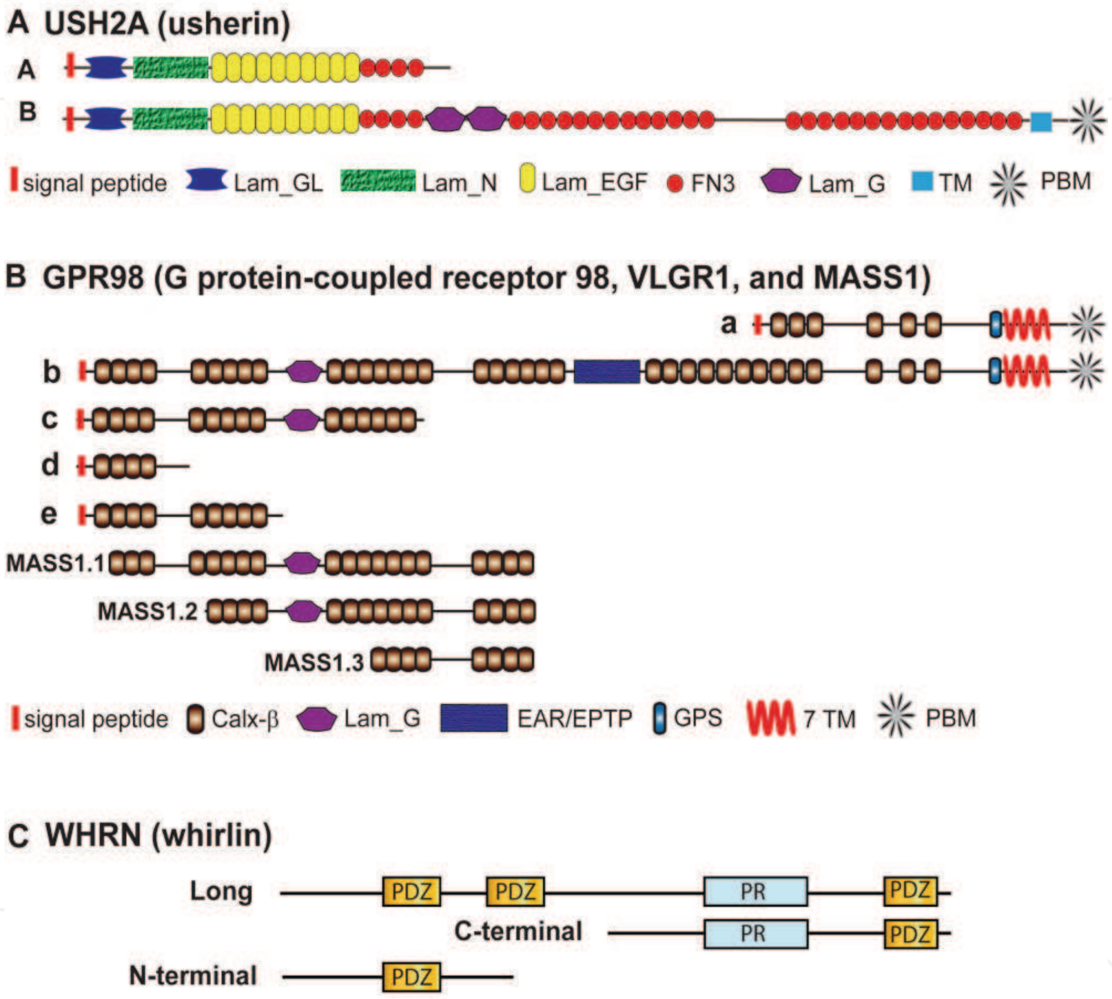

Fig. 2. Domain structures of USH2 proteins

USH2A is the most predominant causative gene in all USHs among different human ethnic populations (Eudy et al., 1998; Dreyer et al., 2000; Weston et al., 2000; Aller et al., 2004; van Wijk et al., 2004; Adato et al., 2005a; Hartong et al., 2006; Baux et al., 2007; Kaiserman et al., 2007; Dreyer et al., 2008; Nakanishi et al., 2009; Yan et al., 2009; McGee et al., 2010). Its mutations lead to a wide spectrum of vision and hearing defects in patients. Some *USH2A* mutations, such as p.C759F and p.G4674R, are known to cause only nonsyndromic retinitis pigmentosa (Rivolta et al., 2002; Seyedahmadi et al., 2004; Kaiserman et al., 2007). *USH2A* has 72 exons and is expressed as isoforms A and B (Figure 2A). Isoform B, the major isoform in the retina (Liu et al., 2007), is an extremely large transmembrane protein with 5202 amino acids (aa) in humans (van Wijk et al., 2004). Its long extracellular region has repeated various laminin (Lam) and fibronectin III (FN3) functional domains common in cell adhesion proteins and extracellular matrix proteins. Its cytoplasmic region has a PBM. Isoform A is an N-terminal 1546-aa fragment of isoform B. USH2A is thought to be involved in cell adhesion.

The *GPR98* gene, also known as *VLGR1* (Very Large G protein-coupled Receptor 1) and *MASS1* (Monogenic Audiogenic Seizure Susceptibility 1), exists only in the vertebrate (Gibert et al., 2005) and is one of the largest genes, with 90 exons (McMillan et al., 2002). Its mRNA is present mostly in the brain and spinal cord during development (McMillan et al., 2002; Weston et al., 2004), but it can also be found in many other tissues (Nikkila et al., 2000; Skradski et al., 2001; McMillan et al., 2002; Weston et al., 2004). *GPR98* expresses multiple mRNA transcripts, including isoforms a, b and c in humans and isoforms b, d, e and Mass1 in rodents (Figure 2B) (Nikkila et al., 2000; Skradski et al., 2001; McMillan et al., 2002; Yagi et al., 2005). Mutations in the longest isoform, isoform b, have been identified in patients with USH2C (Weston et al., 2004; Ebermann et al., 2009; Hilgert et al., 2009). Additionally, different mutations along the murine *Gpr98* gene share common phenotypes in vision and hearing (Skradski et al., 2001; McMillan and White, 2004; Johnson et al., 2005; Yagi et al., 2005; McGee et al., 2006; Michalski et al., 2007; Yagi et al., 2007). These findings suggest that isoform b is the major isoform in both the retina and the inner ear and is essential for vision and hearing. This isoform is 6306 aa long in humans. It has signature domains of family B of G protein-coupled receptors (GPCRs), i.e., a GPCR proteolytic site (GPS) and a 7-transmembrane domain (7TM). Therefore, GPR98 may function in signal transduction. GPR98 also has a PBM at its C-terminus. Along its long extracellular region, it has a laminin globular-like domain (LamG_L), an epilepsy associated repeat (EAR)/epitempin (EPTP) domain, and multiple tandem-arranged Calxβ domains. While the function of EAR/EPTP is unknown, LamG_L is a cell adhesion domain, and the Calxβ domain is able to bind to Ca^{2+} with low affinity in vitro (Nikkila et al., 2000; McMillan and White, 2011).

Mutations of whirlin cause either USH2D or nonsyndromic deafness, *DFNB31*. Interestingly, mutations at the N-terminal half of the gene, such as p.P246HfxX13 and compound heterozygosity of p.Q103X and c.837+1G>A, are manifested as USH2D (Ebermann et al., 2006; Audo et al., 2011), while mutations at the C-terminal half, such as p.R778X and c.2423delG, were found in patients with *DFNB31* (Mburu et al., 2003; Tlili et al., 2005). Whirlin has multiple mRNA transcripts in the inner ear and the retina (Mburu et al., 2003; Belyantseva et al., 2005; van Wijk et al., 2006; Yang et al., 2010), which can be conceptually translated into three groups of proteins, the long, N-terminal, and C-terminal isoforms (Figure 2C). The long isoform contains three PDZ domains and a proline-rich region (PR). Thus, whirlin is a homolog of harmonin. At the protein level, whirlin mainly expresses the long isoform in the retina and the long and C-terminal isoforms in the inner ear (Yang et al., 2010). Because both the PDZ domain and PR region are protein interaction modules, whirlin is believed to be implicated in the assembly of multi-protein complexes at specific subcellular locations, similar to harmonin.

2.3 USH3 and USH related genes

The only gene currently identified in USH3 is clarin-1 for the *USH3A* locus (Joensuu et al., 2001; Adato et al., 2002; Fields et al., 2002). Like other USH genes, clarin-1 has multiple transcript variants due to different splicings and usages of transcription start sites (Vastinsalo et al., 2010). The primary transcript encodes a protein with four predicted transmembrane domains and a C-terminal potential PBM (Figure 3). Clarin-1 shows a sequence homologous to stargazin, an auxiliary subunit of ion channels in the synapse (Osten and Stern-Bach, 2006; Tomita et al., 2007). Presently, several research groups are intensively focusing on understanding this gene (Aarnisalo et al., 2007; Geller et al., 2009; Geng et al., 2009; Tian et al., 2009; Zallocchi et al., 2009). However, the biological function and cellular expression of clarin-1 still remain elusive.

Fig. 3. Domain structure of USH3A

Recently, *PDZD7* was shown to be a modifier gene for the retinal symptom in USH2A patients and, together with *USH2A* or *GPR98*, to contribute to a digenic USH form (Ebermann et al., 2010). Interestingly, this newly identified USH modifier and contributor gene is also a homolog of harmonin. It has several isoforms (Schneider et al., 2009; Ebermann et al., 2010). The long isoform has three PDZ domains and one PR region. The two short isoforms are the N-terminal fragments of the long isoform with only two PDZ domains. However, the short isoforms have not been confirmed at the protein level. Similar to both harmonin and whirlin, different mutations in *PDZD7* are involved in either USH or nonsyndromic deafness. A homozygous reciprocal translocation, 46,XY,t(10;11)(q24;q23), was found to disrupt the *PDZD7* gene at intron 10, which causes nonsyndromic congenital hearing impairment (Schneider et al., 2009). A heterozygous p.R56PfsX mutation of *PDZD7* was found to exacerbate retinal degeneration in an USH2A patient, compared to her sibling carrying the same *USH2A* mutation. Additionally, the heterozygous mutations of *PDZD7*, c.1750-2A>G and p.C732LfsX, are present in USH patients with a heterozygous *USH2A* mutation, p.R1505SfsX, and with a heterozygous *GPR98* mutation, p.C732LfsX, respectively (Ebermann et al., 2010).

3. Animal models

Numerous spontaneous and transgenic USH animal models are now available. Table 1 lists the detailed information about the mouse models. The majority of these models show congenital hearing loss as expected. However, only a few of them, *Ush1c* knockin, *Ush2a* knockout, and whirlin knockout mice, manifest obvious widespread retinal degeneration. $Ush1c^{dfcr}$ mice on some specific genomic background and $Myo7a^{4626SB}$ and $Cdh23^{V}$ double mutant mice show only slight retinal degeneration (Johnson et al., 2003; Lillo et al., 2003; Williams et al., 2009). Among the rest of the USH mouse models, some *Myo7a, Cdh23, Pcdh15, and Grp98* mutant strains show abnormal electroretinogram (ERG) responses but no retinal degeneration (Libby and Steel, 2001; Libby et al., 2003; Haywood-Watson et al., 2006; McGee et al., 2006), indicating that the function of photoreceptors is compromised. The reasons for the discrepancy between USH patient symptoms and USH mutant mouse phenotypes are largely unclear. Many factors could contribute to this, such as the gene isoform composition, mutation type and position in the genes, genomic background, redundant protein compensation, photoreceptor structure and physiology, influence of non-genetic factors, sensitivity of diagnostic measures, etc. (El-Amraoui and Petit, 2005). Additionally, although retinitis pigmentosa in USH is characterized to have an onset before or during puberty (Smith et al., 1994; Petit, 2001), more and more atypical USH patients have been found (Edwards et al., 1998; Sadeghi et al., 2006; Cohen et al., 2007; Fishman et al., 2007; Sandberg et al., 2008; Malm et al, 2010.; Bashir et al., 2011). These patients have relatively late onset vision loss, which may explain the lack of retinal phenotype in most USH mutant mice, whose lifespan is only about two years.

Zebrafish models for several USH genes have also been reported, including mariner (*myo7a*), *ush1c*, sputnik (*cdh23*), and orbiter (*pcdh15*) (Phillips et al., 2011; Nicolson et al., 1998; Ernest et al., 2000; Sollner et al., 2004; Seiler et al., 2005). Defects in hearing, balance, and vision are manifested during the early life in two *ush1c* mutants. Interestingly, zebrafish has two orthologs of *PCDH15*. Disruption of one leads to the auditory and vestibular dysfunction, while disturbance of the other results in defects in the photoreceptor structure and retinal function. Mariner exhibits similar phenotypes to *Myo7a* mice in hearing, balance and vision. Sputnik has problems with the auditory and vestibular system, but its vision phenotype has not been reported. Currently, studies on other USH genes in zebrafish using the morpholino knockdown technique are being actively pursued (Ebermann et al., 2010). Moreover, a rat model with a point mutation leading to premature truncation of *Myo7a* was generated by N-ethyl-N-nitrosourea mutagenesis and named Tornado (Smits et al., 2005). In this model, hearing but not vision defects have been characterized. Therefore, exploration of USH genes in more vertebrate organisms will provide additional ways to understand the biological functions of these genes, in particular, in the retina.

Model name	Mutations	Phenotypes	References
USH1			
Myo7a			
Myo7a^{sh1}	p.R502P	Circling, head tossing, hearing impairment	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{6J}	p.R241P	Circling, head tossing, deafness	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{26SB}	p.F1762I	Circling, head tossing, deafness	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{816SB}	p.L646_Q655del	Circling, head tossing, deafness, reduced ERG	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{3336SB}	p.C2144X	Circling, head tossing, deafness	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{4494SB}	p.A246fs?X5	Circling, head tossing, deafness	(Mburu et al., 1997; Liu et al., 1999; Libby and Steel, 2001)
Myo7a^{4626SB}	p.Q720X	Circling, head tossing, deafness, reduced ERG	(Mburu et al., 1997; Libby and Steel, 2001)

Model name	Mutations	Phenotypes	References
Myo7a^{7J}	p.A1363AfsX27	Circling, head tossing, deafness, reduced ERG	(Mburu et al., 1997; Libby and Steel, 2001; Yang et al., 2011)
Myo7a^{Hdb}	p.I178F	Circling, head tossing, low-frequency hearing impairment	(Rhodes et al., 2004)
Myo7a^{8J}	Not known	Circling, head tossing, deafness, reduced ERG	(Mburu et al., 1997; Libby and Steel, 2001)
Myo7a^{9J}	Not known	Circling?, head tossing?, deafness?, reduced ERG	(Mburu et al., 1997; Libby and Steel, 2001)
Harmonin			
Ush1c knockout	Replacement of exons 1-4 with β-gal/neo cassette	Circling, head tossing, deafness	(Tian et al., 2010)
Ush1c^{dfcr}	A deletion involving exons 12-15, A-D	Circling, head tossing, deafness, slight retinal degeneration at 9 months of age	(Johnson et al., 2003)
Ush1c$^{dfcr\text{-}2J}$	One bp deletion in exon C	Circling, head tossing, deafness	(Johnson et al., 2003)
Ush1c$^{tm1.1Ugds}$	Exon 1 deletion	Circling, head tossing, deafness	(Lefevre et al., 2008)
Ush1c knockin	c.216G>A	Circling, head tossing, deafness, retinal degeneration	(Lentz et al., 2007; Lentz et al., 2010)
Ush1c-PDZ2^{AAA}	Replacement of GLG (221-223aa) in PDZ2 with AAA	Hair bundle defect	(Grillet et al., 2009)
Cdh23			
jera	p.V2360E	deafness	(Manji et al., 2011)
erlong	p.S70P	Circling, head tossing, deafness	(Han et al., 2010)
salsa	p.E737V	Circling, head tossing, deafness	(Schwander et al., 2009)
Cdh23^{V}	p.N279EfsX39	Circling, head tossing, deafness, reduced ERG responses	(Wilson et al., 2001; Libby et al., 2003)
Cdh23$^{V\text{-}J}$	p.E1169NfsX7	Circling, head tossing, deafness	(Wilson et al., 2001)
Cdh23$^{V\text{-}2J}$	c.4104 + 1G>A	Circling, head tossing, deafness, faster ERG responses	(Di Palma et al., 2001b; Libby et al., 2003)

Model name	Mutations	Phenotypes	References
$Cdh23^{V-3J}$	p.W1764X	Circling, head tossing, deafness	(Di Palma et al., 2001a)
$Cdh23^{V4J}$	p.N2718del3	Circling, head tossing, deafness	(Di Palma et al., 2001a)
$Cdh23^{V5J}$	p.R2935X	Circling, head tossing, deafness	(Di Palma et al., 2001a)
$Cdh23^{V-6J}$	p.E302X	Circling, head tossing, deafness	(Di Palma et al., 2001b)
$Cdh23^{V-7J}$	p.Y1197MfsX47	Circling, head tossing, deafness	(Di Palma et al., 2001a)
$Cdh23^{V-ngt}$	p.G49VfsX3	Circling, head tossing, deafness	(Wada et al., 2001)
$Cdh23^{V-Alb}$	c.1635C>Tdel119	Circling, head tossing, deafness, normal ERG responses	(Di Palma et al., 2001b; Libby et al., 2003)
$Cdh23^{Vbus}$	c.9633 + 1G>A	Circling, head tossing, deafness	(Yonezawa et al., 2006)
$Cdh23^{Ahl}$	c.753G>A	Susceptibility to age-related hearing loss	(Noben-Trauth et al., 2003)
Pcdh15			
$Pcdh15^{av-J}$	p.A645_K922del	Circling, head tossing, deafness, normal retinal function	(Alagramam et al., 2001a; Ball et al., 2003)
$Pcdh15^{av-2J}$	p.D31_N57del	Circling, head tossing, deafness, normal retinal function	(Alagramam et al., 2001a; Ball et al., 2003)
$Pcdh15^{av-3J}$	p.E1373RfsX36	Circling, head tossing, deafness, normal retinal function	(Alagramam et al., 2001a; Ball et al., 2003)
$Pcdh15^{av-5J}$	IVS14-2A>G	Circling, head tossing, deafness, reduced ERG responses	(Washington et al., 2005; Haywood-Watson et al., 2006)
$Pcdh15^{av-6J}$	p.G962_K1008del	Circling, head tossing, deafness	(Alagramam et al., 2011)
$Pcdh15^{av-Jfb}$	p.D701GfsX17	Circling, head tossing, deafness, reduced ERG responses	(Hampton et al., 2003; Haywood-Watson et al., 2006)
$Pcdh15^{av-TgN2742Rpw}$	A large insertion	Circling, head tossing, deafness, normal retinal function	(Alagramam et al., 2001a; Ball et al., 2003)
Sans			
$Ush1g^{js}$	p.E228RfsX8	Circling, head tossing, deafness	(Kikkawa et al., 2003)

Model name	Mutations	Phenotypes	References
Ush1g^{js-2J}	p.L81GfsX103	Circling, head tossing, deafness	*
Ush1g^{F1}	Exon 2 flanked with FRT sites	Hearing defects after deletion of exon 2	(Caberlotto et al., 2011)
USH2			
Ush2a			
Ush2a knockout	replacement of exon 5 with a neomycin^r cassette	hearing impairment, retinal degeneration	(Liu et al., 2007)
Gpr98			
Gpr98 knockout	replacement of exons 2-4 with a neomycin^r cassette	audiogenic seizure susceptibility, hearing impairment	(Yagi et al., 2005; Michalski et al., 2007)
Gpr98-EYFP knockin	replacement of exons 2-4 with a EYFP-neomycin^r cassette	defects in hair cell stereocilia	(Yagi et al., 2007)
Frings & BUB/BnJ	a G deletion at 6864 bp (NM_054053) causing a p.V2250X mutation	audiogenic seizure susceptibility, hearing impairment	(Skradski et al., 2001; Johnson et al., 2005)
Gpr98/del7TM	replacement of exon 82 with a HA-neomycin^r cassette	audiogenic seizure susceptibility, hearing impairment, mildly abnormal ERG responses	(McMillan and White, 2004; McGee et al., 2006)
Whrn			
Whrn knockout	partial replacement of exon 1 with a neomycin^r cassette	hearing impairment, retinal degeneration	(Yang et al., 2010)
whirler	a 592-bp deletion causing a p.H433fsX58 mutation	hearing impairment, no retinal degeneration	(Lane, 1963; Holme et al., 2002; Mburu et al., 2003; Yang et al., 2010)
USH3			
Ush3a			
Ush3a knockout	Disruption and deletion of promoter and exon 1	Circling, head tossing, deafness	(Geller et al., 2009)

MYO7A: NP_032689, CDH23: NP_075859, PCDH15: NP_075604, SANS: NP_789817
*: our unpublished data.

Table 1. USH mutant mouse models

4. Cellular localization of USH proteins

Defects in USH proteins result in Usher syndrome, nonsyndromic deafness, or retinitis pigmentosa, indicating that these proteins are essential in the inner ear and the retina. Therefore, extensive efforts have been put to investigate the cellular location of these proteins in these two tissues. The cellular localization of USH proteins in other tissues is relatively unclear, although some USH proteins are known to be present in the kidney, colon, brain, lung, olfactory neuron, ovary, oviduct, testes and intestine (el-Amraoui et al., 1996; Hasson et al., 1997; Wolfrum et al., 1998; Kobayashi et al., 1999; Scanlan et al., 1999; Bhattacharya et al., 2002; Pearsall et al., 2002).

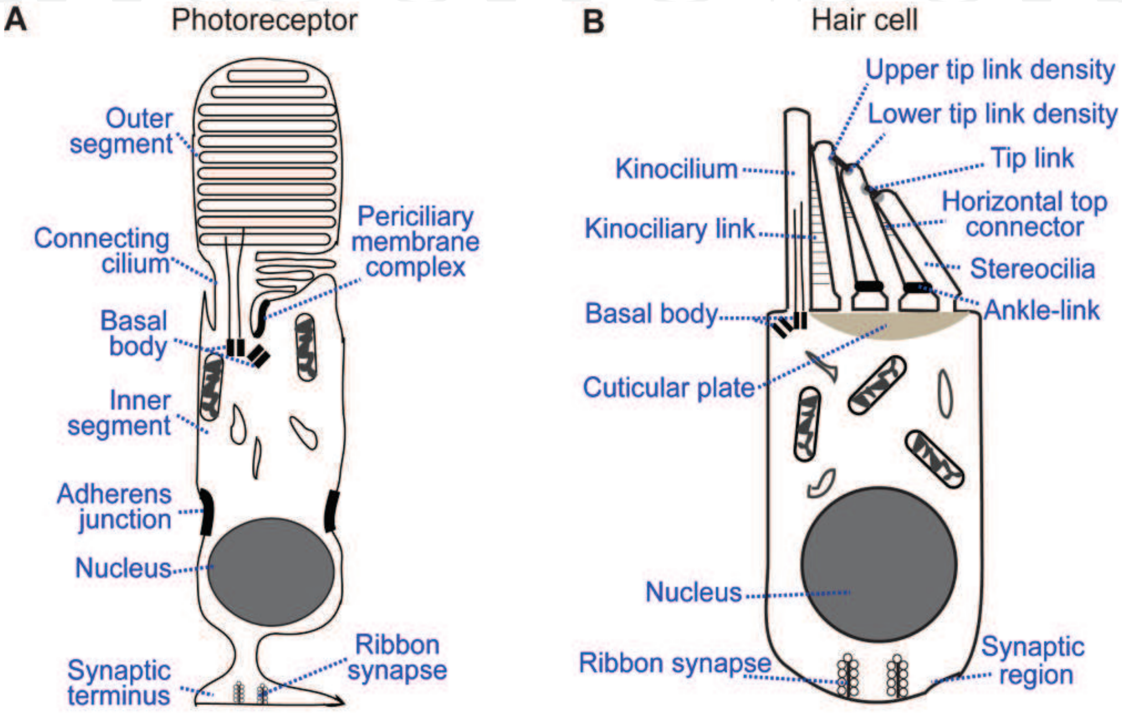

Fig. 4. Schematic diagrams of a rod photoreceptor and a hair cell

4.1 USH proteins in the inner ear

The inner ear is composed of the cochlea and vestibular system for hearing and balance, respectively. In the vestibular system, hair cells exist in the maculae of the saccule and utricle and the cristae ampullares of the semicircular canals. In the cochlea, one row of inner hair cells and three rows of outer hair cells exist in the organ of Corti. The inner hair cells are responsible for mechanoelectric transduction, whereas the electromotile outer hair cells also perform an electromechanical transduction, thereby amplifying the sound-evoked vibrations of the entire sensory epithelium (Leibovici et al., 2008). All types of hair cells have stereocilia on their apical surfaces, which are modified microvilli filled with bundles of actin filaments. The stereocilia are well-organized into rows of different lengths and form a staircase-like hair bundle (Figure 4). Along with the hair bundle, there exists a real cilium, called kinocilium, which is filled with microtubules. Various links have been discovered along the entire length of the stereocilia and the kinocilium during development and in adulthood (Goodyear and Richardson, 1999; Goodyear and Richardson, 2003; Goodyear et al., 2005).

The distribution of USH proteins in hair cells vary dramatically from the emergence of stereocilia to their maturation. All USH1 proteins are present either at the tip, the ankle links, the transient lateral links, or the kinociliary links of the stereocilia during the early stage of development. They are then restricted to the tip link and the accessory structures of the tip link, the upper (UTLD) and lower (LTLD) tip link densities, in mature hair cells (Figure 4) (Kussel-Andermann et al., 2000; Senften et al., 2006; Lefevre et al., 2008; Grillet et al., 2009; Bahloul et al., 2010; Caberlotto et al., 2011; Grati and Kachar, 2011). USH2 proteins are localized at the ankle links of the stereocilia (McGee et al., 2006; van Wijk et al., 2006; Michalski et al., 2007; Yang et al., 2010), which is a transient structure existing only during development (Goodyear et al., 2005). Whirlin is also present at the tip of stereocilia in the vestibular and cochlear hair cells all the time (Belyantseva et al., 2005; Delprat et al., 2005; Kikkawa et al., 2005). Clarin-1 was found at the stereocilia on postnatal day 0 (Zallocchi et al., 2009). Besides their location at the stereocilia, some USH proteins were found at the synaptic region of the outer and inner hair cells (Reiners et al., 2005b; van Wijk et al., 2006; Zallocchi et al., 2009), the cell body of the spinal ganglia (Alagramam et al., 2001b; Adato et al., 2002; van Wijk et al., 2006), the supporting cells (Alagramam et al., 2001b; Adato et al., 2005a; Adato et al., 2005b), various nervous fibers (van Wijk et al., 2006), and Reissner's membrane (Wilson et al., 2001; Lagziel et al., 2005). However, these distributions of USH proteins need to be further verified, because the specificity of antibodies used in the studies were not confirmed in their corresponding mutant mice.

4.2 USH proteins in the retina

In the retina, USH proteins are mainly localized in the photoreceptors (Kremer et al., 2006; Reiners et al., 2006; van Wijk et al., 2006; Liu et al., 2007; Maerker et al., 2008; Yang et al., 2010). The photoreceptor is a highly polarized sensory neuron converting light signals to electrical impulses. It consists of the outer segment, connecting cilium, inner segment, cell body, and synaptic terminus (Figure 4). It contacts Muller cells at the adherens junction (the outer limiting membrane in the retina). Its outer segment is immediately next to the retinal pigment epithelium (RPE) cells.

Compared with the studies in the inner ear, the cellular location of USH proteins is less well defined in the retina. All the USH proteins were once localized in the synaptic ends of photoreceptors (Reiners et al., 2005a; Reiners et al., 2005b; Maerker et al., 2008). However, these results are not conclusive (Williams, 2008; Saihan et al., 2009). They are not supported by the phenotypic analyses in USH mutant mice and the symptom manifestation in USH patients. For instance, ultrastructural abnormalities were not found at the synaptic terminus of photoreceptors in USH mice by electron microscopy (Self et al., 1998; Williams et al., 2009; Yang et al., 2010). No defective ERG waveforms typically resulting from abnormal photoreceptor synaptic transmission have been detected in USH mutant mice (Libby and Steel, 2001; Ball et al., 2003; Libby et al., 2003; Haywood-Watson et al., 2006; McGee et al., 2006; Liu et al., 2007; Yang et al., 2010) or in USH patients.

In addition to the synaptic distribution, MYO7A and SANS were shown to be present around the connecting cilium, harmonin at the outer segment, CDH23 in the inner segment, and PCDH15 at the base of the outer segment by one research group (Ahmed et al., 2003; Reiners et al., 2005a; Maerker et al., 2008). However, other research groups did not find harmonin in the outer segment (Williams et al., 2009), and MYO7A was demonstrated to be predominantly expressed in the RPE cells (Hasson et al., 1995; el-Amraoui et al., 1996; Lopes et al., 2011). USH2 proteins were initially localized to the inner segment, adherens junction, connecting cilium, basal bodies, and synaptic terminus in photoreceptors (Figure 4) (Kremer et al., 2006; Reiners et al., 2006; van Wijk et al., 2006; Maerker et al., 2008; Lagziel et al., 2009). With the antibodies whose specificities have been confirmed in their respective mutant mice, the three USH2 proteins were recently localized to the periciliary membrane complex (PMC) around the connecting cilium (Figure 4) (Liu et al., 2007; Yang et al., 2010; Yang et al., 2011; Zou et al., 2011). Finally, the distribution of clarin-1 in the retina is controversial. One report shows that it is present around the connecting cilium in photoreceptors (Zallocchi et al., 2009), while the other indicates that clarin-1 is restricted to the Muller cells but not photoreceptors (Geller et al., 2009).

The calycal processes in photoreceptors are thought as an analogous structure to the stereocilia in hair cells (Goodyear and Richardson, 1999). They are well developed in humans, frogs and other species. In mice, only cone photoreceptors have obvious calycal processes (Cohen, 1965; Fetter and Corless, 1987; Rana and Taraszka, 1991). GPR98 and CDH23 are localized at the calycal processes in mouse cone photoreceptors, while whirlin is not evident at this structure in frog photoreceptors (Goodyear and Richardson, 1999; Yang et al., 2010).

5. The USH protein complexes

The indistinguishable symptoms within the same USH clinical type and the similar symptoms across different USH clinical types indicate that various USH proteins probably participate in the same cellular pathway in a broad sense. Among the USH proteins, harmonin, whirlin and SANS possess multiple protein-protein interaction domains and are proposed to be scaffold proteins in multi-protein complexes. Biochemical assays have indeed revealed the existence of their self-interactions and interactions with most of other USH proteins in vitro (Table 2). Interestingly, the in vitro interactions among different USH1 and/or USH2 proteins exist extensively (Table 2). One USH protein is generally able to interact with at least three other USH proteins. In most cases, different regions of the same protein are involved in its binding to different USH proteins (Table 2). Although these interactions have not been individually confirmed in vivo, harmonin, MYO7A, and CDH23 were recently reported to form a ternary complex in hair cells (Bahloul et al., 2010). Based on these findings, it has been hypothesized that USH proteins form an interacting network, an interactome, in both hair cells and photoreceptors (Richardson et al.; Kremer et al., 2006; Reiners et al., 2006; Saihan et al., 2009; Millan et al., 2011).

The above hypothesis is supported by the facts that ablation of one USH protein in mice causes mislocation and/or disappearance of at least one other USH protein in hair cells (Table 3). This phenomenon occurs across USH1 and USH2 proteins. Normal distribution of the three USH2 proteins depends on MYO7A and the distribution of some CDH23 isoform at the tip of the stereocilia relies on GPR98 (Table 3). However, the USH1 and USH2 proteins are present at the different interstereociliary links in hair cells during development. Additionally, different USH proteins are localized at two distinct subcellular locations in photoreceptors, the PMC and the synapse. Due to these different cellular locations of USH proteins, it is reasonable to propose that more than one USH protein complex exist and they play different but highly related roles in a broad cellular process (Williams, 2008; Yang et al., 2011).

Proteins/domains	Interacting proteins/domains	References
MYO7A		
MyTH4-FERM	Harmonin/PDZ1	(Boeda et al., 2002)
Tail	CDH23/not determined	(Bahloul et al., 2010)
SH2	PCDH15	(Senften et al., 2006)
MyTH4-FERM	SANS/cen	(Wu et al., 2011; Adato et al., 2005b)
MyTH4-FERM	USH2A/cytoplasmic region	(Michalski et al., 2007)
MyTH4-FERM	GPR98/cytoplasmic region	(Michalski et al., 2007)
Not determined	Whirlin/not determined	(Delprat et al., 2005)
Harmonin		
PDZ1	MYO7A/MyTH4-FERM	(Boeda et al., 2002)
N-terminus, PDZ1/2	CDH23/PBMs	(Boeda et al., 2002; Siemens et al., 2002; Grillet et al., 2009; Pan et al., 2009; Bahloul et al., 2010)
PDZ2	PCDH15/CD1 PBM	(Adato et al., 2005b; Reiners et al., 2005b; Senften et al., 2006)
PDZ1/3	SANS/SAM, PBM	(Adato et al., 2005b; Yan et al., 2010)
PDZ1	USH2A/PBM	(Reiners et al., 2005b)
PDZ1	GPR98/PBM	(Reiners et al., 2005b)
PDZ1/2, CC2	Harmonin/PBM, CC2	(Siemens et al., 2002; Adato et al., 2005b)
CDH23		
not determined	MYO7A/tail	(Bahloul et al., 2010)
2 PBMs	Harmonin/N-terminus, PDZ1, PDZ2	(Boeda et al., 2002; Siemens et al., 2002; Grillet et al., 2009; Pan et al., 2009; Bahloul et al., 2010)
EC1-3	PCDH15/EC1	(Kazmierczak et al., 2007)
Cytoplasmic region	SANS/not determined	(Caberlotto et al., 2011)
ECs	CDH23/ECs	(Siemens et al., 2004; Kazmierczak et al., 2007)
PCDH15		
Cytoplasmic region	MYO7A/SH2	(Senften et al., 2006)
CD1 PBM	Harmonin/PDZ2	(Adato et al., 2005b; Reiners et al., 2005b; Senften et al., 2006)
EC1	CDH23/EC1-3	(Kazmierczak et al., 2007)
CD2/CD3	SANS/not determined	(Caberlotto et al., 2011)
ECs	PCDH15/ECs	(Kazmierczak et al., 2007)

Proteins/domains	Interacting proteins/domains	References
SANS		
cen	MYO7A/MyTH4-FERM	(Wu et al, 2011.; Adato et al., 2005b)
SAM, PBM	Harmonin/PDZ1	(Weil et al., 2003; Yan et al., 2010)
Not determined	CDH23/cytoplasmic region	(Caberlotto et al., 2011)
Not determined	PCDH15/CD2, CD3	(Caberlotto et al., 2011)
PBM	Whirlin/PDZ1-PDZ2	(Maerker et al., 2008)
cen	SANS/cen	(Adato et al., 2005b)
USH2A		
Cytoplasmic region	MYO7A/MyTH4-FERM	(Michalski et al., 2007)
PBM	Harmonin/PDZ1	(Reiners et al., 2005b)
PBM	Whirlin/PDZ1-PDZ2	(Adato et al., 2005a; van Wijk et al., 2006; Yang et al., 2010)
GPR98		
Cytoplasmic region	MYO7A/MyTH4-FERM	(Michalski et al., 2007)
PBM	Harmonin/PDZ1	(Reiners et al., 2005b)
PBM	Whirlin/PDZ1-PDZ2	(Adato et al., 2005a; van Wijk et al., 2006; Yang et al., 2010)
Whirlin		
Not determined	MYO7A/not determined	(Delprat et al., 2005)
PDZ1-PDZ2	SANS/PBM	(Maerker et al., 2008)
PDZ1-PDZ2	USH2A/PBM	(Adato et al., 2005a; van Wijk et al., 2006; Yang et al., 2010)
PDZ1-PDZ2	GPR98/PBM	(Adato et al., 2005a; van Wijk et al., 2006; Yang et al., 2010)
PDZ1-PDZ2, PR-PDZ3	Whirlin/PDZ1-PDZ2, PR-PDZ3	(Delprat et al., 2005; Yang et al., 2010)

Table 2. Interactions among USH proteins

In hair cells, the normal cellular localization of harmonin requires the presence of all other USH1 proteins, and loss of harmonin seems not to affect the localization of other USH1 proteins (Table 3), indicating that harmonin is dispensable for locating these USH1 proteins to their normal position in cells. In contrast, CDH23 is relatively independent on other USH1 proteins, and its loss results in mislocalization of the two putative scaffold proteins, harmonin and SANS (Table 3). Therefore, CDH23 may play a crucial role in anchoring/tethering USH1 proteins. Harmonin and SANS may help hold the USH1 proteins in the complex.

Besides the known USH proteins, many other putative components in the USH complexes has been identified. These components are able to interact with at least one of the USH proteins as shown by biochemical assays. For the currently known USH2-interacting proteins, please see the review (Yang et al., 2011). However, additional experiments are necessary to verify the existence of these putative components in the USH complexes in vivo and reveal their relationship with USH.

	MYO7A	USH1C	CDH23	PCDH15	SANS	USH2
Myo7a$^{-/-}$		+ (Boeda et al., 2002; Lefevre et al., 2008)	- (Boeda et al., 2002; Senften et al., 2006)	+ (Senften et al., 2006)	- (Caberlotto et al., 2011)	+ (Michals al., 2007)
Ush1c$^{-/-}$	+/- (Lefevre et al., 2008; Yan et al., 2011)		- (Lefevre et al., 2008)	+/- (Lefevre et al., 2008; Yan et al., 2011)	+/- (Caberlotto et al., 2011; Yan et al., 2011)	
Cdh23$^{-/-}$	+ (Bahloul et al., 2010)	+ (Lefevre et al., 2008; Bahloul et al., 2010)		- (Senften et al., 2006)	+ (Caberlotto et al., 2011)	
Pcdh15$^{-/-}$	+ (Senften et al., 2006)	+ (Lefevre et al., 2008)	- (Senften et al., 2006)		+ (Caberlotto et al., 2011)	
Sans$^{-/-}$		+ (Lefevre et al., 2008)				
Ush2a$^{-/-}$						
Gpr98$^{-/-}$			+ (Michalski et al., 2007)			+ (Michals al., 2007)
Whrn$^{-/-}$						+ (Michals al., 2007; Yang et 2010)

+: existence of mislocalization, -: normal localization, +/-, contradictory results

Table 3. Interdependence of USH proteins in hair cells

6. Functions of the USH complexes

The severe and early-onset hearing phenotypes in various USH1 and USH2 mouse models make it relatively easier to decipher the functions of USH complexes in the inner ear than in the retina. The following will focus on the three main cellular processes generally believed to involve the USH complexes. Disruption of these USH functions is thought to be the molecular mechanisms underlying USH.

6.1 Hair bundle cohesion

During development, at the apex of hair cells, microvilli grow into stereocilia by recruiting more actin filaments. These stereocilia are bundled with transient lateral links and are connected with the kinocilium through kinociliary links. Following the establishment of the planar cell polarity, the kinocilium moves from the center to the periphery of the cell, and the stereocilia elongate differentially. The staircase-shape hair bundle is eventually formed. At the same time, the transient lateral links are gradually substituted by two distinct sets of interstereociliary links. They are the horizontal top connectors and the ankle links, close to the tip and base of the hair bundle, respectively (Figure 4). The tip links emerge, which are fibrous connections between the tip of medium and low stereocilia and the side of the neighboring taller stereocilia (Figure 4). Finally, the stereocilia grow both in length and in width and reach their mature size. In rodent mature cochlear hair cells, the ankle links and the kinociliary links disappear with the regression of the kinocilium (Frolenkov et al., 2004; Goodyear et al., 2005; Nayak et al., 2007).

CDH23 (Siemens et al., 2004; Lagziel et al., 2005; Michel et al., 2005; Rzadzinska et al., 2005; Lefevre et al., 2008) and PCDH15 (Goodyear et al., 2010; Webb et al., 2011; Lefevre et al., 2008) are localized at the transient lateral links and kinociliary links during early development of hair cells. In their mutant mice, hair bundles are usually splayed into several clumps; kinocilium is mispositioned and disconnected with the hair bundle (Lefevre et al., 2008), indicating that CDH23 and PCDH15, as components of the interstereociliary links, are important for hair bundle cohesion and that loss of the connection between the stereocilia and kinocilium causes the misorientation of the hair bundle. Interestingly, the mutant mouse models of all five USH1 genes share such similar phenotypes. This could be explained by the idea that the five USH1 proteins coordinate in this function. The PST domain of harmonin b binds to and bundles actin filaments (Boeda et al., 2002). MYO7A is a high duty ratio motor, which binds to actin filament strongly. Therefore, these two actin-binding proteins may anchor their interacting partners, CDH23 and PCDH15, to the actin bundle in the stereocilia of hair cells (Table 2). In $Ush1g^{-/-}$ mice, cohesion of stereocilia is disrupted. In $Ush1g^{fl/fl}Myo7a\text{-}cre^{+/-}$ mice, whose expression of SANS is disturbed only after birth, the stereocilia stay cohesive (Caberlotto et al., 2011). Therefore, SANS plays a role in stereocilia cohesion during the prenatal period. It may be involved in the organization of other USH1 proteins through directly interacting with them (Table 2).

All three USH2 proteins, USH2A, GPR98, and whirlin, are positioned at the ankle links of hair cells. Among these proteins, USH2A and GPR98 probably interact with each other or with some unidentified cell adhesion proteins to form the ankle links. Whirlin interacts with USH2A and GPR98 through the PDZ domain-mediated binding to anchor them at the base of the stereocilia. In the absence of GPR98, the ankle links are missing. Thus far, the dependence of the ankle links on USH2A and whirlin has not been examined. In the wild-type mouse, the stereocilia of outer hair cells are organized into a V-shaped staircase-like hair bundle. However, in all three *Ush2* mutant mice, the outer hair cells show various disorganized stereocilia and abnormal U-shape hair bundles (Mburu et al., 2003; McGee et al., 2006; Liu et al., 2007; Michalski et al., 2007; Yang et al., 2010). Accordingly, as components of the ankle links, the three USH2 proteins probably contribute to hair bundle cohesion as well.

6.2 Mechanotransduction

The stereocilia of hair cells are the cellular organelle conducting mechanotransduction. The vibration of the basilar membrane and tectorial membrane or the motion of endolymphatic fluid induces the hair bundle deflection. When the deflection is toward the longest stereocilia (the positive or excitatory direction), the transduction channels are open. The influx of Ca^{2+} and K^{+} through the channels elicits changes of the membrane potential and glutamate release at the ribbon synapse in hair cells. When the hair bundle moves away from the longest stereocilia (the negative or inhibitory direction), the transduction channels close, and the membrane potential and transmitter release resume their resting statuses. Although the molecular machinery of mechanotransduction is not well understood, the 'gating spring' model is popular in the field. In this model, the tip link, whose axis is parallel to the direction of the mechanical sensitivity of the hair bundle, is thought as a sensor to the stretch of the hair bundle. Alternatively, an unknown structure attached to the tip link fulfills this function (Vollrath et al., 2007; Gillespie and Muller, 2009). The transduction channel was recently localized to the plasma membrane at the lower end of the tip link in the stereocilia (Beurg et al., 2008).

In mature hair cells, CDH23 (Siemens et al., 2004; Sollner et al., 2004) and PCDH15 (Ahmed et al., 2006) were found associated with the tip links. CDH23 is mainly at the upper part and PCDH15 at the lower part of the links (Kazmierczak et al., 2007; Alagramam et al., 2011). In *Cdh23*$^{V\text{-}2J}$ and *Pcdh15*$^{av\text{-}6J}$ mice, the tip links are missing. Additionally, the response of the mechanotransduction is reduced. In the absence of stimulus, a fraction of transduction channels keep open in the wild-type hair cells, due to the resting tension of the tip links. However, the transduction channels in these two mutants do not open or take up the styryl dye FM1-43 at rest (Senften et al., 2006; Alagramam et al., 2011). Therefore, CDH23 and PCDH15 are believed to be components of the tip links and to participate in mechanotransduction in mature hair cells.

At the two ends of the tip link immediately beneath the stereocilia plasma membrane, there are electron-dense complexes, the UTLD and LTLD (Figure 4). Harmonin and MYO7A are present at the UTLD (Grillet et al., 2009; Michalski et al., 2009; Caberlotto et al., 2011; Grati and Kachar, 2011). In *Myo7a*^{6J}, *Myo7a*^{4626SB}, *Ush1c*^{dfcr}, and *Ush1c*$^{dfcr\text{-}2J}$ mice, the adaptation of mechanotransduction, a process for the hair cells to recover their sensitivity under sustained mechanical stimulation, was found consistently abnormal, while the amplitude of mechanotransduction responses is sometimes normal (Kros et al., 2002; Grillet et al., 2009; Michalski et al., 2009). These results suggest that harmonin and MYO7A are involved in the transduction adaptation. SANS may exist at both the LTLD and UTLD (Caberlotto et al., 2011; Grati and Kachar, 2011). Its loss in hair cells (*Ush1g*$^{-/-}$) causes elimination of the tip links and reduction in both the amplitude and sensitivity of the transduction currents

(Caberlotto et al., 2011). In *Ush1g$^{fl/fl}$ Myo7a-cre$^{+/-}$* mice, whose hair bundle morphology is intact, only the amplitude of transduction is affected. This finding indicates that SANS is implicated in mechanotransduction and plays a different role from harmonin or MYO7A.

Gpr98 knockout and *Gpr98^{del7TM}* mice also show defects in mechanotransduction, though there are some discrepancies between them (McGee et al., 2006; Michalski et al., 2007). In general, the sensitivity to the stimulation direction is changed in both outer and inner hair cells. The amplitude and sensitivity of the transduction current decrease in the outer hair cells, but are normal in the inner hair cells and the utricular hair cells. It is suggested that the misorganization of hair bundles in *Gpr98* mutant mice accounts of the abnormal sensitivity direction. Alternatively, GPR98 could be indirectly related with the cellular process of mechanotransduction.

6.3 Protein and organelle transport

In photoreceptors, the outer segment is a large specialized cilium filled with many flat membrane disks, where phototransduction occurs (Figure 4). This cellular compartment undergoes continuous and rapid renewal (Young, 1967; LaVail, 1976; Young, 1976; Besharse and Hollyfield, 1979), which requires a large amount of proteins and membrane lipids to be synthesized in the inner segment and to be quickly transported to the base of the outer segment through the connecting cilium (Figure 4). The removal of the old outer segment is achieved through phagocytosis by RPE cells. In addition, in both photoreceptors and RPE cells, several proteins, involved in phototransduction and retinoid cycle, translocate between two different cellular compartments in response to light (Artemyev, 2008; Slepak and Hurley, 2008; Lopes et al., 2011).

Among USH proteins, MYO7A is an actin-based motor. In the retina, it is expressed in both RPE cells and photoreceptors. In RPE cells, MYO7A is essential for the transport of phagosomes to their degradation apparatus (Gibbs et al., 2003), tethering melanosomes during their movement (Gibbs et al., 2004), and the translocation of RPE65 responding to light exposure (Lopes et al., 2011). In photoreceptors, MYO7A is present along the connecting cilium. Loss of MYO7A was found to delay the transport of opsin from the inner to the outer segment (Liu et al., 1999) and the transducin translocation from the outer to the inner segment after light exposure (Peng et al., 2011). In hair cells, without MYO7A, all USH2 proteins are mislocalized from the ankle links (Table 3), suggesting that MYO7A may transport the USH2 proteins. These lines of evidence establish the notion that MYO7A may function in protein and organelle transport in various cells in the retina and the inner ear.

USH2 proteins are positioned at the PMC in mammalian photoreceptors, which is an analogous structure to the periciliary ridge complex (PRC) in frogs (Peters et al., 1983). The PRC is a morphologically-specialized structure with a symmetrical array of 9 ridges and 9 grooves. It has been proposed, based on immunocytochemistry and freeze-fracture electron microscopy, as the membrane fusion site for post-Golgi vesicles carrying opsin and docosahexaenoyl (DHA)-phospholipids before these cargos are transported from the inner to the outer segment (Peters et al., 1983; Papermaster et al., 1986; Rodriguez de Turco et al., 1997; Papermaster, 2002). Additionally, Rab8, rac1, Sec8, moesin, syntaxin 3 and SNAP-25 have been localized around the PRC in frog photoreceptors (Deretic et al., 2004; Mazelova et al., 2009). These proteins are proposed, though not verified using mouse genetics, to participate in and/or regulate the docking and membrane fusion of post-Golgi vesicles to the plasma membrane at the PRC. Therefore, the USH2 complex at the PMC might play either a direct or indirect role in the docking between the post-Golgi vesicles and plasma membrane at the base of the connecting cilium (Roepman and Wolfrum, 2007; Maerker et al., 2008). This proposed function can also be applied in hair cells. The ankle-links exist when stereocilia grow and differentiate from small microvilli. At this time, many vesicles are at the base of stereocilia (Forge et al., 1997; Hasson et al., 1997), which could be the post-Golgi vesicles carrying proteins and membrane lipids from the cell body to the growing stereocilia. Supportively, the *Gpr98* knockout mouse shows delocalization of some CDH23 long isoforms at the tip of the stereocilia and, possibly, loss of some apical links between the stereocilia (Michalski et al., 2007). However, solid evidence supporting this putative function of the USH2 complex is still scarce. For instance, obvious mislocalization of rhodopsin has not been observed in whirlin knockout and *Ush2a* knockout mice (Liu et al., 2007; Yang et al., 2010), and vesicles fused with the plasma membrane have not been demonstrated at the ankle links.

7. Therapeutic studies

Because of the widespread clinical application of the well-developed cochlear implant for hearing loss (Pennings et al., 2006; Liu et al., 2008), more attention is focused on seeking effective treatments for retinitis pigmentosa in USH. Next, I will address the current progress in studies on gene therapy, drug application, cell transplantation, and nutritional supplements (Yang et al., 2011).

Human neural progenitor cells from the post mortem fetal cortical brain have been tested in the *Ush2*a knockout mouse (Lu et al., 2009). The progenitor cells were transplanted between photoreceptors and RPE cells. There, they delayed the cellular changes in photoreceptors and alleviated retinal functional deterioration. However, due to the short follow-up time after the treatment, the study did not examine whether the treatment can rescue photoreceptor loss in this animal model.

Compared to the cell-based therapy, replacement of the mutant gene in the retina is straightforward. The efficiency and efficacy of a lentivirus-mediated gene replacement of MYO7A have been studied in the $Myo7a^{4626SB}$ mouse (Hashimoto et al., 2007). Although the delivery of MYO7A into photoreceptors and RPE cells is not quite efficient, the treated mutant retina does show correction of the histological phenotypes in these two cells. In addition, our laboratory utilized a combination of AAV and a photoreceptor-specific promoter to efficiently target the USH2D gene, whirlin, into both rod and cone photoreceptors. The transgenic whirlin was found to restore the changes of USH2A and GPR98 expression in the whirlin knockout retina (Zou et al., 2011). These encouraging progresses in the USH1B and USH2D mouse models lay a solid foundation for a further and detailed exploration of gene therapy for these and other USH subtypes.

Aminoglycosides and their derivatives can induce a read-through of nonsense mutations by inserting an amino acid at the stop codon. These drugs have been tested in vitro, in cell cultures and in retinal explants to suppress the nonsense mutations found in USH1F (PCDH15) and USH1C (harmonin) patients (Rebibo-Sabbah et al., 2007; Nudelman et al., 2009; Goldmann et al., 2010; Nudelman et al., 2010). However, the high cellular toxicity of these drugs and the low efficiency of their read-through activities set a hindrance for their further application to patients. A recent report has shown that PTC124, a drug unrelated to aminoglycosides, has a relatively low cellular toxicity and high read-through efficacy (Goldmann et al., 2011).

The nutritional supplementation, daily intakes of vitamin A at a dose of 15,000 international units (IU) and vitamin E less than 400 IU, is thought to be a potential effective therapy for retinitis pigmentosa (Berson et al., 1993; Berson, 2000). Although it has already been applied to patients, this vitamin A supplement therapy is still under debate and its underlying mechanism is unknown.

8. Summary and perspective

The research on USH has made tremendous progress since the discovery of its first causative gene, *MYO7A*, in 1995. Currently, nine genes have been identified responsible for this genetic disease. From the functional domain analysis, these genes have been proposed to participate in trafficking, scaffolding, cell adhesion, and signaling in cells. Many spontaneous and transgenic mouse, rat, and zebrafish models are available now. The majority of these animal models reproduce the hearing and balance problems in USH patients. However, not many of them manifest retinal degeneration, which is one of the typical symptoms in USH patients. The reason for this discrepancy is not clear. But lack of retinal phenotypes in these animal models hinders our studies on retinitis pigmentosa in USH patients. A large body of evidence from biochemical and cellular localization studies demonstrate that USH proteins are organized into multi-component complexes mainly in hair cells and photoreceptors. They play a role in hair bundle cohesion, mechanotransduction, and, possibly, protein/organelle transport in vivo. USH is an incurable disease. Effective treatments using different approaches are still being sought and explored.

9. References

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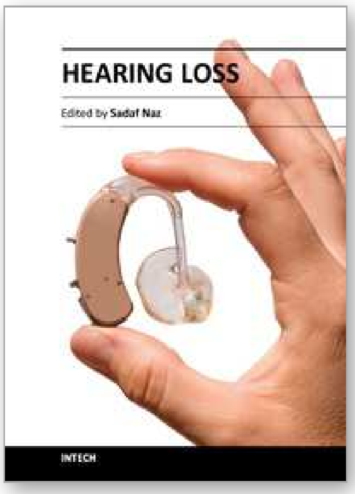

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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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