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Usher syndrome: animal models, retinal function of Usher proteins, and prospects for gene therapy

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Abstract

Usher syndrome is a deafness-blindness disorder. The blindness occurs from a progressive retinal degeneration that begins after deafness and after the retina has developed. Three clinical subtypes of Usher syndrome have been identified, with mutations in any one of six different genes giving rise to type 1, in any one of three different genes to type 2, and in one identified gene causing Usher type 3. Mutant mice for most of the genes have been studied; while they have clear inner ear defects, retinal phenotypes are relatively mild and have been difficult to characterize. The retinal functions of the Usher proteins are still largely unknown. Protein binding studies have suggested many interactions among the proteins, and a model of interaction among all the proteins in the photoreceptor synapse has been proposed. However this model is not supported by localization data from some laboratories, or the indication of any synaptic phenotype in mutant mice. An earlier suggestion, based on patient pathologies, of Usher protein function in the photoreceptor cilium continues to gain support from immunolocalization and mutant mouse studies, which are consistent with Usher protein interaction in the photoreceptor ciliary/periciliary region. So far, the most characterized Usher protein is myosin VIIa. It is present in the apical RPE and photoreceptor ciliary/periciliary region, where it is required for organelle transport and clearance of opsin from the connecting cilium, respectively. Usher syndrome is amenable to gene replacement therapy, but also has some specific challenges. Progress in this treatment approach has been achieved by correction of mutant phenotypes in *Myo7a*-null mouse retinas, following lentiviral delivery of *MYO7A*.

1. Clinical subtypes and genetics of Usher syndrome

Retinitis pigmentosa in combination with deafness was reported ~150 years ago (von Graefe, 1858; Leibreich, 1861), and became known as Usher syndrome, as a result of a report by Charles Usher in 1914 (Usher, 1914). Usher syndrome is inherited in an autosomal recessive manner (Usher, 1914), and is responsible for over half of the cases involving deafness and blindness (Vernon, 1969). It affects about 1 in 23,000 in the U.S. (Boughman et al., 1983), 1 in 29,000 in Scandinavia and 1 in 12,500 in Germany (Otterstedde et al., 2001). Since the frequency of retinitis pigmentosa is 1 per 4000 persons (Berson, 1993), Usher syndrome accounts for about 17% of all cases of RP in the US.

Usher syndrome is clinically and genetically heterogeneous. Three clinical subtypes, which are distinguished from each other primarily by the extent and onset of the deafness, have been

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defined (Smith et al., 1994). Usher type 1 patients are profoundly deaf from birth, and have vestibular dysfunction, which results in retarded motor development. The deafness in Usher 2 is less severe, and vestibular function has been described as normal. Usher 3 patients also have milder deafness, but, unlike in Usher 2, the hearing loss is progressive, and about half have vestibular dysfunction (Sadeghi et al., 2005). RP, which is clinically similar to nonsyndromic retinitis pigmentosa, develops in all types of Usher syndrome (Fishman et al., 1983; Smith et al., 1994).

As listed in Table 1, Usher 1 can be caused by mutations in any one of six different genes, and mutations in any one of three different genes can result in Usher 2. Only one gene has been identified for Usher 3. Usher 1 and 2 are the most common forms of Usher syndrome, with Usher 3 contributing to a large proportion of cases only in isolated areas, such as Finland (Pakarinen et al., 1996) and Birmingham, UK (Hope et al., 1997). In some cases, mutations in these genes do not give rise to both blindness and deafness. Cases of nonsyndromic deafness have been linked to mutations in the Usher 1B, 1C, 1D, 1F and 2D genes (Liu et al., 1997b;Liu et al., 1997c;Weil et al., 1997;Ahmed et al., 2002;Bork et al., 2001;Mburu et al., 2003). Conversely, mutations in the Usher 2A and 3 genes can cause autosomal recessive RP without reported hearing loss (Rivolta et al., 2000;Seyedahmadi et al., 2004a;Seyedahmadi et al., 2004b).

2. Animal models of Usher syndrome

Many of the mouse models for Usher syndrome were identified by early mouse geneticists due to their characteristic circling and head-tossing behavior that results from vestibular dysfunction. They were given various names that describe this aberrant behavior. Thus, shaker1 (*sh1*), deaf circler (*dfcr*), waltzer (*v*), Ames waltzer (*av*), and Jackson shaker (*js*) mice have mutations in genes that are homologous to the Usher 1 genes, 1B, 1C, 1D, 1F, and 1G, respectively (Gibson et al., 1995; Johnson et al., 2003; Di Palma et al., 2001; Alagramam et al., 2001a; Kikkawa et al., 2003). *Ush2a* knockout mice do not exhibit this behavior (Liu et al., 2007), which is consistent with normal vestibular function generally found in Usher 2 patients. Interestingly, whirler (*wi*) mice, the model for Usher 2D, do run in circles (as their name indicates) and toss their heads about (Lane, 1963), suggesting that some Usher 2 patients may indeed possess vestibular dysfunction.

Despite a relatively faithful manifestation of the hearing and balance disorders found in Usher syndrome, these mice do not possess severe mutant phenotypes in their retinas. None of the Usher 1 mouse models undergo retinal degeneration. Some evidence of slight degeneration was noted in the periphery of *dfcr* retinas (Johnson et al., 2003); however, none was observed in an examination of animals in excess of one year old, raised under a controlled light/dark cycle (C. Lillo and D.S. Williams, unpublished observations). Mice expressing mutant *Gpr98*, lacking the transmembrane and cytoplasmic domains (Vlgr1/del7TM), also have normal retinal histology (McGee et al., 2006). A small loss of photoreceptor cells was measured in old double shaker1/waltzer mutant mice (Lillo et al., 2003), but the only Usher mouse model that has so far been reported to possess any convincing retinal degeneration is the *Ush2a* knockout mouse. Individuals have normal photoreceptor morphology and numbers at 10 months of age, but by 20 months over half the photoreceptor cells have been lost (Liu et al., 2007).

Of the mice that show no retinal degeneration, reduced electroretinogram amplitudes have been reported for some of the alleles of shaker1, waltzer and Ames waltzer mice (Libby & Steel, 2001; Libby et al., 2003; Haywood-Watson et al., 2006), as well as *Gpr98*-mutant mice (McGee et al., 2006) and knock-in mice expressing the Acadian *USH1C* mutant gene (Lentz et al., 2007a; Lentz et al., 2007b). At least in the shaker1, waltzer and Ames waltzer mice the a- and

b-wave amplitudes were reduced by a similar proportion, indicating the defect lay within the photoreceptor cell response. Additional mutant retinal phenotypes have been described for the shaker1 mice. These mice possess increased opsin concentration in the photoreceptor connecting cilium (Liu et al., 1999), aberrant RPE melanosome localization and motility (Liu et al., 1998; Gibbs et al., 2004), and defective phagosome localization and digestion (Gibbs et al., 2003), consistent with multiple roles for myosin VIIa in the retina (see below).

There are now a number of zebrafish models with mutant or knocked down genes that represent Usher orthologues. *Mariner* expresses mutant *Myo7a*, and, like shaker1 mice, exhibits circling behavior and possesses sensory hair cells with morphological and functional defects (Ernest et al., 2000). In *mariner* retinas, the apical localization of RPE melanosomes has been reported to be defective (Biehlmaier et al., 2007), comparable to that in shaker1 retinas (Liu et al., 1998). A distinction is that, in many fish, including zebrafish, the apical migration of RPE melanosome has a significant impact on light adaptation (Burnside, 2001), so that in *mariner* this defect may be functionally more relevant (Biehlmaier et al., 2007). Zebrafish have two orthologues of the Usher 1F gene, with *orbiter* having mutant *Pcdh15a*. Mutation and knock down studies have shown that *Pcdh15a* is required for normal auditory and vestibular function, and *Pcdh15b* is required for normal photoreceptor outer segment organization and retinal function (Seiler et al., 2005). *Sputnik* zebrafish express mutant *Cdh23*, and have reduced or absent mechanotransduction (Nicolson et al., 1998; Seiler & Nicolson, 1999; Sollner et al., 2004), although there are not reports on their vision. Morphilino knock down studies of the Usher 1C, 2A and 2C orthologues result in swimming and balance defects in larvae, similar to those observed in *mariner*, and reduced visual function with increased photoreceptor cell death (Phillips et al., 2007).

The utility of these zebrafish models for retinal studies related to Usher syndrome is unclear at present. Some of the orthologous genes possess regions that are not well conserved with the Usher genes, so that their proteins may not have the same function (e.g. Gibert et al., 2005). However, there appear to be at least some overlapping functions (e.g. the role of myosin VIIa in RPE melanosome localization), and the presence of photoreceptor cell death in the zebrafish models provides an important similarity to the human condition, which is lacking in most of the mouse models.

3. Functions of Usher proteins in the retina

The proteins encoded by the known Usher genes are listed in Table 1. *MYO7A* was predicted to encode an unconventional myosin; i.e. a molecular motor that uses energy from ATP hydrolysis to move along actin filaments. Direct experiments have now demonstrated that myosin VIIa is a *bona fide* actin-based motor (Udovichenko et al., 2002;Inoue & Ikebe, 2003). The *USH1C* gene generates a number of different isoforms, belonging to three different classes of harmonin. The isoforms each contain two or three PDZ domains, so that harmonin is predicted to be a scaffolding protein (Verpy et al., 2000). The Usher 1D and 1F genes are both predicted to encode cadherins (Bolz et al., 2001;Bork et al., 2001;Ahmed et al., 2001;Alagramam et al., 2001b). The Usher 1G protein, sans, is another putative scaffolding protein (Weil et al., 2003). Usherin, encoded by *USH2A*, was reported to be an extracellular matrix protein that binds type IV collagen (Bhattacharya et al., 2004), however, more recently, a longer variant of usherin, an exceptionally large protein of ~600 kD, with a membrane anchor and short cytoplasmic, PDZ-binding motif, has been detected in photoreceptor cells (Liu et al., 2007). VLGR1 appears to be a G-protein coupled receptor with a large N-terminal region (Weston et al., 2004). Whirlin is another PDZ-domain protein and potential scaffold (Mburu et al., 2003). Lastly, the only reported Usher 3 gene encodes clarin1, which has been speculated to function in synaptic shaping and maintenance, based on loose homology with a protein known to function in this manner in the cerebellum (Adato et al., 2002).

It has been proposed that many of the proteins might function together in a common cellular mechanism. Such a unifying hypothesis is attractive, and, certainly, the similarities of clinical phenotype within the different types of Usher syndrome suggest that the mutated genes of each type might affect a common cellular mechanism. Experimental evidence to support this notion has come from studies indicating that some of the Usher 1 proteins can interact with each other.

In the first studies to test protein binding among Usher proteins, two groups found binding of the cytoplasmic region of the ear-specific isoform of cadherin23 to the second PDZ domain of harmonin (Boeda et al., 2002; Siemens et al., 2002). One of the groups also reported binding between the first PDZ domain (PDZ1) of harmonin and myosin VIIa (Boeda et al., 2002), while the other group reported that the PDZ1 domain of harmonin binds the isoform of cadherin23 that is found in tissues other than the ear, such as kidney, brain and retina (Siemens et al., 2002). Subsequent binding studies linked more of the Usher proteins together, with harmonin playing a central role in the network (Weil et al., 2003). In the cochlear hair cells, these binding studies have been supported by mutant phenotypes, exhibiting defects in stereociliary development and organization. Myosin VIIa and protocadherin15 have thus been shown to bind each other and interact functionally in the cochlear hair cells (Senften et al., 2006).

The extent of interactions among Usher proteins in the retina is less clear. Protein interaction in vitro is not necessarily relevant in the physiological environment of an intact tissue. It has been proposed that all the Usher 1 and Usher 2 proteins (including NBC3, which was considered previously, but is no longer a candidate for an Usher 2 protein) form a large complex in the photoreceptor synapse (Reiners et al., 2003; Reiners et al., 2005b; Reiners et al., 2005a; Kremer et al., 2006; Reiners et al., 2006; Reiners & Wolfrum, 2006; van Wijk et al., 2006). A weakness of this proposal is the lack of solid evidence that most of these proteins actually reside in the synaptic region. Immunofluorescence images have been presented to demonstrate localization in the photoreceptor synaptic layer of the retina (Reiners et al., 2003; Reiners et al., 2005b; Reiners et al., 2005a; Kremer et al., 2006; Reiners et al., 2006; Reiners & Wolfrum, 2006; van Wijk et al., 2006), however, this localization is not consistent with that reported by other groups (e.g. Gibbs & Williams, 2004; Lillo et al., 2005; Liu et al., 2007). Nor is it supported by retinal phenotypes of mutant mice.

None of the Usher mouse models has a mutant phenotype that could be attributed to photoreceptor synaptic function. The ultrastructure and physiology of the synapses appear normal. Shaker1, waltzer, Ames waltzer, whirler and usherin knockout mice have all been shown to have normal a-wave to b-wave ratios in their electroretinograms (Libby et al., 2003; Libby & Steel, 2001; Haywood-Watson et al., 2006; Sun et al., 2006; Liu et al., 2007), indicating that the photoreceptor cell response (a-wave) is passed on faithfully to the rest of the retina (which generates the b-wave).

The one location where a number of Usher proteins appear to be found together is in the ciliary and periciliary region of the photoreceptor cells (Fig. 1). While some of the Usher proteins might thus interact in this region, it is noteworthy that this is the one region in the photoreceptor cells that harmonin appears to be absent (e.g. Fig. 4E in Reiners et al. 2003;Lillo et al., 2005). Harmonin has been presented as the central scaffold of Usher protein networks in the inner ear and in the photoreceptor synapse, so that a network in the ciliary and periciliary region of the photoreceptor cells would require a different organization. Sans, usherin and whirlin all appear to have scaffolding properties and may thus play such a role.

The first Usher protein to be localized in this ciliary region was myosin VIIa (Liu et al., 1997a). This localization was corroborated by the identification of a mutant phenotype – abnormal accumulation of opsin in the connecting cilium – in studies of shaker1 mice (Liu et al., 1999). While the emphasis on these earlier localization studies was on the localization of

myosin VIIa within the connecting cilium, in retrospect, it is clear from published and unpublished immunoelectron micrographs that the protein can be also detected in the periciliary part of the inner segment (see, for example, Figs. 12–14 in Liu et al., 1997a) (Fig. 1). Full-length usherin has been localized to the periciliary membrane (Liu et al., 2007), and this localization has been reported to be dependent on the PDZ-domain protein, whirlin (Yang et al., 2006; Liu et al., 2007), suggesting that the Usher 1D protein is present here also. Abstracts reporting periciliary localization of protocadherin15 (Sun et al., 2006) and sans (Wolfrum et al., 2007) have also been presented. Earlier, the “ankle link antigen”, now identified as VLGR1 (McGee et al., 2006), was detected in this region (Goodyear & Richardson, 1999)

Hence, the connecting cilium region of the photoreceptor cells is a likely focus for Usher protein interaction and function in the retina. Interestingly, the importance of the photoreceptor cilium in retinal pathogenesis was suggested some time ago as a result of Usher patient studies. Abnormal cilia were described in the photoreceptor cells of postmortem Usher 2 retinas (Hunter et al., 1986; Barrong et al., 1992). Various abnormalities that could be related to cilium defects in other tissues of Usher patients were also reported. They include impaired olfaction (Zrada et al., 1996), decreased sperm motility (Hunter et al., 1986), abnormal nasal cilia (Arden & Fox, 1979; Bonneau et al., 1993), bronchitis (Bonneau et al., 1993), and asthma (Baris et al., 1994). Consistent with a general ciliary function, myosin VIIa was detected in cilia of a variety of tissues (Wolfrum et al., 1998).

Although more is known about the retinal function of myosin VIIa than for any other Usher protein, its role in the photoreceptor connecting cilium and periciliary region is not clear. Lack of myosin VIIa causes an abnormal accumulation of opsin in the connecting cilium, and a retarded rate of the disk membrane renewal, thus indicating impairment of delivery of opsin to the site of disk membrane morphogenesis (Liu et al., 1999). Nevertheless, this defect is not as severe as lack of heterotrimeric kinesin-2 function, for deletion of this motor activity appears to completely block the delivery of opsin to the outer segment, and cause rapid photoreceptor cell death (Marszalek et al., 2000; Jimeno et al., 2006). Hence, kinesin-2 appears more likely to provide motor transport of opsin along the connecting cilium. Myosin VIIa could play an auxiliary role with kinesin-2, consistent with a general theme in which a myosin provides local transport in conjunction with longer-range transport that is powered by a microtubule motor. Alternatively, its effect on opsin transport could be less direct, perhaps acting through structural elements of the cilium and pericilium.

In the ciliary region, myosin VIIa could interact with other Usher proteins, given their colocalization, however, by far the majority of retinal myosin VIIa is located in the apical RPE (Hasson et al., 1995), where it appears to be the only Usher protein. Here, its roles include organelle transport, most likely in concert with microtubule motors. A combination of in vivo studies and analyses of primary cultures of RPE cells from mutant mice indicate that myosin VIIa transports both phagosomes (Gibbs et al., 2003) and melanosomes (Futter et al., 2004; Gibbs et al., 2004; Klomp et al., 2007; Lopes et al., 2007). Phagosomes take longer to travel to the basal RPE and are digested more slowly in RPE cells lacking myosin VIIa (Gibbs et al., 2003). Live cell imaging of melanosomes shows that melanosomes travel further and faster (at the speed of a microtubule motor) in the absence of myosin VIIa, which moves melanosomes at ~200 nm/sec and appears to effect their tethering in the apical processes of the RPE (Gibbs et al., 2004; Klomp et al., 2007; Lopes et al., 2007).

4. Prospects for retinal gene therapy for Usher syndrome

Gene therapy is a potential approach to prevent blindness in Usher syndrome. Indeed, Usher syndrome is potentially a highly suitable form of retinal degeneration for treatment by gene therapy. First, all types appear to be inherited recessively and caused by loss of gene function,

so that therapy need only focus on adding gene function. Second, because of the associated impaired hearing at birth, Usher syndrome patients can be more readily identified prior to the onset of retinal degeneration. Nevertheless, there are some drawbacks. Some of the Usher genes are very large –*USH2A* and *GPR98* encode retinal proteins of 600–700 kD (Liu et al., 2007; McMillan et al., 2002) – making their delivery problematic. Moreover, as noted above, there is presently a paucity of mutant phenotypes that can be assayed to test for efficacy of treatment in animal models. When testing gene therapy, it is important not only to monitor the expression of the gene, but also to determine if the resulting protein is functional.

Some types of Usher syndrome are therefore currently not amenable to gene therapy. However, there has been some progress with treatment for Usher 1B. *MYO7A* cDNA has been delivered to retinas and cultured primary RPE cells of *Myo7a*-null mice, using a lentiviral vector. Using a promoter containing elements of the native *MYO7A* promoter, appropriate levels of myosin VIIa were obtained in the RPE cells, correction of mutant phenotypes – melanosome motility and phagosome digestion in cultured RPE cells, and melanosome localization and opsin clearance from the connecting cilium in vivo – was achieved (Hashimoto et al., 2007).

Concluding comment

Usher syndrome has turned out to be more genetically complex than clinicians would have first envisaged. Nevertheless, the identification of the genes involved now appears to be nearing completion. Understanding the retinal roles of the Usher proteins represents a current major challenge. A clearer picture of the localization, interactions and functions of the Usher proteins in the retina will facilitate progress towards developing gene therapy prevention of Usher blindness.

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Abbreviations

RPE

retinal pigment epithelium

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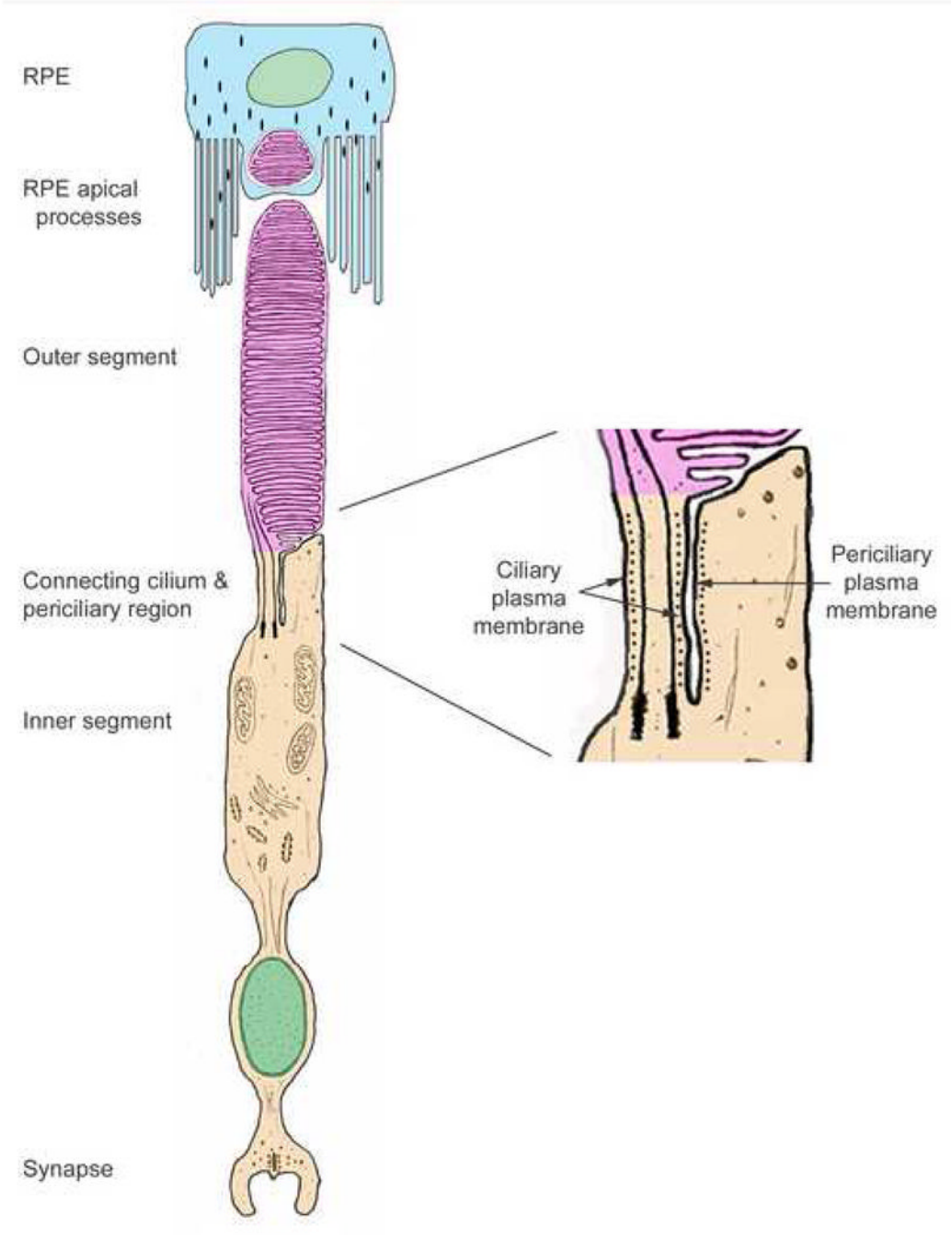

Figure 1.
Diagram of a photoreceptor and RPE cell. The region of the connecting cilium and pericilium is enlarged on the right, with the black dots indicating where myosin VIIa has been detected by immunogold labeling (Liu et al., 1997a). Evidence of the presence of a number of other Usher proteins along the periciliary membrane has now been reported (Liu et al., 2007; Yang et al., 2006; Sun et al., 2006; Wolfrum et al., 2007; Goodyear & Richardson, 1999; McGee et al., 2006). Modified from (Williams, 2002).

Table 1

Usher syndrome genes and proteins

Subtype	Gene	Protein (function[1])	Animal models Mouse (zebrafish)
Usher 1B	*MYO7A*	myosin VIIa (actin motor)	shaker1 (mariner)
Usher 1C	*USH1C*	harmonin (PDZ-domain protein)	deaf circler
Usher 1D	*CDH23*	cadherin23 (adhesion protein)	waltzer (sputnik)
Usher 1E	unknown		
Usher 1F	*PCDH15*	protocadherin15 (adhesion protein)	Ames waltzer (orbiter, *Pcdh15a*)
Usher 1G	*USH1G*	sans (scaffold)	Jackson shaker
Usher 2A	*USH2A*	usherin (transmembrane linkage)	knockout
Usher 2C	*GPR98*	VLGR1 (G-protein coupled receptor)	Vlgr1/del7TM
Usher 2D	*DFNB31*	whirlin (PDZ-domain protein)	whirler
Usher 3	*CLRN1*	clarin (synaptic shaping)	none reported

[1] Some of the indicated functions have not been demonstrated and are merely speculations based on primary sequence.

References: Usher 1B, (Kimberling et al., 1992; Weil et al., 1995; Gibson et al., 1995; Ernest et al., 2000); 1C, (Smith et al., 1992; Verpy et al., 2000; Johnson et al., 2003); 1D, (Wayne et al., 1996; Bolz et al., 2001; Bork et al., 2001; Di Palma et al., 2001; Sollner et al., 2004); 1E, (Chaib et al., 1997); 1F, (Ahmed et al., 2001; Alagramam et al., 2001b; Alagramam et al., 2001a; Seiler et al., 2005); 1G, (Mustapha et al., 2002; Weil et al., 2003; Kikkawa et al., 2003); 2A, (Eudy et al., 1998a; Eudy et al., 1998b; Liu et al., 2007); 2C, (Pieke-Dahl et al., 2000; Weston et al., 2004; McMillan & White, 2004); 2D, (Ebermann et al., 2007; Mburu et al., 2003); 3 (Sankila et al., 1995; Adato et al., 2002). A previously reported locus for Usher syndrome type 1A (Kaplan et al., 1992) has now been shown to be false (Gerber et al., 2006), and a previously reported locus for Usher 2B (Hmani et al., 1999) has not been subsequently verified.