Published in final edited form as:

J Am Acad Audiol. 2014 March ; 25(3): 289–301. doi:10.3766/jaaa.25.3.8.

Genetics of Peripheral Vestibular Dysfunction: Lessons from Mutant Mouse Strains

Sherri M. Jones and

University of Nebraska Lincoln

Timothy A. Jones

University of Nebraska Lincoln

Abstract

Background—A considerable amount of research has been published about genetic hearing impairment. Fifty to sixty percent of hearing loss is thought to have a genetic cause. Genes may also play a significant role in acquired hearing loss due to aging, noise exposure, or ototoxic medications. Between 1995 and 2012, over 100 causative genes have been identified for syndromic and nonsyndromic forms of hereditary hearing loss (see Hereditary Hearing Loss Homepage <http://hereditaryhearingloss.org>). Mouse models have been extremely valuable in facilitating the discovery of hearing loss genes, and in understanding inner ear pathology due to genetic mutations or elucidating fundamental mechanisms of inner ear development.

Purpose—Whereas much is being learned about hereditary hearing loss and the genetics of cochlear disorders, relatively little is known about the role genes may play in peripheral vestibular impairment. Here we review the literature with regard to genetics of vestibular dysfunction and discuss what we have learned from studies using mutant mouse models and direct measures of peripheral vestibular neural function.

Results—Several genes are considered that when mutated lead to varying degrees of inner ear vestibular dysfunction due to deficits in otoconia, stereocilia, hair cells, or neurons. Behavior often does not reveal the inner ear deficit. Many of the examples presented are also known to cause human disorders.

Conclusions—Knowledge regarding the roles of particular genes in the operation of the vestibular sensory apparatus is growing and it is clear that gene products co-expressed in the cochlea and vestibule may play different roles in the respective end organs. The discovery of new genes mediating critical inner ear vestibular function carries the promise of new strategies in diagnosing, treating and managing patients as well as predicting the course and level of morbidity in human vestibular disease.

Keywords

Genetics; vestibular; vestibular evoked potentials; mutant mouse models; hereditary vestibular disorders

Prevalence and relationship between heritable auditory and vestibular disorders in humans

The inner ear houses the sensory organs responsible for hearing and balance. The organ of Corti within the cochlea transduces sound and initiates sensory signals underlying hearing. Vestibular receptors within the two maculae and three ampullae transduce linear or angular motion of the head, respectively. Deficits in one or more of these inner ear end organs or their neural innervation can lead to hearing loss, vestibular dysfunction, or both. Hearing loss due to peripheral injury most commonly is represented as elevated hearing thresholds at particular frequencies, which may or may not be accompanied by altered oto-acoustic emissions. Vestibular dysfunction may be manifested in many ways including abnormal posturing and imbalance, rhythmic eye movements (nystagmus), abnormal vestibulo-ocular reflexes (VOR), abnormal vestibulo-collic reflexes (VCR), and/or reports of disorientation, altered subjective vertical, spinning sensations, dizziness, nausea, and blurred vision. Unless otherwise stated, the designation of “vestibular dysfunction”, “disorder”, “impairment” etc., throughout this review is meant to imply a peripheral functional loss involving vestibular sensors and/or eighth nerve. In this case there is either direct functional or structural evidence or strong indirect evidence for involvement of the peripheral vestibular system. Examples of direct evidence would include anatomical or physiological measures of the peripheral end organs or vestibular nerve. Examples of strong indirect evidence might include absent VOR or caloric responses.

One to three per 1000 children are born with severe to profound hearing impairment and many others develop significant hearing impairment before adulthood. The percentage of adults with hearing impairment increases with advanced age and a significant portion of age related hearing loss (as much as 30%) is thought to have a genetic cause (see reviews by Nadol and Merchant, 2001; Petersen, 2002). Over 400 syndromes with associated hearing loss have been described (Toriello et al., 2004). Nearly 100 chromosomal loci have been identified for nonsyndromic hearing loss with genes identified for over 40 forms (Van Camp and Smith, Hereditary Hearing Loss Homepage: <http://hereditaryhearingloss.org>; also see reviews by Nadol and Merchant, 2001; Petit et al., 2001; Petersen, 2002; Bitner-Glindzicz, 2002).

While much is being learned about the genetics of hearing loss, relatively little is known about the role genes may play in vestibular impairment. Estimates of vestibular dysfunction range from around 30 to 90% among children with hearing impairment of various causes (Shinjo et al. 2007; Steel, 1991; Tribukait et al., 2004; Zhou et al., 2009) and 34% among children with hereditary hearing impairment (Arnvig, 1955). Not all genetic mutations produce both cochlear and vestibular abnormalities. The heterogeneity of Usher syndrome is one example. Retinal degeneration and auditory impairment are common to Usher Syndrome, but vestibular function varies considerably (e.g., see reviews by Keats and Corey, 1999; Keats, 2002; Van Camp and Smith, Hereditary Hearing Loss Homepage: <http://hereditaryhearingloss.org>). Usher Type I syndrome, due to mutations in a variety of genes including MYO7A (myosin 7A), USH1C (harmonin), CDH23 (cadherin 23), or PCDH15 (protocadherin 15), has profound inner ear vestibular deficits. Usher Type II

syndrome, due to USH2A (usherin) mutations, does not show vestibular deficits (at least to the extent that vestibular function has been tested and reported in the literature), and Usher Type III syndrome, due to mutations in CLRN1 (Clarin 1) shows variable vestibular dysfunction [See summary in Table 1]. DFNA9, one form of nonsyndromic hereditary hearing loss, caused by mutations in the COCH gene, has also been reported to have variable inner ear vestibular dysfunction (Robertson et al., 2008). Therefore, depending upon the gene and the protein encoded by that gene, along with other factors, vestibular dysfunction may accompany peripheral cochlear impairment and hearing loss or it may not.

Considering the large number of genes identified for hearing loss, it is noteworthy that no genetic causes for nonsyndromic peripheral vestibulopathies have been identified in humans (Jen, 2011; Eppsteiner and Smith, 2011; Gazquez and Lopez-Escamez, 2011). A few central disturbances in balance or motor control such as episodic ataxia or spinocerebellar ataxia have been linked to neuronal genes KCNA1 (encodes a voltage-gated potassium channel) and CACNA1 (encodes the $\alpha 1A$ subunit of a voltage-gated calcium channel; Gazquez and Lopez-Escamez, 2011; Baloh, 2012; Jen, 2008). Studies on peripheral vestibular disorders such as Menière's disease or bilateral vestibular hypofunction have reported no definitive genetic linkage (Birgersson et al, 1987; Frykholm et al, 2006; Klockars and Kentala, 2007). Could there be a genetic basis for peripheral vestibular disorders? Additionally, are there individuals wherein a peripheral vestibular impairment goes undetected because of compensation or adaptation by the central nervous system? Peripheral vestibular dysfunction has been implicated as a potential cause of delayed motor development (e.g., Takiguchi et al., 1991; Tsuzuku and Kaga, 1992; Admiraal and Huygen, 1997; Kaga, 1999; Rine et al., 2000). However, the subjects in a number of these studies also had deficits in other systems (e.g., hearing loss, brain injury), which makes it difficult to evaluate the consequences of peripheral vestibular dysfunction independently. The potential correlation is compelling nonetheless and suggests the need for further studies of genetic vestibular deficits.

Basis for our meager understanding of genetic vestibular disorders

There are several reasons for the paucity of data regarding hereditary vestibular impairment. First, peripheral vestibular dysfunction in humans is difficult to assess directly. Current clinical tests of vestibular function evaluate the final motor output of control systems that maintain eye position or postural balance during movement. Such measures encompass the input, integration and output components of nervous system function, making it more difficult to ascertain the functional status of the vestibular periphery and then correlate function with genetic data. Second, relatively few investigators are systematically looking for vestibular impairment in human or animal genetic studies. Vestibular assessment is often not part of routine phenotyping in suspected cases of hereditary abnormalities or broad scale studies of genetic mouse mutants. Third, if peripheral vestibular impairment is present at birth or deficits appear gradually, the central nervous system likely compensates for the altered vestibular sensory input rendering any deficit undetectable via case histories, questionnaires or gross behavioral observations. In cases where motor delays, imbalance, or abnormal postural behaviors are apparent, vestibular function is often not tested as a possible etiology so the functional status of the vestibular periphery remains unknown.

Approaches for the direct study of vestibular function

Direct measures of peripheral vestibular function are available for use in animal models. Measuring the discharge patterns of single primary afferent neurons in response to head motion is an excellent direct approach to use. The study of isolated vestibular hair cells is also a powerful direct approach. These and other methods require surgical access to vestibular structures and the resources required for such studies often restrict their general use in genetic studies. The relative simplicity of far-field recording of vestibular compound action potentials lends them to more general use; particularly for an initial general assessment of peripheral vestibular function in genetically altered or mutant animals, especially mice. The vestibular sensory evoked potential (VsEP) is one such measure. The VsEP should not be confused with the vestibular-evoked myogenic potential (VEMP). The VEMP is an electrical recording of muscle activity that is modulated by vestibulo-spinal reflex circuits and thus is an indirect measure of peripheral vestibular function. Linear VsEPs provide a direct measure of peripheral vestibular function because they are compound action potentials generated by the vestibular portion of the eighth nerve and central vestibular relays in response to transient linear acceleration of the head. The neural responses can be recorded from the surface of the skull much like the widely used auditory brainstem response (ABR, e.g., Jones, 1992; Jones and Jones, 1996, 1999; also see reviews by Jones and Jones, 2007; Jones, 2008). VsEP response waveforms consist of a series of three or more positive and negative peaks that occur within 8 to 10 ms after stimulus onset. Intense acoustic masking or cochlear extirpation does not affect responses, but they disappear after death, bilateral surgical labyrinthectomy, or pharmacological blockade of the eighth nerve (Jones and Pedersen, 1989; Jones, 1992; Jones and Jones, 1999). The earliest response components reflect activity of the peripheral vestibular nerve whereas later response peaks reflect activity of vestibular relays within the brainstem and higher centers (Jones, 1992; Nazareth and Jones, 1998). The cerebellum does not contribute significantly to the mammalian VsEP (Gaines, 2012). In mammals, our laboratory has shown that linear VsEPs depend strictly upon the utricle and saccule (also known as the otolithic organs or gravity receptors) of the inner ear (Jones et al., 1999). Furthermore, linear VsEP amplitudes are directly proportional to the amount of otoconia present in macular organs (Jones et al., 2004) and response thresholds are inversely related to the density of hair cell synaptic elements in the macular neuroepithelium (Pierce, 2012). The VsEP has been useful in studying vestibular development, aging, plasticity, pharmacology, and genetics, and will likely find many other uses as it comes into more general use.

Another useful but indirect measure of vestibular function is the vestibulo-ocular reflex (VOR). It provides an objective quantitative measure of the reflex arc mediated primarily by horizontal canal afferents, central vestibular neural relays and motor outflow to the extraocular muscles. The reflex serves to control the position of the eyes in the head in order to maintain gaze on a particular object in the visual scene during horizontal rotation of the head. Measurement of the VOR in rodents is challenging, but several laboratories have developed the method for use in mice (e.g., Beraneck et al., 2012, Stahl et al., 2000; 2006; van Alphen et al., 2001). Some of the attributes of this approach include the ability to quantify the behavior of a vestibular reflex and characterize the combined effects of changes

in peripheral afferent and efferent function as well as in central processing of vestibular sensory input. The disadvantage of this approach is that vestibular deficits may be masked by central plastic changes and ultimately compensation for peripheral vestibular loss. The combined use of the VOR and direct measures of peripheral vestibular function presumably would be most effective and provide a means to distinguish changes in central relays and motor outflow from changes in vestibular sensory input (e.g., Alagramam et al., 2005).

Learning about genetic vestibular impairment from mouse models

The mouse has a long history as a genetic model for hearing loss and imbalance behaviors (e.g., Yerkes, 1907; Lord and Gates, 1929; Lyon, 1953; Deol, 1954; see also Ruben, 1991; Steel and Brown, 1994; Steel, 1995; Lyon et al., 1996; Petit et al., 2001; Ahituv and Avraham, 2002). Many early studies described behaviors characteristic of imbalance such as head bobbing, circling, hyperactivity, and such behaviors have often been attributed solely to inner ear dysfunction. Behavior alone is often a poor indicator of inner ear function. Imbalance behaviors may be due to deficits at a variety of levels of the neuraxis or may even be due to muscular deficits. In addition, behavior may be completely normal despite the presence of profound deficits in the inner ear.

Genetic mouse models wherein peripheral vestibular function and morphology have been quantified have proven to be quite powerful in shedding light on the role of genes in inner ear vestibular function. Indeed, structural investigations of the vestibular system in mutant mice have identified or further characterized structural defects in otoconia (e.g., Lyon, 1953; Lyon and Meredith, 1969; Rauch, 1979; Trune and Lim, 1983; Erway and Grider, 1984; Bergstrom et al., 1998; Jones et al., 2004), stereociliary bundles (e.g., Avraham et al., 1995; Moriyama et al., 1997; Di Palma et al., 2001; Alagramam et al., 2001; 2005), hair cells (e.g., Deol, 1954; Anniko et al., 1980; Dememes and Sans, 1985; Wenngren and Anniko, 1989; Sjoström and Anniko, 1990; Kitamura et al., 1991; Otani et al., 1995; Kozel et al., 1998; Ma et al., 2000), inner ear pigment (Cable et al., 1994, 1995), and vestibular ganglion (e.g., Ernfors et al., 1995; Liebl et al., 1997; Ma et al., 2000).

Recent work has clarified the role of widely recognized genes (as noted above) in the vestibular periphery as well as brought to light new genes underlying vestibular function. We review here several examples of genes and gene products contributing to peripheral vestibular function, specifically macular receptor function that we have studied. In the discussion that follows, the reader may notice a different representation for the gene names. Human genes are represented by non-italicized upper case letters as used in the above discussion. Mouse genes are written with italicized upper and lower case letters. Protein products may appear as the gene name, but are not italicized. Table I summarizes general features of genes discussed.

Mutations affecting otoconia

Many altered genes produce a loss of otoconia and a corresponding loss of macular receptor function. Several genes have proven to be critical for the formation of otoconia [e.g., *Nox3* (NADPH oxidase 3, Paffenholz et al., 2004), *Otop1*, (otopetrin 1, Hurle et al., 2003) *Slc30a4* (solute carrier family 30 member 4, Huang and Gitschier 1997), *Pldn* (pallidin, Hermansky-

Pudlak Syndrome, Huang et al., 1999), *Cyba* (Cytochrome b-245 light chain (p22^{phox}), Nakano et al., 2008). In the absence of otoconia, responses to linear translation are absent (figure 1, Jones et al., 1999; 2004; 2008). This is the case despite an otherwise intact sensory apparatus including the normal complement of type I and type II vestibular hair cells, ribbon synapses and corresponding calyceal, dimorph and bouton primary afferent terminals (Hoffman et al., 2006; 2007a; 2007b). Although neural responses to head translation are absent, macular primary afferent spontaneous activity is normal in some otoconia deficient animals (Jones et al., 2008). Moreover, responses of ampullar primary afferents to head rotation (Jones et al., 2008; Harrod and Baker, 2003) and cochlear responses to sound are preserved (figure 1).

There can also be significant behavioral consequences with the absence of otoconia. General postures and locomotion in otoconia deficient mice appear relatively normal although an “experienced eye” might note altered static head positions (tilting) in some animals. However, because animals lacking otoconia cannot sense the direction of the gravity vector, they cannot swim normally, and they are easily disoriented in water losing all sense of up and down. In some cases, otoconial loss is graded and compound neural responses to head translation (i.e., VSEPs) in these cases varies in direct proportion to the amount of otoconia preserved (Jones et al., 2004). One interesting observation has been that in the presence of even small amounts of otoconia and reduced VsEP responses to translation, behavioral measures remain normal or near normal (e.g., Ornitz et al., 1998; Zhao et al., 2008; Jones et al., 2004). Indeed, from our experience, it appears that even the least bit of peripheral sensory input from the maculae provides a sufficient sensory cue to the central nervous system to support normal behaviors requiring detection of the gravity vector (e.g., swimming).

Identification of genes critical for the formation of normal otoconia provides insight into the basic mechanisms underlying the formation and maintenance of otoconia (e.g., Zhao et al., 2007; Nakano et al., 2008). Moreover, in some cases human genetic homologs have been identified thus shedding light on mechanisms underlying human disease. One example is seen in a report by Nakano et al, (2008). The protein p22^{phox} forms the central enzymatic core of the NADPH oxidase complex found primarily in cells of the endolymphatic duct and sac. In the human, mutations in *CYBA* (the gene that encodes p22^{phox}) leads to a serious immune disorder called chronic granulomatous disease (CGD), which is related to the inability to generate reactive oxygen species in defense of invading pathogens. Nakano and coworkers reported that the absence of p22^{phox} leads to major otoconial dysgenesis and absent VsEPs. These and other findings led to the proposal that during development, NADPH oxidases produce superoxide, which in turn acts to increase pH levels and Ca²⁺ concentration within the embryonic endolymph. Increased (alkaline) pH and elevated Ca²⁺ concentrations are physical requirements for the crystallization of calcium carbonate and formation of otoconia (Nakaya et al., 2007; Chou et al., 1989). Such conditions are not present in the endolymph of an adult and thus must be present during development when otoconia form. Hypothetically, in the absence of a functional NADPH oxidase complex these conditions are not met and otoconia do not form.

Mutations affecting stereocilia and hair cells

Hair cell stereociliary bundles are critical for transduction and encoding of vestibular and auditory stimuli. They represent complex elaborate specializations located at the apical surface of the hair cell. The hair bundle is held together by many extracellular protein links that connect adjacent stereocilia. These include tip links, shaft links, ankle links, lateral links, and kinocilial links (Nayak et al., 2007). At least 18 genes have been identified as components of the stereociliary bundle. Genetic mutations leading to the deletion of stereociliary proteins generally lead to hair cell dysfunction and deafness. Examples include genes associated with human Usher syndrome (MYO7A, CDH23, PCDH15, Bork et al., 2001, Ahmed et al., 2001; Alagramam et al., 2001) and many others (see Hereditary Hearing Loss Homepage; <http://hereditaryhearingloss.org>). Deletion of the receptor-like inositol lipid phosphatase, *Ptprq* (Oganesian et al., 2003), produces a progressive loss of auditory function in mice. The protein phosphatidylinositol phosphatase (PTPRQ) forms part of the shaft links and genetic deletions produce hair cell bundle defects, loss of hair cells in the base of the cochlea and deafness (Goodyear et al., 2003). These studies in mice reported no overt vestibular behaviors or structural damage although auditory dysfunction was clearly evident (a nonsyndromic deafness). More recent work (Goodyear et al., 2012) also reported the absence of overt behavioral signs of vestibular deficits. Only subtle changes in swimming behaviors were noted. However, VsEPs, (figure 2) indicated severe to profound macular receptor dysfunction and detailed structural studies revealed significant stereociliary bundle defects in the vestibular maculae. These findings reflect the important role *Ptprq* plays in maintaining normal vestibular stereociliary bundles and vestibular function. In humans, mutations in PTPRQ cause autosomal, non-syndromic recessive deafness (DFNB84, Schraders et al., 2010; Shahin et al., 2010). Of interest is the observation that some DFNB84 families reportedly had vestibular deficits, which may be understood and explained by findings in *Ptprq* mutant mice.

Protocadherin 15 is a protein constituent of kinociliary links and stereociliary tip links of hair cell stereociliary bundles (e.g., Goodyear et al., 2010; Gillespie and Muller 2009). Spontaneous mutations in the protocadherin 15 gene (PCDH15) produce profound auditory and vestibular deficits in both humans (Ahmed et al., 2003; Ben-Yosef et al., 2003) and animals (Alagramam et al., 2001; Alagramam et al., 2005). Milder forms of inner ear deficits have been produced in mice by removing specific coding segments of the *Pcdh15* gene (e.g., exons 35, 38 and 39, Webb et al., 2011). Removing exon 38 for example, resulted in profound auditory deficits but spared vestibular function based on VOR testing. Such experiments reveal the complexities of hair cell stereociliary bundle structures and the subtle but remarkable differences that exist between auditory and vestibular hair cells. It is interesting that VOR testing was normal in these animals despite the absence of kinociliary links and presence of other vestibular morphological abnormalities. It would be of interest to evaluate these animal models using a direct measure of peripheral vestibular function, which may reveal a peripheral loss corresponding with the structural anomalies.

As previously mentioned, Usher syndrome presents as congenital deafness and blindness (Petit, 2001). The distinction among the different types of Usher Syndrome in large part depends on the severity of hearing loss and presence of vestibular deficit. Usher Type 3

manifests as a variable loss of vestibular function and progressive hearing loss. The exact function of the CLRN1 gene is unknown but in the human, loss of CLRN1 function is associated with Usher Syndrome 3A (USH3A) an autosomal recessive disorder, which manifests as a progressive loss of hearing and variable vestibular loss of function. In mice, the *Cln1* gene is expressed in hair cells and primary afferent ganglia of the vestibular and auditory end organs (Geng et al., 2009), an observation that is consistent with a role in peripheral hearing and vestibular function. In the *Cln1* knockout mouse, auditory function degrades rapidly after birth and is absent by postnatal day 30. This is accompanied by severe structural changes in the cochlea including the loss of almost all cochlear hair cells as well as degradation of basal supporting cells. Behavioral evidence of vestibular dysfunction (swimming tests, general behavioral observations) is subtle and equivocal at ages younger than 90 days. By the age of 6 months, behavioral signs such as head bobbing become more apparent in *Cln1* knockout animals. On the other hand, VsEPs indicated an early loss of function between postnatal day 14 and 30 characterized by increased thresholds and prolonged latencies (figure 3) suggesting altered hair cell or primary afferent function. Clearly these findings indicate that *Cln1* is critical for normal auditory and vestibular function in both the mouse and human, and the nature of inner ear loss of function is comparable to that shown in USH3A. The *Cln1* mouse model may prove helpful in finding the functional role of the gene and in understanding the basis of USH3A.

Mutations affecting hair cell synapses

The synaptic apparatus of hair cells is essential for the activation of primary afferent neurons and the encoding of the physical characteristics of a sound or head motion into neural discharge patterns. Synaptic transmission in the hair cell involves a structure called the synaptic ribbon. Synaptic vesicles containing neurotransmitter are initially tethered to the synaptic ribbon and then docked to the plasma membrane in the active zone. In the presence of Ca^{2+} , docked vesicles fuse with the cell membrane and release neurotransmitter (i.e., glutamate) into the extracellular synaptic space; a process called exocytosis. Transmitter release increases when transduction currents depolarize the hair cell, which activates voltage sensitive Ca^{2+} channels near the active zones of ribbon synapses. Local increases in Ca^{2+} trigger exocytosis. Otoferlin (Otof) is a protein associated with the membranes of synaptic vesicles. It is believed to be a Ca^{2+} sensor and when activated, otoferlin facilitates fusion of docked vesicles at the active zone. The presence of otoferlin and its contribution to auditory hair cell function has been appreciated for some time (Yasunaga et al., 1999; Roux et al., 2006). Mutations of otoferlin in humans cause nonsyndromic deafness, DFNB9. *Otof* mutant mice evidence defective Ca^{2+} -dependent exocytosis and severely impaired hearing (Roux et al., 2006; Beurg et al., 2008). Otoferlin is found associated with synaptic vesicles in both type I and II vestibular hair cells (Dulon et al., 2009; Yasunaga et al., 1999; Roux et al., 2006; Schug et al., 2006). The functional role of otoferlin in vestibular sensors has also been evaluated using the *Otof* mouse model (Dulon et al., 2009). In the absence of *Otof*, VsEPs evidence significantly elevated thresholds, prolonged latencies and decreased amplitudes (figure 4), findings consistent with a substantial presynaptic defect causing slowed or reduced Ca^{2+} -dependent transmitter release. Additional direct measurements of spontaneous primary afferent discharge and dendritic excitatory postsynaptic potentials revealed no

changes in spontaneous activity. However, Ca^{2+} -dependent exocytosis in vestibular hair cells was markedly impaired, more so in Type I than Type II hair cells. Moreover, the normal linear relationship between Ca^{2+} flux and the rate of exocytosis was dramatically reduced and transformed into a shallow nonlinear function. All of these dramatic functional changes in the absence of *Otof* occurred despite the appearance of structurally normal vestibular ribbon synapses. Thus otoferlin appears to be of critical importance to normal synaptic transmission in both auditory and vestibular hair cells. Given these substantial effects, it is remarkable that there is no apparent vestibular deficits in the gross behavior of *Otof* mutant mice (Roux et al., 2006; Schwander et al., 2007).

Mutations affecting ionic homeostasis

Human corneal hereditary dystrophy type 2 (CHED2) and Harboyan syndrome are caused by mutations in the *SLC4A11* gene, the symptoms of which include corneal defects, nystagmus and hearing loss. Little was known regarding the functional role of this gene until recently. Moreover, the underlying etiology for these symptoms was unclear. Park et al. (2004) showed that the gene product of *SLC4A11* was a sodium-coupled borate cotransporter, which is a pump that moves the borate ion across the cell membrane using the energy supplied by the sodium concentration gradient. Lopez et al. (2009) showed that *SLC4A11* is expressed in fibrocytes of the cochlea and inner ear vestibular system as well as in other tissues including the cornea and may serve some role in potassium recycling. To investigate the role of the sodium coupled borate cotransporter in the cornea and inner ear of mice, Lopez and colleagues (2009) generated an *Slc4a11* mutant mouse model. Although behavior was normal in *Slc4a11* mutant mice, deficits in both ABR and VsEPs were evident. Figure 5 illustrates vestibular functional deficits in *Slc4a11* mice. Latencies of N1 of the VsEP were prolonged suggesting prolonged conduction times in the eighth nerve. Moreover, amplitudes of the eighth nerve response parameter (P1-N1) were significantly reduced and the slope of the relationship between amplitude and stimulus level was essentially flat. Interestingly, changes in P2 and N2 suggested central deficits as well as peripheral. In addition, the absence of the cotransporter resulted in remarkable structural changes in the vestibule including collapse of the membranous labyrinth and subtle corneal structural changes. Swelling or collapse of the membranous labyrinth suggest altered fluid balance and that the *Slc4a11* mutant mouse may serve as a new model for the study of hydrops and labyrinth fluid homeostasis in addition to CHED2 and Harboyan syndromes. Moreover, these findings suggest the possibility of an underlying occult vestibular deficit in patients with CHED2 and Harboyan syndrome and may explain reports of nystagmus in some patients.

Although it is not clear how the absence of *Slc4a11* causes inner ear dysfunction, it is reasonable to hypothesize that the cotransporter plays an important role in maintenance of normal fluid balance and electrolyte homeostasis. Transport mechanisms in fibrocytes of the inner ear have been shown to be essential for inner ear function and potassium recycling (e.g., Zdebik et al 2009). The loss of *Slc4a11* in fibrocytes may interfere with inner ear homeostatic mechanisms through some as yet unknown mechanism.

Summary

Knowledge regarding the roles of particular genes in the operation of the peripheral vestibular sensory apparatus is growing and it is clear that gene products co-expressed in the cochlea and vestibule may play very different roles, including no functional role, in the respective structures. Historically, vestibular deficits often missed detection owing to intended focus on other sensory modalities or the inherent difficulty in making objective direct vestibular assessments. Powerful direct measures of vestibular function are available and, when used in combination with measures of behavior and VOR, can provide a considerable amount of detail regarding peripheral defects as well as central compensation for peripheral deficits. The discovery of new genes mediating critical peripheral vestibular function carries the promise of new strategies in diagnosing, treating and managing patients as well as predicting the course and level of morbidity in human vestibular disease.

Acknowledgments

The work reported herein was supported by research grants NIH R01 DC004477, NIH R01 DC R01 DC006443, and NASA NAG5 4067.

Abbreviations

VsEP	vestibular evoked potentials
VOR	vestibulo-ocular reflex
MYO7A	myosin 7A
CDH23	cadherin 23
PCDH15	protocadherin 15
NOX3	NADPH oxidase 3
OTOP1	otopetrin 1
SLC30A4	solute carrier family 30 member 4
PLDN	pallidin
CYBA	Cytochrome b-245 light chain (p22phox)
PTPRQ	protein-tyrosine phosphatase, receptor-type, Q
OTOF	otoferlin
ABR	auditory brainstem response
CLRN1	clarin 1
USH2A	usherin
USH1C	harmonin
KCNA1	potassium voltage-gated channel subfamily A member 1
CACNA1	voltage-dependent P/Q-type calcium channel subunit alpha-1A

SLC4A11	solute carrier family 4 member 11
CHED2	corneal endothelial dystrophy 2

References

- Admiraal RJ, Huygen PL. Vestibular areflexia as a cause of delayed motor skill development in children with the CHARGE association. *Int J Ped Otorhinolaryngol.* 1997; 39:205–222.
- Ahituv N, Avraham KB. Mouse models for human deafness: Current tools for new fashions. *Trends Mol Med.* 2002; 8:447–451. [PubMed: 12223317]
- Ahmed ZM, Riazuddin S, Bernstein SL, Ahmed Z, Khan S, Griffith AJ, Morell RJ, Friedman TB, Riazuddin S, Wilcox ER. Mutations of the protocadherin gene PCDH15 cause Usher syndrome type 1F. *Am J Hum Genet.* 2001; 69:25–34. [PubMed: 11398101]
- Ahmed ZM, Riazuddin S, Ahmad J, Bernstein SL, Guo Y, Sabar MF, Sieving P, Griffith AJ, Friedman TB, Belyantseva IA, Wilcox ER. PCDH15 is expressed in the neurosensory epithelium of the eye and ear and mutant alleles are responsible for both USH1F and DFNB23. *Hum Mol Genet.* 2003; 12:3215–3223. [PubMed: 14570705]
- Aragamam KN, Murcia CL, Kwon HY, Pawlowski KS, Wright CG, Woychik RP. The mouse Ames waltzer hearing-loss mutant is caused by mutation of Pcdh15, a novel protocadherin gene. *Nat Genet.* 2001; 27:99–102. [PubMed: 11138007]
- Aragamam KN, Stahl JS, Jones SM, Pawlowski KS, Wright CG. Characterization of vestibular dysfunction in the mouse model for Usher syndrome 1F. *J Assoc Res Otolaryngol.* 2005; 6(2):106–118. [PubMed: 15952048]
- Anniko M, Sobin A, Wersall J. Vestibular hair cell pathology in the Shaker-2 mouse. *Arch Oto-Rhino-Laryngol.* 1980; 226:45–50.
- Arnvig J. Vestibular function in deafness and severe hardness of hearing. *Acta Otolaryngol.* 1955; 45:283–288. [PubMed: 13275292]
- Avraham KB, Hasson T, Steel KP, Kingsley DM, Russell LB, Mooseker MS, Copeland NG, Jenkins NA. The mouse Snell's waltzer deafness gene encodes an unconventional myosin required for structural integrity of inner ear hair cells. *Nat Genet.* 1995; 11:369–375. [PubMed: 7493015]
- Baloh RW. Episodic ataxias 1 and 2. *Handb Clin Neurol.* 2012; 103:595–602. [PubMed: 21827920]
- Ben-Yosef T, Ness SL, Madeo AC, Baar-Lev A, Wolfman JH, Ahmed ZM, Desnick RJ, Willner JP, Avraham KB, Ostrero H, et al. Brief report--A mutation of PCDH15 among Ashkenazi Jews with the type 1 Usher syndrome. *N Engl J Med.* 2003; 348:1664–1670. [PubMed: 12711741]
- Beranek M, Bojados M, Le Seach A, Jamon M, Vidal PP. Ontogeny of mouse vestibulo-ocular reflex following genetic or environmental alteration of gravity sensing. *PLoS ONE.* 2012; 7(7):e40414. [PubMed: 22808156]
- Bergstrom RA, You Y, Erway LC, Lyon MF, Schimenti JC. Deletion mapping of the head tilt (*het*) gene in mice: A vestibular mutation causing specific absence of otoliths. *Genetics.* 1998; 150:815–822. [PubMed: 9755211]
- Beurg M, Safieddine S, Roux I, Bouleau Y, Petit C, Dulon D. Calcium- and otoferlin-dependent exocytosis by immature outer hair cells. *J Neurosci.* 2008; 28:1798–1803. [PubMed: 18287496]
- Birgerson L, Gustavson K, Stahle J. Familial Menière's disease: a genetic investigation. *American Journal of Otology.* 1987; 8:323–326. [PubMed: 3631240]
- Bitner-Glindzicz M. Hereditary deafness and phenotyping in humans. *Brit Med Bull.* 2002; 63:73–94. [PubMed: 12324385]
- Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, Polomeno R, Ramesh A, Schloss M, Srisailpathy CR, Wayne S, Bellman S, Desmukh D, Ahmed Z, Khan SN, Kaloustian VM, Li XC, Lalwani A, Riazuddin S, Bitner-Glindzicz M, Nance WE, Liu XZ, Wistow G, Smith RJ, Griffith AJ, Wilcox ER, Friedman TB, Morell RJ. Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. *Am J Hum Genet.* 2001; 68:26–37. [PubMed: 11090341]

- Cable J, Huszar D, Jaenisch R, Steel KP. Effects of mutations at the W locus (c-kit) on inner ear pigmentation and function in the mouse. *Pigment Cell Res.* 1994; 7(1):17–32. [PubMed: 7521050]
- Cable J, Jackson IJ, Steel KP. Mutations at the W locus affect survival of neural-crest derived melanocytes in the mouse. *Mech Dev.* 1995; 50(2–3):139–50. [PubMed: 7619726]
- Chou L, Garrels RM, Wallast R. Comparative study of the kinetics and mechanisms of dissolution of carbonate minerals. *Chem Geol.* 1989; 78:269–282.
- Dememes D, Sans A. Pathological changes during the development of the vestibular sensory and ganglion cells of the Bronx waltzer mouse. *Scanning and transmission electron microscopy. Brain Res.* 1985; 350:285–295. [PubMed: 3986619]
- Deol MS. The anomalies of the labyrinth of the mutants varitint-waddler, shaker-2 and jerker in the mouse. *J Genet.* 1954; 52:562–588.
- Di Palma F, Holme RH, Bryda EC, Belyantseva IA, Pellegrino R, Kacha B, Steel KP, Noben-Trauth K. Mutations in *Cdh23*, encoding a new type of cadherin, cause stereocilia disorganization in waltzer, the mouse model for Usher syndrome type 1D. *Nat Genet.* 2001; 27(1):103–107. [PubMed: 11138008]
- Dulon D, Safieddine S, Jones SM, Petit C. Otoferlin is critical for linear Ca^{2+} dependence of exocytosis at vestibular hair cell ribbon synapses. *J Neurosci.* 2009; 29(34):10474–10487. [PubMed: 19710301]
- Eppsteiner RW, Smith RJ. Genetic disorders of the vestibular system. *Curr Opin Otolaryngol Head Neck Surg.* 2011; 19:397–402. [PubMed: 21825995]
- Ernfors P, Van de Water T, Loring J, Jaenisch R. Complementary roles of BDNF and NT-3 in vestibular and auditory development. *Neuron.* 1995; 14:1153–1164. [PubMed: 7605630]
- Erway LC, Grider A. Zinc metabolism in lethal-milk mice. Otolith, lactation, and aging effects. *J Heredity.* 1984; 75:480–484.
- Frykholm C, Larsen H, Dahl N, Klar J, Rask-Andersen H, Friberg U. Familial Ménière's disease in five generations. *Otology and Neurotology.* 2006; 27:681–686. [PubMed: 16868516]
- Gaines, GC. PhD Dissertation. Communication Sciences & Disorders, East Carolina University. Dept; 2012. Generators of mammalian vestibular surface responses to head motion.
- Gazquez I, Lopez-Escamez JA. Genetics of recurrent vertigo and vestibular disorders. *Curr Genomics.* 2011; 12:443–450. [PubMed: 22379397]
- Geng R, Geller SF, Hayashi T, Ray C, Reh TA, Birmingham-McDonogh O, Jones SM, Wright CG, Imanishi Y, Palczewski K, Alagramam KN, Flannery JG. Usher syndrome IIIA gene *clarin-1* is essential for hair cell function and associated neural activation. *Human Mol Genet.* 2009; 18(15):2748–2760. [PubMed: 19414487]
- Gillespie PG, Muller U. Mechanotransduction by hair cells: Models, molecules and mechanisms. *Cell.* 2009; 139:33–44. [PubMed: 19804752]
- Goodyear RJ, Legan PK, Wright MB, Marcotti W, Oganessian A, Coats SA, Booth CJ, Kros CJ, Seifert RA, Bowen-Pope DF, Richardson GP. A receptor-like inositol lipid phosphatase is required for the maturation of developing cochlear hair bundles. *J Neurosci.* 2003; 23:9208–9219. [PubMed: 14534255]
- Goodyear RJ, Forge A, Legan PK, Richardson GP. Asymmetric distribution of cadherin 23 and protocadherin 15 in kinocilial links of avian sensory hair cells. *J Comp Neurol.* 2010; 518:4288–4297. [PubMed: 20853507]
- Goodyear RJ, Jones SM, Sharifi L, Forge A, Richardson GP. Hair bundle defects and loss of function in the vestibular end organs of mice lacking the receptor-like inositol lipid phosphatase PTPRQ. *J Neuroscience.* 2012; 32:2762–2772.
- Harrod CJ, Baker JF. The vestibulo-ocular reflex in otoconia deficient head tilt (het) mutant mice versus wild-type C57BL/6J mice. *Brain Res.* 2003; 972:75–83. [PubMed: 12711080]
- Hoffman LF, Hu R, Jones TA. Dendritic arbor architecture within the murine utricle. *Assoc Res Otolaryngol Abs.* 2007a; 30:#243.
- Hoffman LF, Siegeman C, Su D, Jones TA. Spatial Distribution of Utricular Hair Cell Morphologic Polarization Vectors: Role of Natural Stimuli. *Assoc Res Otolaryngol Abs.* 2007b; 30:#1210.
- Hoffman LF, Ross MD, Varelas J, Jones SM, Jones TA. Afferent synapses are present in utricular hair cells from otoconia-deficient mice. *Hear Res.* 2006; 222:35–42. [PubMed: 17023128]

- Huang L, Gitschier J. A novel gene involved in zinc transport is deficient in the lethal milk mouse. *Nat Genet.* 1997; 17:292–297. [PubMed: 9354792]
- Huang L, Kuo YM, Gitschier J. The pallid gene encodes a novel, syntaxin 13-interacting protein involved in platelet storage pool deficiency. *Nat Genet.* 1999; 23:329–332. [PubMed: 10610180]
- Hurle B, Ignatova E, Massironi SM, Mashimo T, Rios X, Thalmann I, Thalmann R, Ornitz DM. Non-syndromic vestibular disorder with otoconial agenesis in tilted/mergulhador mice caused by mutations in otopenin 1. *Hum Mol Genet.* 2003; 12:777–789. [PubMed: 12651873]
- Jen JC. Recent advances in the genetics of recurrent vertigo and vestibulopathy. *Current Opinion in Neurology.* 2008; 21:3–7. [PubMed: 18180645]
- Jen JC. Genetics of vestibulopathies. *Advances in Oto-rhino-laryngology.* 2011; 70:130–134. [PubMed: 21358195]
- Jones, SM. Vestibular sensory evoked potentials. In: Jacobson, G.; Gans, R.; Shepard, N., editors. *Balance Function Assessment and Management.* Plural Publishing; San Diego, CA: 2008. p. 379-404.
- Jones SM, Jones TA. Short latency vestibular evoked potentials in the chicken embryo. *Journal of Vestibular Research.* 1996; 6(2):71–83. [PubMed: 8925118]
- Jones SM, Erway LC, Bergstrom RA, Schimenti JC, Jones TA. Vestibular responses to linear acceleration are absent in otoconia-deficient C57BL/6J*Ei-het* mice. *Hear Res.* 1999; 135:56–60. [PubMed: 10491954]
- Jones SM, Erway LC, Yu H, Johnson KR, Jones TA. Gravity receptor function in mice with graded otoconial deficiencies. *Hear Res.* 2004; 191:34–40. [PubMed: 15109702]
- Jones SM, Johnson KR, Yu H, Erway LC, Alagramam KN, Pollak N, Jones TA. A quantitative survey of gravity receptor function in mutant mouse strains. *J Assoc Res Otolaryngol.* 2005; 6(4):297–310.
- Jones TA. Vestibular short latency responses to pulsed linear acceleration in unanesthetized animals. *Electroenceph Clin Neurophysiol.* 1992; 82:377–386. [PubMed: 1374706]
- Jones TA, Jones SM. Short latency compound action potentials from mammalian gravity receptor organs. *Hear Res.* 1999; 136:75–85. [PubMed: 10511626]
- Jones, TA.; Jones, SM. Vestibular evoked potentials. In: Burkard, RF.; Don, M.; Eggermont, JJ., editors. *Auditory Evoked Potentials: Basic Principles and Clinical Applications.* Lippincott Williams & Wilkins; Baltimore, MD: 2007. p. 622-650.(Peer reviewed)
- Jones TA, Pedersen T. Short latency vestibular responses to pulsed linear acceleration. *American Journal of Otolaryngology.* 1989; 10:327–335. [PubMed: 2817248]
- Jones TA, Jones SM, Hoffman LF. Resting Discharge Patterns of Macular Primary Afferents in Otoconia-Deficient Mice. *J Assoc Res Otolaryngol.* 2008; 9(4):490–505. [PubMed: 18661184]
- Kaga K. Vestibular compensation in infants and children with congenital and acquired vestibular loss in both ears. *Int J Ped Otorhinolaryngol.* 1999; 49:215–224.
- Keats BJ. Genes and syndromic hearing loss. *J Commun Disord.* 2002; 35:355–366. [PubMed: 12160354]
- Keats BJ, Corey DP. The usher syndromes. *Am J Med Genet.* 1999; 89:158–166. [PubMed: 10704190]
- Kitamura K, Yagi M, Yoshikawa Y, Ochidubo F, Kato M. Vestibular pathology in a new-mutant mouse. *Acta Otolaryngol Suppl.* 1991; 481:121–124. [PubMed: 1927362]
- Klockars T, Kentala E. Inheritance of Meniere's disease in the Finnish population. *Archives of Otolaryngology -- Head and Neck Surgery.* 2007; 133:73–77. [PubMed: 17224529]
- Kozel PJ, Friedman RA, Erway LC, Yamoah EN, Liu LH, Riddle T, Duffy JJ, Doetschman T, Miller ML, Cardell EL, Shull GE. Balance and hearing deficits in mice with a null mutation in the gene encoding plasma membrane Ca²⁺-ATPase isoform 2. *J Biol Chem.* 1998; 273:18693–18696. [PubMed: 9668038]
- Liebl DJ, Tessarollo L, Palko ME, Parada LF. Absence of sensory neurons before target innervation in brain-derived neurotrophic factor-, neurotrophic 3-, and TrkC deficient embryonic mice. *J Neurosci.* 1997; 17:9113–9121. [PubMed: 9364058]

- Lopez IA, Rosenblatt MI, Kim C, Galbraith GC, Jones SM, Kao L, Newman D, Liu W, Yeh S, Pushkin A, Abuladze N, Kurtz I. Slc4a11 gene disruption in mice, cellular targets of sensorineuronal abnormalities. *J Biol Chem*. 2009; 284:26882–26896. [PubMed: 19586905]
- Lord EM, Gates WH. Shaker, a new mutation in the house mouse (*mus musculus*). *American Naturalist*. 1929; 63:435–442.
- Lyon MF. Absence of otoliths in the mouse: An effect of the pallid mutant. *J Genet*. 1953; 51:638–650.
- Lyon MF, Meredith R. *Muted*, a new mutant affecting coat colour and otoliths of the mouse, and its position in linkage group XIV. *Genet Res*. 1969; 14:163–166. [PubMed: 5367369]
- Lyon, MF.; Rastan, S.; Brown, SDM. *Genetic Variants and Strains of the Laboratory Mouse*. Vol. 1 & 2. Oxford University Press; New York, NY: 1996.
- Ma Q, Anderson DJ, Fritsch B. Neurogenin 1 null mutant ears develop fewer, morphologically normal hair cells in smaller sensory epithelia devoid of innervation. *J Assoc Res Otolaryngol*. 2000; 1:129–143. [PubMed: 11545141]
- Moriyama K, Hashimoto R, Hanai A, Yoshizaki N, Yonezawa S, Otani H. Degenerative hairlets on the vestibular sensory cells in mutant bustling (BUS/Idr) mice. *Acta Otolaryngol*. 1997; 117:20–24. [PubMed: 9039475]
- Nadol JB, Merchant SN. Histopathology and molecular genetics of hearing loss in the human. *Int J Ped Otorhinolaryngol*. 2001; 61:1–15.
- Nakano Y, Longo-Guess CM, Bergstrom DE, Nauseef WM, Jones SM, Bánfi B. Mutation of the *Cyba* gene encoding p22^{phox} causes vestibular and immune defects in mice. *J Clin Invest*. 2008; 118:1176–1185. [PubMed: 18292807]
- Nakaya K, Harbidge DG, Wangemann P, Schultz BD, Green ED, Wall SM, Marcus DC. Lack of pendrin HCO₃⁻ transport elevates vestibular endolymphatic [Ca²⁺] by inhibition of acid-sensitive TRPV5 and TRPV6 channels. *Am J Physiol Renal Physiol*. 2007; 292:F1314–1321. [PubMed: 17200157]
- Nayak GD, Ratnayaka HS, Goodyear RJ, Richardson GP. Development of the hair bundle and mechanotransduction. *Int J Devel Biol*. 2007; 51:597–608. [PubMed: 17891720]
- Nazareth AM, Jones TA. Central and peripheral components of short latency vestibular evoked potentials. *J Vestib Res*. 1998; 8(3):233–252. [PubMed: 9626650]
- Oganesian A, Poot M, Daum G, Coats SA, Wright MB, Seifert RA, Bowen-Pope DF. Protein tyrosine phosphatase RQ is a phosphatidylinositol phosphatase that can regulate cell survival and proliferation. *Proc Natl Acad Sci U S A*. 2003; 100:7563–7568. [PubMed: 12802008]
- Ornitz DM, Bohne B, Thalmann I, Harding GW, Thalmann R. Otoconia agenesis in tilted mutant mice. *Hear Res*. 1998; 112:60–70. [PubMed: 9714575]
- Otani H, Moriyama K, Yonezawa S, Shoji R, Tanaka O. Vestibulocochlear defects and effects of deuterium oxide in mutant bustling (BUS) mice. *Acta Otolaryngologica Supplement*. 1995; 519:286–293.
- Paffenholz R, Bergstrom RA, Pasutto F, Wabnitz P, Munroe RJ, Jagla W, Heinzmann U, Marquardt A, Bareiss A, Laufs J, Russ A, Stumm G, Schimenti JC, Bergstrom DE. Vestibular defects in head-tilt mice result from mutations in *Nox3*, encoding an NADPH oxidase. *Genes Dev*. 2004; 18:486–491. [PubMed: 15014044]
- Park M, Li Q, Shcheynikov N, Zeng W, Muallem S. NaBC1 is a ubiquitous electrogenic Na⁺-coupled borate transporter essential for cellular boron homeostasis and cell growth and proliferation. *Molecular Cell*. 2004; 16:331–341. [PubMed: 15525507]
- Petersen MB. Non-syndromic autosomal-dominant deafness. *Clin Genet*. 2002; 62:1–13. [PubMed: 12123480]
- Petit C. Usher syndrome: from genetics to pathogenesis. *Ann Rev Genomics Hum Genet*. 2001; 2:271–297. [PubMed: 11701652]
- Petit C, Levilliers J, Hardelin JP. Molecular genetics of hearing loss. *Ann Rev Genet*. 2001; 35:589–646. [PubMed: 11700295]
- Pierce, J. PhD Dissertation. Dept. Communication Sciences & Disorders, East Carolina University; 2012. Structural aging of the utricular macula in mice.

- Rauch TM. The additive effects of two mutant genes on otolith formation in mice: An animal model to assess otolith function. *J Aud Res.* 1979; 19:259–265. [PubMed: 262462]
- Rine RM, Cornwall G, Gan K, LoCascio C, O'Hare T, Robinson E, Rice M. Evidence of progressive delay of motor development in children with sensorineural hearing loss and concurrent vestibular dysfunction. *Perc Motor Skills.* 2000; 90:1101–1112.
- Robertson NG, Jones SM, Sivakumaran TA, Giersch ABS, Jurado SA, Call LM, Miller CE, Maison SF, Liberman MC, Morton CC. A targeted *Coch* missense mutation: A knock-in mouse model for DFNA9 late-onset hearing loss and vestibular dysfunction. *Human Mol Genet.* 2008; 17(21): 3426–3434. [PubMed: 18697796]
- Roux I, Safieddine S, Nouvian R, Grati M, Simmler MC, et al. Petit C. Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. *Cell.* 2006; 127:277–289. [PubMed: 17055430]
- Ruben RJ. The history of the genetics of hearing impairment. *Ann New York Acad Sci.* 1991; 630:6–15. [PubMed: 1952624]
- Schraders M, Oostrik J, Huygen PL, Strom TM, van Wijk E, Kunst HP, Hoefsloot LH, Cremers CW, Admiraal RJ, Kremer H. Mutations in *PTPRQ* are a cause of autosomal-recessive nonsyndromic hearing impairment DFNB84 and associated with vestibular dysfunction. *Am J Hum Genet.* 2010; 86:604–610. [PubMed: 20346435]
- Schug N, Braig C, Zimmermann U, Engel J, Winter H, Ruth P, Blin N, Pfister M, Kalbacher H, Knipper M. Differential expression of otoferlin in brain, vestibular system, immature and mature cochlea of the rat. *Eur J Neurosci.* 2006; 24:3372–3380. [PubMed: 17229086]
- Schwander M, Scaniecka A, Grillet N, Bailey JS, Avenarius M, Najmabadi H, Steffy BM, Federe GC, Lagler EA, Banan R, Hice R, Grabowski-Boase L, Keithley EM, Ryan AF, Housley GD, Wiltshire T, Smith RJ, Tarantino LM, Muller U. A forward genetics screen in mice identifies recessive deafness traits and reveals that *pejvakin* is essential for outer hair cell function. *J Neurosci.* 2007; 27:2163–2175. [PubMed: 17329413]
- Shahin H, Rahil M, Abu Rayan A, Avraham KB, King MC, Kanaan M, Walsh T. Nonsense mutation of the stereociliar membrane protein gene *PTPRQ* in human hearing loss DFNB84. *J Med Genet.* 2010; 47:643–645. [PubMed: 20472657]
- Shinjo Y, Jin Y, Kaga K. Assessment of vestibular function of infants and children with congenital and acquired deafness using the ice-water caloric test, rotational chair test and vestibular-evoked myogenic potential recording. *Acta Otolaryngol.* 2007; 127:736–747. [PubMed: 17573570]
- Sjostrom B, Anniko M. Morphologically specific vestibular hair cell degeneration in the jerker mouse mutant. *Eur Arch Oto-Rhino-Laryngol.* 1990; 247:51–55.
- Stahl JS, James RA, Oommen BS, Hoebeek FE, De Zeeuw CI. Eye movements of the murine P/Q calcium channel mutant tottering, and the impact of aging. *J Neurophys.* 2006; 95(3):1588–1607.
- Stahl JS, van Alphen AM, De Zeeuw CI. A comparison of video and magnetic search coil recordings of mouse eye movements. *J Neurosci Meth.* 2000; 99(1–2):101–110.
- Steel K. Similarities between mice and humans with hereditary deafness. *Ann New York Acad Sci.* 1991; 630:68–79. [PubMed: 1952625]
- Steel KP. Inherited hearing defects in mice. *Ann Rev Genet.* 1995; 29:675–701. [PubMed: 8825490]
- Steel KP, Brown SD. Genes and deafness. *Trends in Genet.* 1994; 10:428–435. [PubMed: 7871592]
- Sun JC, van Alphen AM, Waagenar M, et al. The origin of vestibular dysfunction in Usher syndrome type 1B. *Neurobiol Disease.* 2001; 8(1):69–77.
- Takiguchi T, Honda M, Kaga K, Myokai K, Ogawa T, Goto S. Results of damped-rotation tests in brain damaged infants and children. *Acta Otolaryngol Suppl.* 1991; 481:536–542. [PubMed: 1927464]
- Toriello, HV.; Reardon, W.; Gorlin, RJ. Hereditary hearing loss and its syndromes. Oxford University Press; 2004.
- Tribukait A, Brantberg K, Bergenius J. Function of semicircular canals, utricles and saccules in deaf children. *Acta Otolaryngol.* 2004; 124:41–48. [PubMed: 14977077]
- Trune DR, Lim DJ. A morphometric study of the pallid mutant mouse inner ear. *Am J Otolaryngol.* 1983; 4:261–272. [PubMed: 6605096]

- Tsuzuku T, Kaga K. Delayed motor function and results of vestibular function tests in children with inner ear anomalies. *Int J Ped Otorhinolaryngol*. 1992; 23:261–268.
- van Alphen AM, Stahl JS, De Zeeuw CI. The dynamic characteristics of the mouse horizontal vestibulo-ocular and optokinetic response. *Brain Res*. 2001; 890(2):296–305. [PubMed: 11164796]
- Webb SW, Grillet N, Andrade LR, Xiong W, Swarthout L, Della Santina CC, Kachar B, Muller U. Regulation of PCDH15 function in mechanosensory hair cells by alternative splicing of the cytoplasmic domain. *Development*. 2011; 138:1607–1617. [PubMed: 21427143]
- Wenngren BI, Anniko M. Vestibular hair cell pathology in the dancer mouse mutant. *Acta Otolaryngol*. 1989; 107:182–190. [PubMed: 2784612]
- Yasunaga S, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, El-Zir E, Loiselet J, Petit C. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. *Nat Genet*. 1999; 21:363–369. [PubMed: 10192385]
- Yerkes, RM. *The Dancing Mouse: A Study in Animal Behavior*. Macmillan Co; New York, NY: 1907. The Animals Behavior Series 1
- Zdebik AA, Wangemann P, Jentsch TJ. Potassium ion movement in the inner ear: Insights from genetic disease and mouse models. *Physiology*. 2009; 24:307–316. [PubMed: 19815857]
- Zhao X, Yang H, Yamoah EN, Lundberg YW. Gene targeting reveals the role of Oc90 as the essential organizer of the otoconial organic matrix. *Dev Biol*. 2007; 304(2):508–524. [PubMed: 17300776]
- Zhao X, Jones SM, Yamoah EN, Lundberg YW. Otoconin-90 deletion leads to imbalance but normal hearing: A comparison with other otoconia mutants. *Neuroscience*. 2008; 153(1):289–299. [PubMed: 18355969]
- Zhou G, Kenna MA, Stevens K, et al. Assessment of saccular function in children with sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg*. 2009; 135:40–44. [PubMed: 19153306]

Figure 1.

Photomicrographs (left) of a section through the utricle of one normal mouse (C57BL/6J) and one mutant mouse B6Ei.GL-*Nox3*^{het}/J. The normal mouse exhibits darkly stained otoconial matrix (arrows), while the *Nox3* mutant mouse does not possess any stained otoconial matrix (arrows). On the right are representative auditory brainstem responses (ABR) and vestibular evoked potentials (VsEP) for the two mouse strains. Both strains exhibit normal auditory function as measured by ABR. Normal mice exhibit robust VsEPs. The *Nox3* mice with complete loss of otoconia have absent VsEPs. From Hearing Research, 135, Jones SM, Erway LC, Bergstrom RA, Schimenti JC, Jones TA. Vestibular responses to linear acceleration are absent in otoconia-deficient C57BL/6JEi-*het* mice, 56–60, 1999, with permission from Elsevier.

Figure 2.

Representative VsEP waveforms recorded at the maximum stimulus level (+6 dB re: 1.0 g/ms) for nine *P1prq*^{+/-} and nine *P1prq*^{-/-} mice (A). Most *P1prq*^{+/-} mice show robust responses; however, a few show reduced amplitudes. *P1prq*^{-/-} mice have variable function with several showing absent VsEPs or VsEPs with reduced amplitudes, prolonged latencies, and elevated thresholds. From Goodyear et al., (2012).

Figure 3.

Mutations in *clarin1* are responsible for Usher Type 3 syndrome characterized by profound hearing loss, blindness, and variable vestibular function. VsEPs in *Cln1* mouse strain show VsEPs with significantly prolonged latencies, reduced amplitudes, and elevated thresholds. From Geng R, Geller SF, Hayashi T, Ray C, Reh TA, Bermingham-McDonogh O, Jones SM, Wright CG, Imanishi Y, Palczewski K, Alagramam KN, Flannery JG. Usher syndrome IIIA gene *clarin-1* is essential for hair cell function and associated neural activation. *Human Mol. Genet.*, 2009, 18(15), 2756 with permission of Oxford University Press.

Figure 4.

Otoferlin, a membrane bound protein found in association with the synaptic ribbon, is essential for normal exocytosis and synaptic transmission between the sensory hair cell and the primary afferent neurons. Otoferlin mutations result in profound hearing loss. Otoferlin has also been shown to be critical for vestibular type I hair cells, but vestibular function is not completely lost. *Otof* mutant mice show altered latency-intensity and amplitude-intensity functions. From Dulon et al., (2009).

Figure 5.

Slc4a11 mutations cause Harboyan Syndrome. VsEPs in *Slc4a11* mutant mice show dramatically altered waveform morphology with large broad response peaks, and prolonged latencies. VsEP thresholds are unaffected. ABR waveforms (not shown) also show prolonged latencies. This research was originally published in the *Journal of Biological Chemistry*. Lopez IA, Rosenblatt MI, Kim C, Galbraith GC, Jones SM, Kao L, Newman D, Liu W, Yeh S, Pushkin A, Abuladze N, Kurtz I. *Slc4a11* gene disruption in mice, cellular targets of sensorineuronal abnormalities. *Journal of Biological Chemistry*. 2009; 284: 26882–26896. © the American Society for Biochemistry and Molecular Biology.

Table 1

Genes discussed in the text that have strong evidence for peripheral vestibular dysfunction. Most of these genes are known to cause significant hearing impairment in humans as indicated by the human disorders listed. The peripheral vestibular involvement represents evidence from human or mouse studies as indicated.

Gene	Protein	Human Disorder	Peripheral Vestibular Involvement
MYO7A	Myosin 7A	Usher Type 1B	Yes (human and mouse)
USH1C	Harmonin	Usher Type 1C	Yes (human and mouse)
CDH23	Cadherin 23	Usher Type 1D	Yes (human and mouse)
PCDH15	Protocadherin 15	Usher Type 1F	Yes (human and mouse)
USH2A	Usherin	Usher Type 2A	No (human)
CLRN1	Clarin 1	Usher Type 3A	Variable (human and mouse)
COCH	Cochlin	DFNA9	Variable (human and mouse)
KCNA1	Potassium voltage-gated channel subfamily A member 1	Episodic Ataxia Type1	Unknown
CACNA1A	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	Episodic Ataxia Type2 Spinocerebellar Ataxia	Unknown
NOX3	NADPH oxidase 3		Yes (mouse)
OTOP1	Otopettrin 1		Yes (mouse)
SLC30A4	Zinc transporter 4		Yes (mouse)
CYBA	Cytochrome b-245 light chain (p22-phox)	Chronic Granulomatosis Disease	Yes (mouse)
PLDN (BLOC1S6)	Biogenesis of lysosome-related organelles complex 1 subunit 6	Hermansky Pudlak Syndrome 9	Yes (mouse)
PTPRQ	Phosphatidylinositol phosphatase PTPRQ	DFNB84	Yes (mouse)
OTOF	Otoferlin	DFNB9	Yes (mouse)
SLC4A11	Sodium bicarbonate transporter-like protein 11	Corneal Endothelial Dystrophy Type 2; Harboyan Syndrome; Corneal Dystrophy and Perceptive Deafness	Yes (mouse) Nystagmus reported (human)

Information from Online Mendelian Inheritance in Man (www.omim.org), UniProt (www.uniprot.org), HUGO Gene Nomenclature Committee (www.genenames.org), and references cited throughout the text.