Published in final edited form as:

Curr Opin Otolaryngol Head Neck Surg. 2011 October ; 19(5): 397–402. doi:10.1097/MOO.0b013e32834a9852.

Genetic disorders of the vestibular system

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Abstract

Purpose of review—This review highlights the current body of literature related to the genetics of inherited vestibular disorders and provides a framework for the characterization of these disorders. We emphasize peripheral causes of vestibular dysfunction and highlight recent advances in the field, point out gaps in understanding, and focus on key areas for future investigation.

Recent findings—The discovery of a modifier gene that leads to a more severe Usher syndrome phenotype calls into question the assumption that Usher syndrome is universally a monogenic disorder. Despite the use of several investigational approaches, the genetic basis of Menière's disease remains poorly understood. Evidence for a vestibular phenotype associated with DFNB1 suggests that mutations in other genes causally related to nonsyndromic hearing loss also may have an unrecognized vestibular phenotype.

Summary—Our understanding of the genetic basis for vestibular disorders is superficial. Significant challenges include defining the genetics of inherited isolated vestibular dysfunction and understanding the pathological basis of Menière's disease. However, improved characterization of inherited vestibular dysfunction, coupled with advanced genetic techniques such as targeted genome capture and massively parallel sequencing, provides an opportunity to investigate these diseases at the genetic level.

Keywords

genetics; Menière's disease; Usher syndrome; vertigo; vestibular dysfunction

Introduction

Dizziness is a common complaint in the elderly, with an estimated lifetime prevalence of 30% in persons over the age of 60 [1]. Vertigo, the perceived sensation that oneself or one's surroundings are in motion, is also common, with a lifetime prevalence of 7.4% in the adult

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Conflicts of interest There are no conflicts of interest.

population [2]. Not only is vertigo common but it is debilitating – most cases of vertigo are recurrent (88%) and cause severe impairment by disrupting work or daily activities [3]. Vertigo is also associated with a poorer health-related quality of life and places a significant burden on the healthcare system [3]. For example, in a study of emergency room visits between 1995 and 2004, dizziness resulted in 26 million visits and an average of 3.6 diagnostic tests per patient, including cranial computed tomography (CT) or MRI in 17% of cases [4]. Vertigo in the elderly also increases the risk of falling, which can result in considerable morbidity, including hip fracture and cerebral hemorrhage. In one study, 90% of hip fractures in the elderly were secondary to falls, and in that patient group there was a higher incidence of abnormal vestibuloocular reflex testing (89% in the hip fracture group compared with 62% in the nonhip fracture group) [5].

The objective of this review is to characterize disorders of the vestibular system and to summarize recent advances in our understanding of the genetic basis of inherited disorders of the vestibular system. The last two decades have seen major advancements in our understanding of the genetics of nonsyndromic deafness: allele variants in over 60 genes have been causally linked to this phenotype. By comparison, relatively little is known about the genetics of vestibular disorders, a disparity that reflects the challenges involved in the diagnosis of vertigo, which can often be based on subjective symptoms rather than objective findings. In the absence of other associated findings, it can therefore be difficult to track inheritance patterns, making rigorous genetic studies problematic.

Central versus peripheral vestibular disorders

The sensory end organs responsible for balance in humans include the three paired semicircular canals, which sense angular acceleration, and the saccule and utricle, which sense linear acceleration. These structures send afferent signals via the vestibular nerve to the cerebellum and higher cortical processing centers. Vertigo is caused by aberrant excitation of any part of this pathway and may be central or peripheral in origin. Peripheral vertigo involves the vestibular end organs or the vestibular nerve; central vertigo involves the cerebellum or cerebral cortex. This simplistic classification does not fit all vestibular disorders, as the causative lesions for some disorders have not yet been identified. However, for simplicity we have developed a general characterization for vestibular disorders, which is shown in Fig. 1. As otolaryngologists are primarily responsible for treatment of peripheral vertigo, it will be the focus of this review.

Central vestibular disorders

Central vestibular disorders may be acquired or genetic. Acquired central vestibular disorders can result from cerebellar pathology, such as infarction in the posterior inferior cerebellar artery distribution or a mass lesion. Genetic central vestibular disorders include: the familial episodic ataxia syndromes; migraine-associated vertigo; and vertigo, migraine and essential tremor syndrome. This review will focus on peripheral vestibular disorders; however, refer to Jen [6] for a more detailed review of central disorders.

Peripheral vestibular disorders

Peripheral vestibular disorders may be acquired or genetic. We will define acquired disorders as those not present until adulthood and without clear family history. Genetic causes are generally congenital and have a positive family history.

Acquired peripheral vestibular disorders

These include benign paroxysmal positional vertigo and vestibular neuronitis, among others. No genetic association has been described with these disorders, suggesting that they are likely acquired.

Genetic peripheral vestibular disorders with associated hearing loss

Genetic peripheral vestibular disorders can occur in isolation or in association with hearing loss. Those with associated hearing loss include Menière's disease, DFNA9, and Usher syndrome. Isolated genetic vestibular disorders are rare; however, several families have been identified. Each of these disorders will be considered in turn.

Menière's disease—Menière's disease is a peripheral vestibular disorder characterized by the diagnostic triad of fluctuating hearing loss, vertigo, and tinnitus. The pathophysiology is poorly understood, and, while several theories have been proposed, including endolymphatic hydrops, auto-immune, viral and allergic, none has gained acceptance. Most cases of Menière's disease are sporadic, although, with a careful history, 7–15% of affected persons will report other family members with similar symptoms, suggesting autosomal dominant inheritance with incomplete penetrance [7,8]. Further evidence supporting a genetic basis for Menière's disease is its high prevalence in the Caucasian population (1–2 per 1000) [9]. Early investigations into the causes of Menière's disease focused on autoimmunity and sought to identify human leukocyte antigen (HLA) associations, and, although many have been proposed, none has been proven [10,11]. A recent study examined the effect of circulating immune complexes, based on the hypothesis that impaired clearance of these complexes by innate immune cell receptors may be important in Menière's disease; however, a case-control study showed no association between polymorphisms in these receptors or levels of circulating immune complexes and Menière's disease [12*].

Other investigations have focused on inner ear homeostasis in the endolymphatic sac using a candidate gene approach. In this approach, genes hypothesized to be involved in Menière's disease are screened in affected individuals. Several studies have focused on aquaporin, a transmembrane protein expressed in the endolymphatic sac that transports water and other solutes through the cell membrane. Two studies searched for mutations in several aquaporin genes, *AQP1–AQP4*, in affected individuals; however, no causative mutations were identified [13,14]. Investigations into the genes *KCNE1* and *KCNE3*, two voltage-gated potassium channels expressed in the inner ear, have been similarly inconclusive: Doi *et al.* [15] found that single nucleotide polymorphisms (SNPs) in *KCNE1* and *KCNE3* are associated with Menière's disease in the Japanese population, whereas Campbell *et al.* [16] found no association in the Caucasian population and could not duplicate the Doi results. Two studies have shown associations with Menière's disease and SNPs: one variation in

heat shock protein *HSP70-1*, which is thought to be involved in the cellular stress response [17]; and another variation which causes elevated activity of Na,K-ATPase [18]. Neither of these associations has been corroborated.

Another approach that has been applied to the study of Menière's disease is linkage analysis, which relies on evaluation of genomic markers to identify the region of the genome that segregates with the disease. This approach was used in a large Swedish family to define a linkage interval on chromosome 12p12.3 [19]. Although the same investigators subsequently refined the region to 1.48 Mb and screened two candidate genes (*RERGL* and *PIK3C2G*), the Menière's disease gene on chromosome 12 has yet to be found [20*].

Most exciting has been our recent finding identifying the first Menière's disease gene by using two complementary human genetic approaches – segregation analysis and rare-variant detection – in an exceptionally well characterized Menière's disease cohort (Smith *et al.*, unpublished data). This advance provides a genetic inroad to understanding the pathophysiology of Menière's disease at the molecular and mechanistic level, and may lead to targeted treatment for this disease.

DFNA9—DFNA9 is a type of autosomal dominant nonsyndromic (DFNA) hearing loss (ninth locus to be mapped). The causative gene is *COCH* and, although some persons with *COCH* mutations have nonsyndromic hearing loss, many also have an associated vestibulopathy that shares some features with Menière's disease, including vertigo, tinnitus, aural fullness, and hearing loss [21]. On the basis of these similarities, *COCH* has been screened in a large number of Menière's disease patients of different ethnicities but no associations have been found [22–24]. DFNA9 and Menière's disease are now considered separate entities: DFNA9 is characterized by early-onset high-frequency hearing loss and vertigo, both of which progress to severe impairment, whereas the hearing loss and vertigo of Menière's disease are late onset and low frequency [25*].

The Usher syndromes—The Usher syndromes (USH) are a heterogeneous group of autosomal recessive disorders characterized by congenital hearing loss, retinitis pigmentosa, and vestibular dysfunction. To date 10 Usher syndrome genes (including one modifier gene) have been identified (Table 1) [26*]. We will focus on Usher syndrome type 1 (USH1) and type 3 (USH3) as these Usher types have associated vestibulopathy. For a comprehensive review of the genetics of the Usher syndromes refer to Yan *et al.* [27*].

USH1 accounts for 30–40% of Usher syndrome and is divided into subtypes USH1B–USH1H based on the causative gene (Table 1) [27*]. USH1 is also associated with the most severe phenotype: affected persons have congenital, bilateral, profound sensorineural hearing loss (SNHL) and vestibular areflexia, and develop prepubertal blindness secondary to retinitis pigmentosa. The complete vestibular areflexia generally manifests in the first year of life, as affected infants generally do not walk until after 18 months of age [28]. As children, they demonstrate poor coordination and have difficulty with activities requiring balance, such as riding a bicycle [29].

The most common form of USH1 is USH1B (about 50% of cases), which is caused by mutations in *MYO7A*. Mutation of *MYO7A* can result in the classic USH1 phenotype (congenital deafness, vestibular areflexia, and blindness), atypical Usher syndrome (progressive hearing loss with variable vestibular dysfunction), and both recessive (DFNB2) and dominant (DFNA11) non-syndromic hearing loss [27*,30]. It is noteworthy that mutations in three other USH1 genes (*USH1C*, *CDH23*, and *PCDH15*) can also cause either an USH1 phenotype or only nonsyndromic hearing loss [31]. In addition, genotype/phenotype studies have shown that nontruncating mutations (missense mutations) in *CDH23* carry a less severe phenotype as compared with truncating mutations (frameshift and stop) [32].

USH3, which accounts for 2–4% of Usher syndrome cases, is associated with variable degrees of sensorineural hearing loss, retinitis pigmentosa, and vestibular dysfunction. In a cohort of 22 individuals with USH3, Sadeghi *et al.* [33] demonstrated that 45% had caloric hypofunction or vestibular areflexia, whereas 55% had normal vestibular function. Furthermore, 36% of the cohort who walked before 16 months of age subsequently demonstrated a variable amount of vestibular dysfunction, suggesting the progressive nature of vestibulopathy associated with USH3. The USH3 locus is located on chromosome 3q21–25, which encodes the *USH3A* gene. Similarly to USH1, there is considerable genetic and phenotypic heterogeneity in USH3. Mutations in *USH3* can result in both syndromic and nonsyndromic phenotypes with isolated retinitis pigmentosa [34*]. Protein expression of USH3A is complex as multiple alternative splice variants exist, which contribute to the diverse phenotypic variability associated with USH3 mutations [35*].

In addition to the nine genes that have been shown to cause various Usher syndrome subtypes, one modifier gene has been discovered. The gene *PDZD7*, when mutated in conjunction with another Usher syndrome gene, has been shown to cause both a more severe phenotype and an accelerated onset of retinitis pigmentosa [36*]. This finding challenges the assumption that Usher syndrome is a monogenetic disease with a strict Mendelian inheritance. It is likely that more modifier genes will be discovered to explain the heterogeneity in the vestibular phenotypes of Usher syndrome.

Others—Mutations in the genes *GJB2* and *GJB6*, located at the DFNB1 locus, are the most common cause of autosomal recessive nonsyndromic hearing loss. Classically, *GJB2* mutations are considered to result in a hearing-loss phenotype without vestibular dysfunction. However, Dodson *et al.* [37*] recently reported that 127 of 235 persons with DFNB1-related hearing loss (54%) had vestibular dysfunction based on survey responses (response rate, 235 of 515), which was significantly higher than non-DFNB1 deaf controls. These results suggest that objective testing of vestibular function should be completed in a large genotyped deaf cohort to determine whether vestibular dysfunction is a common but unrecognized component of nonsyndromic deafness.

Peripheral vestibular disorders without associated hearing loss

Several families have been identified that segregate vestibular dysfunction with normal hearing (non-syndromic vestibular dysfunction) [38]. In one family, an autosomal recessive inheritance pattern is suggested; however, no causative gene has been identified.

Genetic testing

For the vestibular disorders for which causative genes are known (i.e., USH, DFNA9), genetic testing is often available, although the indications for ordering this testing are not driven by the vestibular pathology. For example, genetic testing is of particular importance to confirm the diagnosis of Usher syndrome before retinal findings are clinically apparent. This push is made because early genetic diagnosis may afford families the ability to delay the onset of retinitis pigmentosa by using sunglasses [39].

Conclusion

Recent advances in high throughput sequencing coupled with comprehensive genomic sequence analysis should make it possible to identify genes causally related to nonsyndromic vestibular dysfunction. Discovering these genes will provide a foundation to understand peripheral vestibular disorders at a molecular level. With this knowledge will come the promise of new therapies for vertigo and dizziness that will help to alleviate the burden associated with vestibular dysfunction.

Acknowledgements

RJHS receives funding from the American Otologic Society and the National Institute on Deafness and Other Communication Disorders (NIDCD) grant DC002842. Authors thank Allan Arkush, PhD, Professor of Judaic Studies and History at Binghamton University, who assisted with Hebrew translation.

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Key points

- A recently discovered ‘modifier’ gene leads to a more severe Usher syndrome phenotype and explains some of the phenotypic heterogeneity associated with this disorder.
- Objective studies are needed to determine whether many nonsyndromic causes of hearing loss (such as mutations in *GJB2*) are also associated with vestibular dysfunction.
- Recent technological advances in sequencing and sequence analysis will make it possible to identify genes for nonsyndromic vestibular dysfunction.

Figure 1. Classification of vestibular disorders

This simplistic classification may not fit all vestibular disorders, as the causative lesions for some disorders have yet to be identified. BPPV, benign paroxysmal positional vertigo.

Table 1

Molecular classification of Usher syndrome

Locus	Location	Gene	Protein	Function
USH1A	(14q32)	Nonexistent	None	None
USH1B	11q13.5	<i>MYO7A</i>	Myosin VIIa	Motor protein
USH1C	11p15.1	<i>USH1C</i>	Harmonin	Scaffold protein
USH1D	10q22.1	<i>CDH23</i>	Cadherin 23	Cell adhesion protein
USH1E	21q21	Unknown	Unknown	Unknown
USH1F	10q21–22	<i>PCDH15</i>	Protocadherin 15	Cell adhesion protein
USH1G	17q24–25	<i>SANS</i>	SANS	Scaffold protein
USH1H	15q22–23	Unknown	Unknown	Unknown
USH2A	1q41	<i>USH2A</i>	Usherin	Transmembrane protein
USH2B	3p23–24.2	Unknown	Unknown	Unknown
USH2C	5q14.3-q21.3	<i>VLGR1</i>	VLGR1	Transmembrane receptor protein
USH2D	9q32	<i>WHRN</i>	Whirlin	Scaffold protein
USH3	3q21-q25	<i>USH3A</i>	Claritin-1	Transmembrane protein
Modifier	10q24.31	<i>PDZD7</i>	PDZD7	Scaffold protein

Adapted from [25••,26••].