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REVIEW

Genetic contribution to vestibular diseases

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Abstract
Growing evidence supports the contribution of allelic variation to vestibular disorders. Heritability attributed to rare allelic variants is found in familial vestibular syndromes such as enlarged vestibular aqueduct syndrome or familial Meniere disease. However, the involvement of common allelic variants as key regulators of physiological processes in common and rare vestibular diseases is starting to be deciphered, including motion sickness or sporadic Meniere disease. The genetic contribution to most of the vestibular disorders is still largely unknown. This review will outline the role of common and rare variants in human genome to episodic vestibular syndromes, progressive vestibular syndrome, and hereditary sensorineural hearing loss associated with vestibular phenotype. Future genomic studies and network analyses of omic data will clarify the pathway towards a personalized stratification of treatments.

Keywords Dizziness · Vestibular disorders · Genetics · Meniere disease · Vestibular migraine

Phenotype heterogeneity in vestibular diseases

Vestibular disorders include a group of inner ear diseases involving the posterior labyrinth, but also the connections between the labyrinth and the brainstem. Vertigo, dizziness, and unsteadiness are the main symptoms of vestibular disorders, although other symptoms like oscillopsia could also be present in these patients. The clinical phenotype can vary not only according to the type of symptoms, but also to the age of onset, the progression of disease symptoms, and the association with other comorbidities. The lack of biomarkers implies that the diagnosis of these disorders relies on clinical criteria; however, some patients present overlapping symptoms and the clinical diagnosis is not clear [1, 2].

The Bárány Society has promoted an International Classification of Vestibular Disorders that includes three main syndromes: acute vestibular syndrome, episodic vestibular syndrome, and chronic vestibular syndrome [3].

The role of inheritance in vestibular disorders has growing evidence [4, 5] and it is supported by epidemiological studies, including the familiar aggregation described for some diseases and a higher prevalence in some ethnical groups [6]. Familial vestibular disorders segregate according to a Mendelian inheritance pattern, but incomplete penetrance is observed [7]. Therefore, some individuals present the vestibular phenotype, while others do not exhibit it, even though they carry identical mutant alleles.

Vestibular disorders are also characterized by variable expressivity. This means that individuals with the same genotype can also show different degrees of the same phenotype. Recent discoveries on vestibular disorder genetics show difficulties linking common or rare variants with the severity of symptoms, since regulatory variants and epigenetic modifications can contribute significantly to phenotype variation [7].

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Episodic vestibular syndromes

The clinical presentation of vestibular disorders usually occurs in the form of episodes of vertigo or dizziness and they are characterized by complete or partial restoration of the vestibular function after each attack. Motion sickness (MoS) and vestibular migraine (VM) are the most common vestibular disorders, and both of them seem to have a potential genetic component [5, 6].

Epidemiological and clinical data suggest that the episodic vestibular syndrome could be associated with hearing loss and/or migraine and it should be considered as a clinical spectrum ranging from bilateral Meniere's disease (MD; extreme phenotype with hearing loss associated with rare variants in families) to migraine without aura (mild phenotype associated with hundreds of rare and common variants). Therefore, several intermediate phenotypes could be considered such us unilateral MD, VM, or migraine with aura; and they would form a continuum of symptoms able to explain the variable expressivity (Fig. 1).

Motion sickness

Motion sickness is a very common disorder characterized by dizziness, nausea, and vomiting, and other autonomic symptoms that appear in specific situations where there is a sensory mismatch between the subjective expected vertical and the sensed vertical. When using mean of transport, but also in virtual reality condition and simulators, a conflict between visuo-vestibular, canal–otolith, and utricle–saccule inputs may arise. MoS is not a primarily vestibular disorder; it is the result of a combined transient mismatch of vestibular and visual information with vagal dysfunction. However, the causes of this condition are not well understood, and a high heritability is observed.

A large genome-wide association study (GWAS) conducted in 80,494 individuals with MoS found 35 single-nucleotide variants (SNVs) associated [8]. A few associated SNVs are located in genes involved in eye and ear development or in the synthesis of otoliths. Several other associated SNVs are located near genes involved in neurological processes including synapse development and function. However, other associated SNVs are in regions involved in glucose and insulin homeostasis, and hypoxia, suggesting a role of glucose levels and a potential relationship between MoS and hypoxia.

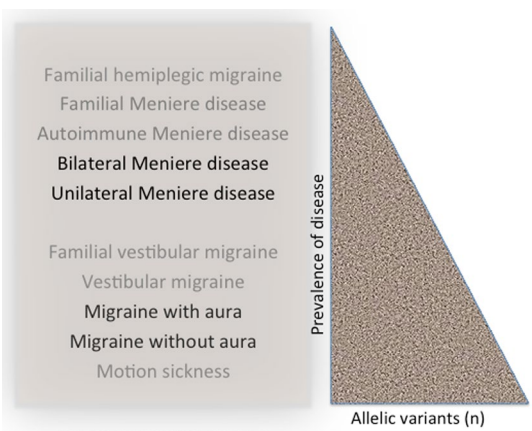

Fig. 1 Episodic vestibular syndrome (EVS) model. Disorders are ranked according to their prevalence. The number of allelic variants (or genes) involved in each disorder is associated with its prevalence. Therefore, rare diseases such as familial Meniere disease are associated with few genes and motion sickness will be associated with hundred of genes. This model aims to explain clinical heterogeneity found in the EVS based on the combined additive effect of genetic and epigenetic variation with different environmental triggers. Vestibular migraine and MD are defined by a set of core symptoms (complete phenotype). Some individuals may have only some of these symptoms (incomplete phenotype), although others may share diagnostic criteria for both disorders (overlap phenotype)

Vestibular migraine

Vestibular migraine is a common disorder that occurs in patients with the previous or current history of migraine who experience recurrent episodes of vestibular symptoms with migrainous features during these attacks. Although VM is underdiagnosed, it is considered the second most common cause of episodic vertigo after benign paroxysmal positional vertigo. The pathophysiology of VM is poorly understood and several hypotheses have been proposed [9]. There is no biological marker for VM, so the diagnosis is made on the basis of the clinical history according to clinical diagnostic criteria [10].

Familial occurrence of VM supports the hypothesis of heritability with an autosomal dominant inheritance pattern and incomplete penetrance [11]. Nevertheless, although GWAS have revealed linkage to chromosome 5q35, 11q, and 22q12, no candidate gene has been validated. Mutations in the CACNA1A gene, which encodes the central pore-forming subunit of the voltage-gated CaV2.1 (P/Q-type) calcium channels, cause three neurological calcium channelopathies: episodic ataxia type 2, familial hemiplegic migraine type 1, and spinocerebellar ataxia type 6 [6]; however, its relationship to VM has not been demonstrated.

Progressive vestibular syndromes

This category includes diseases with a progressive loss of vestibular function, which might be affected by the genetic background.

Vestibular schwannoma

Vestibular schwannomas (VS) are slow-growing benign Schwann cell tumors that initiate along the vestibulocochlear nerve, usually from the vestibular part. Common symptoms of VS are hearing loss, tinnitus, dizziness, and facial paresthesia. Depending on whether it affects one or both vestibulocochlear nerves, VS are classified into unilateral or bilateral VS, respectively. The most common form of VS affects only one vestibulocochlear nerve, representing about 95% of cases. Few rare cases develop bilateral VS, commonly linked to neurofibromatosis type 2 (*NF2*), a known autosomal dominant disease caused by mutations in the *NF2* gene [12].

Moreover, the microRNA miR-1 seems to affect to the development of the tumor growth by regulating cell proliferation and apoptosis on tumor cells, and it could be considered as a new therapeutic target for VS [13]. A whole-exome sequencing (WES) study on 46 sporadic unilateral VS cases shows that VS exhibit large heterogeneity; however, variants in *NF2* gene were detected in a large number of cases. Most of the rare variants were found in axonal guidance pathway genes, and *CDC27* and *USP8* genes were considered as novel oncogenic candidates [14].

Enlarged vestibular aqueduct syndrome

The enlargement of the vestibular aqueduct syndrome (EVAS) is a developmental disorder of the inner ear where the vestibular aqueduct expands and dilates. EVAS is usually associated with two different disorders, according to the presence or absence of inner ear malformations: Pendred syndrome (hearing loss associated with goiter) or non-syndromic autosomal recessive deafness type 4 (DFNB4). EVAS is largely associated with allelic variations in the *SLC26A4* gene and to a lesser extent with *FOXI* and *KCNJ10* genes. *SLC26A4* gene encodes a hydrophobic membrane protein called pendrin. This protein manages ion exchange in many cells, including epithelial cells in the endolymphatic sac, cochlea, or vestibular labyrinth. There are 200 pathogenic/likely pathogenic variants described for *SLC26A4* [5].

Bilateral vestibulopathy

Bilateral vestibular hypofunction (BVH), or bilateral vestibulopathy, is a chronic condition in which both vestibular organs and VIIIth nerves are damaged, simultaneously or sequentially. BVH is characterized by unsteadiness, postural imbalance, oscillopsia and impaired spatial memory and navigation. Ototoxic drugs, bilateral MD, and meningitis are the main causes, but the etiology remains unclear in more than 50% of the patients. A linkage study was carried out in four families with members affected by BVH, identifying a region on chromosome 6q which was segregated in these four families [15]. However, there are no genes identified as related with BVH.

Cerebellar ataxia, neuronopathy, and vestibular areflexia syndrome (CANVAS)

Cerebellar ataxia, neuropathy and bilateral vestibular areflexia syndrome is a late-onset, slowly progressive multisystem ataxia likely secondary to a neurodegenerative ganglionopathy. In 2016, diagnostic criteria for CANVAS were proposed [16]. The combination of cerebellar ataxia and vestibular impairment produces a characteristic oculomotor sign of impaired visually enhanced vestibulo-ocular reflex. However, patients show clinical heterogeneity with overlapping symptoms with type 3 spinocerebellar ataxia and partial syndromes. Although most cases are sporadic, the finding of several affected sibling pairs suggests a recessive disorder or a dominant inheritance with incomplete penetrance and variable expressivity [17]. A missense rare variant in the *ELF2* gene has been described in a British CANVAS family with three patients. This mutation regulated the expression of *ATXN2* and *ELOVL5* genes in transduced BE (2)-M17 cells, suggesting a molecular link with type 2 and type 38 spinocerebellar ataxias [18].

Hereditary sensorineural hearing loss with vestibular dysfunction

Sensorineural hearing loss (SNHL) refers to a hearing loss caused by cochlear or auditory nerve damage associated with a variable vestibular loss. Monogenic syndromic and non-syndromic hereditary SNHL includes 15 genes causing SNHL with vestibular symptoms (Table 1). Non-syndromic autosomal dominant hearing loss (DFNA) is usually associated with postlingual onset SNHL, while prelingual onset is present with greater frequency in patients with non-syndromic autosomal recessive hearing loss (DFNB) or Usher type 1 syndrome (USH1).

Monogenic sensorineural hearing loss with vestibular involvement

DFNA9

Non-syndromic autosomal dominant SNHL with vestibular dysfunction type 9 (DFNA9) is a late-onset, rare disorder caused by heterozygous mutations in the *COCH* (coagulation factor C homology) gene [19]. This disorder is mostly shown as a progressive high-frequency SNHL, and the phenotype usually includes variable vestibular dysfunction (gait imbalance, oscillopsia). Fourteen mutations have

Table 1 Genes associated in different monogenic and polygenic disorders with sensorineural hearing loss (SNHL) with vestibular phenotype

Disorder	Type of inheritance	Gene	SNHL phenotype	Vestibular phenotype	Cell type involved	Cell location
DFNA9	AD	COCH	HF	Progressive	Supporting cell	Extracellular
DFNA11	AD	MYO7A	Flat	Variable	Hair cell	Cytosol, lysosome, cytoskeleton
DFNA15	AD	POU4F3	HF	Variable	Hair cell	Nucleus
DFNB4	AR	SLC26A4	Fluctuating	Variable	Supporting cell	Plasma membrane, extracellular
DFNB36	AR	ESPN	Flat	Progressive	Hair cell	Cytoskeleton
DFNB37	AR	MYO6	Flat	Poorly characterized	Hair cell	Plasma membrane, extracellular, cytoskeleton, nucleus, cytosol
DFNB59	AR	PJVK	Flat	Poorly characterized	Hair cell	Mitochondrion, nucleus, cytosol
DFNB84A	AR	PTPRQ	Flat	Poorly characterized	Hair cell	Plasma membrane
DFNB103	AR	CLIC5	Flat	Progressive	Hair cell	Extracellular, cytoskeleton
USH1	AR	MYO7A	HF	Progressive	Hair cell	Cytosol, lysosome, cytoskeleton
USH1	AR	USH1C	HF	Progressive	Hair cell/supporting cell	Cytosol, plasma membrane, cytoskeleton
USH1	AR	CDH23	HF	Progressive	Hair cell	Plasma membrane
USH1	AR	PCDH15	HF	Progressive	Hair cell	Plasma membrane, extracellular
USH1	AR	USH1G	HF	Progressive	Hair cell	Cytoskeleton, cytosol
USH1	AR	CIB2	HF	Progressive	Hair cell	Extracellular, cytoskeleton
DFNX2	XLR	POU3F4	Flat	Poorly characterized	Supporting cell	Nucleus

Type of inheritance: AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked. SNHL phenotype: HF, high-frequency hearing loss; flat, all frequencies affected

been found in the *COCH* gene in multiple unrelated families with DFNA9. Human temporal bone histopathology showed eosinophilic ground substance deposits in the lateral wall of the cochlea, possible related to the difficulty of transportation and secretion of cochlin in nerve fibers between the auditory ganglion and sensory epithelium [20].

DFNA11

DFNA11 is a non-syndromic progressive SNHL with vestibular dysfunction caused by mutations in the *MYO7A* gene, an unconventional myosin involved in the structural organization of hair bundles at the sensory hair cells. Patients show a late-onset low-to-middle frequency hearing loss with variable vestibular dysfunction. The symptoms progress to severe cochlear impairment. Mutations in *MYO7A* have been described as the main cause of the disorder, as shown in a family with eight cases with DFNA11 all with the same deletion in the *MYO7A* gene [21].

DFNA15

Patients with DFNA15 show an early onset progressive high-frequency SNHL associated with vestibular phenotype. It has been described as caused by several missense mutations in the *POU4F3* gene, a gene encoding a member of POU-domain family of transcription factors. In some patients, vestibular function shows great variability, including cases from the same family, suggesting that epigenetic factors or additional genes should be involved in the vestibular phenotype [22].

DFNB103

DFNB103 is a rare **autosomal** recessive SNHL disorder with vestibular areflexia described in a Turkish family. Mutations in the *CLIC5* gene have been described as causative of this disorder after been observed in a family with two affected siblings. Studies in mutant mice revealed that mutation c.96T>A in the *CLIC5* gene segregated the hearing loss phenotype [23].

Familial Meniere disease

Meniere's disease is a chronic inner ear syndrome characterized by episodes of vertigo, sensorineural hearing loss, tinnitus and aural fullness. Its symptoms may overlap with other diseases such as VM. MD is a rare condition afflicting approximately 0.5–1 out of 1000 people, most of them sporadic cases. However, roughly 10% of patients have at least one other relative (first degree or second degree) with MD, confirming the familial aggregation of this syndrome. MD inheritance has been widely discussed, being usually

autosomal dominant, but recessive and mitochondrial inheritance patterns have been observed as well [24].

Some familial studies resulted in the discovery of different genes related to MD. Using WES technology, pathogenic variants in *FAM136* and *DTNA* genes were detected in a single family with MD [25]. Other three different families showed mutations in *PRKCB*, *DPT,* and *SEMA3D* genes. As shown, genetic heterogeneity between MD families was observed, as well as incomplete penetrance of the disease in most families. *PRKCB* encodes protein kinase C beta type, a serine- and threonine-specific protein kinase involved in diverse cellular functions (e.g., apoptosis induction or regulation of neuronal functions) and it shows tonotopic gene expression in tectal cells and inner border cells in the mouse cochlea. The identified heterozygous mutation at position chr16: 23999898 G>T in the *PRKCB* gene segregated the hearing phenotype in the family, and it involves two protein encoding transcripts, and both are expressed in the human ear transcriptome [26]. *DPT* encodes dermatopontin, a non-collagenous matrix protein required for cellular adhesion, and the regulation of TGFβ activity. A missense variant was identified at chr1: 168665849 G>A in the *DPT* gene and it probably produces a functional change in the protein sequence. Finally, *SEMA3D* encodes a member of the semaphorin III family, and its main function is to guide the axonal growth cone. A novel missense variant was described at chr7: 84642128 G>A, modifying an important repeated domain of this protein [7].

Autoimmune Meniere disease

Several epidemiological studies have found a higher prevalence of autoimmune diseases in patients with both familial and sporadic MD. Autoimmune MD has been addressed lately as a separated clinical subgroup with an estimated prevalence of 7–14 cases in 100,000. We have identified that the allelic variation in rs4947296, at 6p21.33, is associated with bilateral MD [OR 2.089 (1.661–2.627); $p = 1.39 \times 10^{-9}$] and enriched in MD patients with autoimmune comorbidities [26]. This SNV is a trans-expression quantitative trait locus (trans-eQTL) regulating cellular proliferation in lymphoid cells through the TWEAK/Fn14 pathway and increasing NF-κB-mediated inflammatory response [27].

Superior canal dehiscence syndrome

Superior canal dehiscence syndrome (SCDS) is a rare condition caused by an opening on the bone around the superior semicircular canal. Hearing loss and vestibular symptoms of SCDS are usually triggered by loud sounds, pressure stimuli, or trauma. Its etiology is not clear; however, a recent study describing 7 SCDS cases in three families provides evidence of a genetic contribution [28]. Furthermore, studies in pediatric patients with Usher syndrome and non-syndromic deafness associate variants in *CDH23* gene as a risk marker for SCDS [29].

Conclusions

1. Rare allelic variants in coding regions of different genes are causal in familial vestibular syndromes, including enlarged vestibular aqueduct syndrome or familial Meniere's disease.
2. Common variants in non-coding regions are considered regulators of gene expression of multiple physiological processes in vestibular diseases such as motion sickness or sporadic Meniere's disease.

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Compliance with ethical standards

Conflicts of interest The authors declare no competing conflict of interest.

References

1. Lopez-Escamez JA, Dlugaiczyk J, Jacobs J, Lempert T, Teggi R, von Brevern M, Bisdorff A (2014) Accompanying symptoms overlap during attacks in Meniere's disease and vestibular migraine. Front Neurol 5:265
2. Teggi R, Colombo B, Albera R, Asprella Libonati G, Balzanelli C, Batuecas Caletrio A, Casani A, Espinoza-Sanchez JM, Gamba P, Lopez-Escamez JA et al (2017) Clinical features, familial history, and migraine precursors in patients with definite vestibular migraine: the VM-phenotypes projects. Headache. https://doi.org/10.1111/head.13240
3. Bisdorff AR, Staab JP (2015) Overview of the International Classification of Vestibular Disorders. Neurol Clin 33:541–550
4. Frejo L, Giegling I, Teggi R, Lopez-Escamez JA, Rujescu D (2016) Genetics of vestibular disorders: pathophysiological insights. J Neurol 263:45–53
5. Roman-Naranjo P, Gallego-Martinez A, Lopez Escamez JA (2017) Genetics of vestibular syndromes. Curr Opin Neurol 31:1
6. Requena T, Espinosa-Sanchez JM, Lopez-Escamez JA (2014) Genetics of dizziness: cerebellar and vestibular disorders. Curr Opin Neurol 27:98–104
7. Martín-Sierra C, Gallego-Martinez A, Requena T, Frejo L, Batuecas-Caletrío A, Lopez-Escamez JA (2017) Variable expressivity and genetic heterogeneity involving DPT and SEMA3D genes in autosomal dominant familial Meniere's disease. Eur J Hum Genet 25:200–207
8. Hromatka BS, Tung JY, Kiefer AK, Do CB, Hinds DA, Eriksson N (2015) Genetic variants associated with motion sickness point to roles for inner ear development, neurological processes and glucose homeostasis. Hum Mol Genet 24:2700–2708

9. Espinosa-Sanchez JM, Lopez-Escamez JA (2015) New insights into pathophysiology of vestibular migraine. Front Neurol 6:12
10. Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, Bisdorff A, Versino M, Evers S, Newman-Toker D (2012) Vestibular migraine: diagnostic criteria. J Vestib Res Equilib Orientat 22:167–172
11. Oh AK, Lee H, Jen JC, Corona S, Jacobson KM, Baloh RW (2001) Familial benign recurrent vertigo. Am J Med Genet 100:287–291
12. Evans DGR, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R (2005) Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol 26:93–97
13. Li SL, Ma XH, Ji JF, Li H, Liu W, Lu FZ, Wu ST, Zhang Y (2016) miR-1 association with cell proliferation inhibition and apoptosis in vestibular schwannoma by targeting VEGFA. Genet Mol Res 15:1–8. https://doi.org/10.4238/gmr15048923
14. Håvik AL, Bruland O, Myrseth E, Miletic H, Aarhus M, Knappskog P-M, Lund-Johansen M (2018) Genetic landscape of sporadic vestibular schwannoma. J Neurosurg 128:911–922. https://doi.org/10.3171/2016.10.JNS161384
15. Jen JC, Wang H, Lee H, Sabatti C, Trent R, Hannigan I, Brantberg K, Halmagyi GM, Nelson SF, Baloh RW (2004) Suggestive linkage to chromosome 6q in families with bilateral vestibulopathy. Neurology 63:2376–2379
16. Szmulewicz DJ, Roberts L, McLean CA, MacDougall HG, Halmagyi GM, Storey E (2016) Proposed diagnostic criteria for cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). Neurol Clin Pract 6:61–68
17. Szmulewicz DJ, McLean CA, MacDougall HG, Roberts L, Storey E, Halmagyi GM (2014) CANVAS an update: clinical presentation, investigation and management. J Vestib Res 24:465–474
18. Ahmad H, Requena T, Frejo L, Cobo M, Gallego-Martinez A, Martin F, Lopez-Escamez JA, Bronstein AM (2018) Clinical and functional characterization of a missense ELF2 variant in a CANVAS family. Front Genet 9:85. https://doi.org/10.3389/fgene.2018.00085
19. Robertson NG, Lu L, Heller S, Merchant SN, Eavey RD, McKenna M, Nadol JB, Miyamoto RT, Linthicum FH, Lubianca Neto JF et al (1998) Mutations in a novel cochlear gene cause DFNA9, a human nonsyndromic deafness with vestibular dysfunction. Nat Genet 20:299–303
20. Robertson NG, Cremers CWRJ, Huygen PLM, Ikezono T, Krastins B, Kremer H, Kuo SF, Liberman MC, Merchant SN, Miller CE et al (2006) Cochlin immunostaining of inner ear pathologic deposits and proteomic analysis in DFNA9 deafness and vestibular dysfunction. Hum Mol Genet 15:1071–1085
21. Tamagawa Y, Ishikawa K, Ishikawa K, Ishida T, Kitamura K, Makino S, Tsuru T, Ichimura K (2002) Phenotype of DFNA11: a nonsyndromic hearing loss caused by a myosin VIIA mutation. Laryngoscope 112:292–297
22. Van Drunen FJW, Pauw RJ, Collin RWJ, Kremer H, Huygen PLM, Cremers CWRJ (2009) Vestibular impairment in a Dutch DFNA15 family with an L289F mutation in POU4F3. Audiol Neurotol 14:303–307
23. Seco CZ, Oonk AMM, Domínguez-Ruiz M, Draaisma JMT, Gandía M, Oostrik J, Neveling K, Kunst HPM, Hoefsloot LH, del Castillo I et al (2015) Progressive hearing loss and vestibular dysfunction caused by a homozygous nonsense mutation in CLIC5. Eur J Hum Genet 23:189–194
24. Requena T, Espinosa-Sanchez JM, Cabrera S, Trinidad G, Soto-Varela A, Santos-Perez S, Teggi R, Perez P, Batuecas-Caletrio A, Fraile J et al (2014) Familial clustering and genetic heterogeneity in Meniere's disease. Clin Genet 85:245–252
25. Requena T, Cabrera S, Martín-Sierra C, Price SD, Lysakowski A, Lopez-Escamez JA (2015) Identification of two novel mutations in FAM136A and DTNA genes in autosomal-dominant familial Meniere's disease. Hum Mol Genet 24:1119–1126
26. Martín-Sierra C, Requena T, Frejo L, Price SD, Gallego-Martinez Á, Batuecas-Caletrio Á, Santos-Perez S, Soto-Varela A, Lysakowski A, Lopez-Escamez JA (2016) A novel missense variant in PRKCB segregates low-frequency hearing loss in an autosomal dominant family with Meniere's disease. Hum Mol Genet 25:3407–3415
27. Frejo L, Requena T, Okawa S, Gallego-Martinez A, Martinez-Bueno M, Aran I, Batuecas-Caletrio A, Benitez-Rosario J, Espinosa-Sanchez JM, Fraile-Rodrigo JJ et al (2017) Regulation of Fn14 receptor and NF-κB underlies inflammation in Meniere's disease. Front Immunol 8:1739. https://doi.org/10.3389/fimmu.2017.01739
28. Heidenreich KD, Kileny PR, Ahmed S, El-Kashlan HK, Melendez TL, Basura GJ, Lesperance MM (2017) Superior canal dehiscence syndrome affecting 3 families. JAMA Otolaryngol Head Neck Surg 143:656–662
29. Noonan KY, Russo J, Shen J, Rehm H, Halbach S, Hopp E, Noon S, Hoover J, Eskey C, Saunders JE (2016) CDH23 related hearing loss. Otol Neurotol 37:1583–1588