Estrella Martinez-Gomez*, Alvaro Gallego-Martinez, Pablo Roman-Naranjo, and Jose A. Lopez-Escamez

Clinical and molecular genetics of Meniere disease

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Abstract: Meniere disease (MD) represents a heterogeneous group of relatively rare disorders of the inner ear that causes vertigo attacks, fluctuating sensorineural hearing loss (SNHL) involving low and medium frequencies, tinnitus, and aural fullness. MD has been attributed to an accumulation of endolymph in the cochlear duct. The diagnosis of MD is based on the phenomenological association of clinical symptoms including SNHL during the vertigo attacks. At least two mechanisms are involved in MD: (a) a pro-inflammatory immune response mediated by interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), and IL-6, and (b) nuclear factor-kappa B (NF-κB)-mediated inflammation in the carriers of the single nucleotide variant rs4947296. The majority of MD cases are considered sporadic, although familial aggregation has been recognized in European and East Asian populations in multiplex families, supporting a genetic contribution to the disease. In sporadic MD cases, the main genetic findings involve multiplex rare variants in several SNHL genes, such as *GJB2*, *USH1G*, *SLC26A4*, *ESRRB*, and *CLDN14*, and axonal guidance signaling genes, such as *NTN4* and *NOX3*. Familial aggregation has been reported in 6–8 % of MD cases, and most families show an autosomal dominant inheritance. Few rare missense heterozygous variants have been described in simplex families in six genes (*COCH*, *FAM136A*, *DTNA*, *PRKCB*, *SEMA3D*, and *DPT*). Of note, 33 % of familial MD individuals show singleton and multiplex rare missense variants in the *OTOG* gene, suggesting a multiallelic inheritance. Moreover, potentially pathogenic rare variants in the familial genes *FAM136A*, *DTNA*, and *DPT* have been reported in Korean singletons with sporadic MD. Rare variants may have a significant contribution to sporadic and familial MD. The interaction of common cis-regulatory variants located in non-coding regions and rare variants in coding regions in one or more genes will determine the variation on the phenotype in MD. Further studies on genotype–phenotype correlations are required to improve the yield of genetic diagnosis, and different types of variants seem to contribute to the genetic structure of MD.

Keywords: Meniere disease, genetic background, genomic variations, heritability, genetic diagnosis

***Corresponding author: Estrella Martinez-Gomez,** Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain, e-mail: estrella.martinez@genyo.es
Alvaro Gallego-Martinez, Pablo Roman-Naranjo, Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain
Jose A. Lopez-Escamez, Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain; and Department of Otolaryngology, Instituto de Investigación Biosanitaria Ibs.GRANADA, Hospital Universitario Virgen de las Nieves, Universidad de Granada, 18016 Granada, Spain; and Department of Surgery, Division of Otolaryngology, Universidad de Granada, Granada, Spain

Clinical aspects of Meniere disease

Meniere disease (MD) is an inner ear syndrome characterized by episodes of vertigo, sensorineural hearing loss (SNHL), tinnitus, and aural fullness. Its clinical features vary widely, and it may overlap with vestibular migraine. Patients with MD can demonstrate a wide clinical spectrum with fluctuations in hearing loss (either uni- or bilateral), tinnitus, aural fullness, and vertigo, which often varies significantly with respect to onset, duration, frequency, and disease course [1]. Clinical symptoms during the attacks and audiometric tests are the basis for the diagnosis of the disease. Hearing loss becomes permanent as MD progresses [2]. Most patients develop symptoms in one ear and usually several years later hearing loss and tinnitus start to fluctuate in the second ear. However, few patients show SNHL in both ears since the onset of the condition [3].

The Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) defined diagnostic criteria and guidelines for treatment in 1995, defining MD as an idiopathic syndrome of endolymphatic hydrops [4]. The diagnosis of MD is based on the description of symptoms during the attacks, and the symptoms may resemble other pathologies associated with tinnitus, such as hearing loss, migraine,

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Table 1: Diagnostic criteria for Meniere disease proposed by the International Vestibular Disorders Classification Committee of the Barany Society (2015).

Definitive Meniere disease*	
A.	Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours
B.	Audiometrically documented low to medium frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during, or after one of the episodes of vertigo
C.	Fluctuating aural symptoms (hearing, tinnitus, and fullness) in the affected ear
D.	Not better accounted for by another vestibular diagnosis
Probable Meniere disease	
A.	Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours
B.	Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
C.	Not better accounted for by another vestibular diagnosis

*No serological or genetic marker is considered for the diagnosis of MD.

metabolic disorders, sleep problems, or anxiety. The diagnostic criteria for MD were revised in 2015 by a panel of representatives of five international scientific societies: the Barany Society, the Korean Balance Society, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology, and the Equilibrium Committee of the AAO-HNS. This international panel developed a consensus document with diagnostic criteria based on clinical symptoms and did not consider different subgroups of patients, laboratory markers, or imaging data, dividing the disease in two categories: definite and probable MD (Table 1) [5]. MD is usually diagnosed around the fourth decade of life, but the condition likely develops a few years before [6]. Since the clinical syndrome is not complete in most patients in the early stages of the disease, patients are diagnosed after several months or years after the onset of the symptoms [7].

Epidemiology of MD

The prevalence of MD ranges from 17 to 200 cases/100,000, according to the geographical region of the population studied [8]. In general, MD is more common in European descendants, particularly in Scandinavian countries [9]. The genetic underpinnings of MD may include some rare monogenic inheritance in isolated families and a multiallelic contribution in most familial and sporadic cases. The prevalence in Finland has been reported to be 43/100,000 [10], which is lower than the prevalence reported in Americans of European descendance (200/100,000) [8] and England (56/100,000) [6]. In contrast, the prevalence is 17–34.5/100,000 in the Japanese population [11]. An earlier age of MD onset has been observed, and usually in patients with a familial history of MD [12, 13]. Nevertheless, most patients are considered sporadic MD, without a familial history of MD [14].

Several lines of epidemiological evidence support a genetic contribution in MD, including (a) the higher prevalence observed in the European population compared with other ethnicities and (b) a strong familial aggregation found in Europeans and South Koreans, ranging from 6 % to 10 % of cases with a high sibling recurrence risk [15]. Paparella conducted a review of 500 patients with diagnosed MD, where he found that 20 % of cases have a positive family history. This discovery gave strength to the possibility of a genetic background of the disease together with other factors [16]. According to the estimated sibling recurrence risk ratio, the disorder is 16 to 48 times more common in siblings and 4 to 12 times more common in offspring of affected individuals compared with the estimated prevalence of MD in Spain. This strong familial aggregation supports a genetic or shared environmental factor that may interact to facilitate the development of MD. Familial MD has an autosomal dominant inheritance pattern with an estimated gene penetrance of 60 % [17]. Some studies show evidence of anticipation and a severe phenotype in early onset descendants compared with sporadic cases [6]. Thus, two criteria—differences according to the racial distribution and familial clustering—point toward a complex disorder with a genetic predisposition.

Migraine has been reported in 15 % of unilateral MD patients [7]. Migraine can be regarded as a conserved, adaptive response that occurs in individuals with a genetic predisposition [18] and it has been suggested that these could be extrapolated to MD. Some studies conducted across different populations found a strong correlation with family history of hearing loss or recurrent vertigo in some patients with MD [12].

Genetic studies in MD

Early candidate gene studies

Early investigations focused on selecting candidate genes involved in the inner ear homeostasis in the endolymphatic sac. In this approach, genes hypothesized to be in-

volved in MD are screened in affected individuals. Several studies have focused on aquaporins (AQPs), a group of transmembrane proteins that transport water and other solutes through the cell membrane. The water permeability of AQPs is regulated by vasopressin, which has been reported to be increased in MD subjects before a vertigo attack. Two studies searched for mutations in several aquaporin genes (*AQP1–AQP4*); however, no causative mutations were identified [19]. Investigations into the genes *KCNE1* and *KCNE3*, which encode two voltage-gated potassium channels expressed in the inner ear, have been similarly inconclusive [20]. Although the allelic frequencies of two common variants were associated in Japanese patients with MD (rs1805127 for *KCNE1* and rs2270676 for *KCNE3*), these findings were not replicated in Non-Finnish European [21] and Finnish populations [22]. However, the Finnish study reported a novel rare variant (c.259T>C; p.Trp87Arg) in the *KCNE1* gene in one singleton MD patient which was not found in controls [22] or the gnomAD browser. Two studies have shown associations with MD, i. e., one variation in the heat shock protein HSP70-1, which is thought to be involved in the cellular stress response, and another variation in the *ADD1* gene, which causes elevated activity of the Na^+,K^+-ATPase transporter. However, these findings were not replicated in an independent cohort and more evidence is needed to confirm these associations [22]. The lack of replication for the results derived from candidate gene studies is a general pattern in human genetic association studies and this is probably related to a biased selection of cases and controls and differences in the genetic structure across different populations.

Systematic studies in familial MD

Another approach that has been applied to study familial MD is linkage analysis in multiplex families with MD, which relies on the evaluation of genomic markers to identify the region of the genome that segregates with the disease. Approximately 6–10 % of MD cases have at least one first- or second-degree relative with MD [5]. The most frequent inheritance pattern in familiar MD is autosomal dominant with incomplete penetrance [17, 12], but autosomal recessive and mitochondrial patterns have also been suggested [12].

Shared rare variants in multiplex families

By exome sequencing, Requena *et al.* identified two rare single nucleotide variants (SNVs), probably pathogenic, in the *DTNA* and *FAM136A* genes in a single family from the Southeast of Spain [23]. *DTNA* encodes a membrane protein called alpha-dystrobrevin, which interacts with transmembrane proteins and actin in the basolateral membranes of epithelial cells. *DTNA* has been associated with the blood–brain barrier in the dystrophin complex as part of the cytoskeleton connecting with the plasma membrane. *FAM136A* encodes a mitochondrial protein that is expressed in the utricle and cochlea during prenatal development. This protein is suspected to be an important protein in the early stages of inner ear development. The novel SNV in *FAM136A* is heterozygous and leads to a novel stop codon, which shortens the protein product [12]. These novel variants segregated with the phenotype in all affected cases. However, both genes have not been reported in additional families with MD.

Martin-Sierra *et al.* (2016) found a candidate variant in the *PRKCB* gene in another MD family, segregating with a low frequency hearing loss phenotype. *PRKCB* encodes a protein kinase C beta subunit, a serine-specific and threonine-specific protein kinase involved in diverse cellular functions (e. g., apoptosis induction or regulation of neuronal functions). The protein is highly abundant in tectorial cells and Hensen cells, and it shows a tonotopic labeling from base to apex. Of note, this protein shows a lower expression in the supporting cells of the utricle. The heterozygous SNV in the *PRKCB* gene showing segregation involved two protein-coding transcripts expressed in the human ear transcriptome [24].

Two additional missense variants were found in *SEMA3D* and *DPT* genes in two different families, illustrating the genetic heterogeneity in familial MD [25]. *SEMA3D* encodes a semaphoring protein related to axonal guidance signaling and neuronal growth. A novel missense variant modifies an important repeated domain of this protein. *DPT* encodes dermatopontin, an extracellular matrix protein involved in cellular adhesion and the regulation of TGFβ.

The *COCH* gene, which encodes cochlin, one of the most abundant proteins in the inner ear, has been associated in several familial studies with an MD-like phenotype; however, this has never been proven in a large MD cohort. In fact, population stratification bias seems to be a critical issue in the association of MD symptoms with *DFNA9*, since some British and Belgian families with *COCH* variants were included [26]. Allelic variations in the *COCH* gene have been found in Korean families with

DFNA9. Distinct vestibular phenotypes were observed according to the position of the mutation in the gene, including fluctuating or progressive bilateral vestibular loss without episodic vertigo or a MD-like phenotype with severe vertigo attacks. This study found a correlation between the p.G38D substitution in cochlin and complete bilateral vestibular loss, suggesting that bilateral vestibular loss may also occur in patients with *DFNA9*, especially when the LCCL domain is mutated, despite the apparent absence of dizziness episodes [27].

In a Swedish family, episodic vertigo segregating *DFNB16* and *STRC* variants was diagnosed in two brothers and their first-degree cousin. The brothers had a homozygous *STRC* nonsense variant, whereas their cousin was carrier of a compound heterozygous variant including the nonsense variant in the *STRC* gene and a 97 kb deletion spanning the *STRC* gene. Variants in *STRC* cause *DFNB16B*, representing at least 10 % of cases with autosomal recessive SNHL [28].

In another recent study, two variants were found in a Finnish family with an early onset MD patient. One of them was found in the *HMX2* gene and the second variant was found in the *TMEM55B* gene, with a very low frequency in the Finnish population. Both variants were shared between relatives with definite MD. This study confirms the role of rare variants in individuals with early onset MD [13]. The genes associated or related with familial MD are shown in Table 2.

Gene burden analysis of rare variants in familial MD

Studies in multiplex MD families using exome sequencing show genetic heterogeneity with several candidate genes for MD. The "one variant–one disease" hypothesis, described for classic Mendelian inheritance, cannot explain the incomplete penetrance or variable expressivity observed in MD, and more complex inheritance models are needed. Although the genomic data of multiplex families are still limited to less than 100 familial cases, a burden of rare variants in the *OTOG* gene has been reported in 15 Spanish unrelated families [31]. Most of these rare variants were found in two, three, or four individuals in unrelated multiplex families, but complete segregation in most of them could not be demonstrated. The hearing profile of these patients is characterized by a rapid progression with bilateral SNHL starting at 60 dB in the first year involving all frequencies in most cases [31].

Systematic studies in sporadic cases

The allelic variant rs4947296 is associated with bilateral MD in the Spanish population and has been found in 18 % of patients with a comorbid autoimmune disorder. This region on chromosome 6 is a trans-expression quantitative trait locus (eQTL), and regulates the expression of multiple genes involved in the TWEAK/Fn14 pathway in peripheral mononuclear cells, leading to an NF-κB-mediated inflammatory response in MD [32]. This pathway showed a total of 31/34 differentially expressed genes according to the allelic variation of this eQTL, pointing to the TNF-related pathways for apoptosis and inflammation as potential mechanisms of the autoimmune MD subtype through the upregulation of NF-κB, and an increased inflammatory response in MD. This variant may define an endophenotype and it could be used as a genetic biomarker for autoimmunity in patients with MD.

Cohort-based studies

Most of the described MD individuals do not report any relatives with MD in their family. To demonstrate a burden of rare variants in singletons will require a large sample size; in this sense, we have started to investigate the genetic contribution of rare variants in certain hearing loss genes in sporadic cases [29, 33].

The list of hearing loss genes with a burden of rare variants in sporadic MD includes genes related to the ionic regulation of the endolymph, such as *SLC26A4* and *CLDN14*, and known genes causing with *DFNA*/*DFNB*, such as *GJB2* or *ESRRB*, but also the *USH1G* gene, which is related to Usher syndrome, a stereociliopathy with hearing and vestibular loss [29]. These findings were also considered in some hearing loss variants in Asian and European cohorts, which were reclassified as variants of unknown significance (VUS) due to their changes in allelic frequencies in some populations. In fact, these first studies in sporadic MD highlight how Spanish MD patients seem to have a burden of VUS and pathogenic variants in genes such as *ESRRB*, *SLC24A6*, *USH1G*, *CLDN14*, and *GJB2*, with a higher frequency than the Spanish reference population [3]. Moreover, the trophic signals that regulate the innervation of the hair cells in the axonal guidance signaling pathway have been involved in sporadic MD. So, a burden of rare variants in genes of this pathway, such as *NTN4* or *NOX3*, has been found in sporadic MD in a large Spanish MD cohort [30]. The excess of rare variants in these genes (listed in Table 2) could contribute to modify the expressivity of the hearing loss phenotype in sporadic MD.

Table 2: List of genes with rare variants potentially involved in familial and sporadic MD.

	Gene	Locus	Protein name	Description	Variant location	Ethnicity	Reference
Sporadic MD	***GJB2***	13q12.11	Gap junction protein, beta-2, 26 kD (connexin 26)	Forms a hexamer with a transmembrane channel function, has been determined as possibly affected by these changes in their interactions.	chr13:20763264 C>T	Iberian population	[29]
	CLDN14	21q22.13	Claudin 14	Crucial for generating the K^+ gradient between perilymph and endolymph in the inner ear.	chr21:37832869-37948917	Iberian population	[29]
	SLC26A4	7q22.3	Solute carrier family 26 (sulphate transporter), member 4	Its alteration is one of the most common causes of syndromic deafness and autosomal recessive SNHL. It is also associated with enlarged vestibular aqueduct syndrome.	chr7:107,336,408 A>C	Iberian population	[29]
	ESRRB	14q24.3	Estrogen-related receptor beta	Encodes a protein like the estrogen receptor but with a different and unknown role. Mutations in the mouse ortholog have been involved in the placental development and autosomal recessive SNHL.	chr14:76,957,891 G>A chr14:76,966,336 G>A chr14:76,966,347 C>T	Iberian population	[29]
	USH1G	17q25.1	Scaffold protein containing ankyrin repeats and SAM domain	This protein plays a role in the development and maintenance of the auditory and visual systems and functions as scaffold protein in the tip links and transient lateral links of hair bundles formed by inner ear sensory cells. Alterations in the integrity of the protein seem to be the cause of Usher syndrome type 1G.	chr17:72,915,919 C>T chr17:72,916,543 T>G	Iberian population	[29]
	NTN4	12q22	Netrin 4	Associated with axon guidance signaling pathways in patients with sporadic MD.	chr12:96181003 C>T chr12:96181085 G>A chr12:96181202 A>G	European population	[30]

Table 2: (continued)

	Gene	Locus	Protein name	Description	Variant location	Ethnicity	Reference
Familial MD	***OTOG****	11p15.1	Otogelin	Structural protein found in tectorial and otolithic membranes forming homodimers that interact with otogelin-like and stereocilin in the formation of the TM attachment to hair bundles in outer hair cells.	chr11:17574758 G>A chr11:17578774 G>A chr11:17632921 C>T chr11:17663747 G>A chr11:17667139 G>C	Iberian population	[31]
	PRKCB	16p12.2-p12.1	Protein kinase C, beta subunit	Found in a tonotopic gradient in tectal cells, inner border cells, and afferent boutons innervating inner hair cells.	chr16:23999898 G>T	European population	[24]
	FAM136	2p13.3	Family with sequence similarity 136, member A	Involved in the mitochondrial respiratory chain, co-localized with mitochondrial marker COX4 in adult rat inner ear.	chr2:70527974 G>A	European population	[23]
	DTNA	18q12.1	Dystrobrevin, alpha	Part of the dystrophin-associated protein complex along with syntrophins in the cytoplasmic complex. Provides a link between the dystrophin protein complex and the intermediate filament network in neuromuscular junctions.	chr18:32462094 G>T	European population	[23]
	SEMA3D	7q21.11	Semaphorin 3D	Related with axon guidance signaling in the semaphorin complex during the extension of axon branches.	chr7:84642128 C>T	Spanish population	[25]
	DPT	1q24.2	Dermatopontin	Found in the extracellular matrix, binding dermatan sulphate proteoglycans in endothelial cells.	chr1:168665849 G>A	Spanish population	[25]
	COCH	14q12	Cochlin	Structural protein located in the lateral wall of the cochlea. Involved in *DFNA9* with variable vestibular loss.	p.G38D	Korean population	[27]
	STRC	15q15.3	Stereocilin	Encodes Stereocilin in the cochlea and in the vestibular organ, where it unsheathes the kinocilium of the otolithic membranes.	chr15:43896948 G>A chr21:47808772 G>A	European population	[28]
	HMX2	10q26.13	Home box (H6 family)	Affects inner ear development and structural integrity and thus might predispose to the onset of MD.	p.Y273N	Finnish population	[13]
	TMEM55B	14q11.2	phosphatidylinositol 4,5-bisphosphate 4-phosphatase, type I	Involved in the formation of cell membranes or the cytoskeleton and in genes participating in cell death or gene regulation pathways.	p.L229F	Finnish population	[13]

*Each of the five heterozygous missense rare variants found in the *OTOG* gene were reported in three or more unrelated families with MD.

Discussion

The results of genetic testing in MD are still in an early stage, without a main validated gene across different populations. While specifications exist for other diseases, MD genetic diagnosis lacks casual variants, similarly to some autosomal hearing loss disorders. Focusing on more symptoms than hearing loss, vertigo and tinnitus could help in the elaboration of a set of rules refining MD phenotypes and its genetic diagnosis. Deep phenotyping and cluster analyses have found few clinical predictors for several subgroups of patients with MD, which may indicate different mechanisms of disease, including genetic and autoimmune factors. The finding and interpretation of rare variants in singletons and multiplex families is an important step of the learning process to improve the genetic diagnosis, and the lack of accessible, larger population-specific datasets that can be used as a reference is a major limitation for the genetic diagnosis of MD. The interaction of common cis-regulatory variants located in non-coding regions and rare variants in coding regions in one or more genes will determine the variation on the phenotype in MD. Finally, a personalized treatment should consider the investigation of pro-inflammatory cytokines and the eQTL rs4947296 as markers of NF-κB-mediated inflammation [32].

Conclusions

1. MD is a complex set of rare disorders with a strong genetic contribution.
2. Common and rare variants contribute to explain the genetic structure and phenotypic heterogeneity.
3. Rare variants with large effect size reported in multiplex families and singletons may help to define driver genes such as *DTNA*, *FAM136A*, *DPT*, or *OTOG*.
4. Common variants such as rs4947296 are associated with bilateral MD and may regulate inflammation; in the future, they could be used to develop personalized treatment.

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Estrella Martinez-Gomez
Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain
estrella.martinez@genyo.es

Alvaro Gallego-Martinez
Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain

Pablo Roman-Naranjo
Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain

Jose A. Lopez-Escamez
Otology & Neurotology Group CTS 495, Department of Genomic Medicine, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, PTS Granada, Avenida de la Ilustración, 114, 18016 Granada, Spain
Department of Otolaryngology, Instituto de Investigación Biosanitaria Ibs.GRANADA, Hospital Universitario Virgen de las Nieves, Universidad de Granada, 18016 Granada, Spain
Department of Surgery, Division of Otolaryngology, Universidad de Granada, Granada, Spain