

The genetics of Ménière's disease

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Abstract: Our understanding of the genetic basis of Ménière's disease (MD) is still limited. Although the familial clustering and the geographical and racial differences in incidence strongly suggest a certain role for genetic factors in the development of MD, no convincing evidence for an association with any gene exists, at present. In this review, starting from rational bases for a genetic approach to MD, we explored the numerous reports published in literature and summarize the recent advances in understanding of the genetic fundaments of the disease.

Keywords: Ménière's disease, gene, vertigo, etiology, pathogenesis

Introduction

Ménière's disease (MD) is a disorder of the inner ear characterized by both cochlear and vestibular dysfunction, defined by the symptom complex of fluctuating sensorineural hearing loss, vertigo, tinnitus, and aural fullness. It is a chronic illness, with recurrence of symptoms without prevision, as they fluctuate within periods of activity and may be in remission for much time.

The prevalence of MD has been reported in literature by numerous investigators to be between 17 and 513 of 100,000 individuals, depending on the geographical localization of study.¹⁻⁴ Bilateral disease is reported to develop in 8% to 20% of cases, rarely simultaneously.⁵ MD in children and younger people is reported only in a few rare cases, the majority of reported children are 10 years and older.⁶⁻⁸ Most cases of MD are sporadic (SMD), but there are numerous affected persons who report other family members with similar symptoms suggesting the possibility of familial MD (FMD).^{9,10} No clinical differences have been reported between sporadic and familial form but patients affected with FMD seem to suffer from earlier onset and more severe manifestation of the disease.¹¹⁻¹³

In this review, starting from rational bases for a genetic approach to MD, we will explore the numerous reports published in literature and summarize the recent advances in understanding of the genetic fundaments of this disease.

Limits to a successful genetic approach to MD

In an effort to develop uniform reporting criteria for MD, the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium published guidelines for diagnosing this entity in 1995.¹⁴ To be diagnosed with definite MD, a patient must show two or more episodes of characteristic vertigo (each episode longer than 20 minutes), documented hearing loss (usually fluctuating low frequency sensorineural loss seen on serial audiograms), and presence of aural fullness and/or

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tinnitus in the affected ear. Other causes of vertigo must be excluded.

A general problem in most of the investigations is the definition of MD. Although the American Academy of Otolaryngology-Head and Neck Surgery criteria are almost always cited, often there are patients included only showing “partial MD”, with not all of the symptoms. Because of these poorly defined samples, the resulting numbers concerning frequency of familial and/or isolated MD cannot always be considered as accurate.

MD has a clinical heterogeneity and the time course of the episodes of vertigo and hearing loss is variable. Another obstacle for an accurate selection of familial cases is that the onset of the disease is almost always in adult age.¹⁵

It is simple to understand how the diagnosis based on clinical criteria exposes to high risk of bias in study of epidemiology and generally in the selection of patients affected by MD.

Beyond the clinical diagnosis with no truly objective data we have some other problems approaching MD.

First of all, the histological feature of MD patients has been historically addressed in endolymphatic hydrops (EH)¹⁶ with the consequent speculation that this condition is the base of the MD clinical picture. However, recent studies on temporal bone¹⁷ described similar conditions of EH in specimens from people with and without the characteristic symptoms of MD. On the other side, Wangemann¹⁸ described patients with MD without hydrops on histologic examination hypothesizing that the presence of hydrops is neither essential nor specific to MD. This unreliability is confirmed in a recent, very interesting, review from Foster and Breeze (2013). Autopsy data from numerous studies do not support the interpretations that the association of MD and EH is an epiphenomenon or that MD causes EH; this opens the door to the probability that EH causes MD: however, if it is causative, hydrops alone is insufficient to cause MD, indicating that there must be one or more additional cofactors that cause asymptomatic hydrops to become symptomatic MD.¹⁹

As a consequence, MD pathophysiology is poorly understood. There are many proposed theories, several intrinsic (genetic, anatomic, metabolic, endocrine, autoimmune, or vascular), other extrinsic (allergic, viral, or traumatic). None of these hypotheses has really been accepted: each theory is in need of confirmation.

Intriguing possibilities (also for genetic implications that we will see later) are MD as migraine variant, or as a consequence of recrudescence herpes virus infection or of an autoimmune mechanism.

Up to 56% of all patients with MD has concomitant migraine.²⁰ This suggests a common pathway for symptoms in MD and migraine.²¹ Cha et al suggested that the frequent association of episodic vertigo, migraine, and MD in closely related individuals, including identical twins, supports the heritability of a “migraine-Ménière’s syndrome”, with variable expression of the individual features of hearing loss, episodic vertigo, and migraine headaches.²² Moreover, it is reported that agents for migraine prophylaxis have shown benefit in some patients with MD.²³ The genetic implications of migraine is quite well documented with numerous loci identified that determine some mechanisms of ion channel dysfunction, potentially superposable on MD symptoms.⁹

The viral infection theory has been taken into account for the ease of transmission and the diffusion of the potential infectious agents. The best similarity with the clinical course of MD with intermittent symptoms within periods of quiescence, recurrence provoked by stress, variable severity, and symptoms that tend to decrease with time are from neurotrophic DNA viruses, capable of establishing a latent infection in sensory nerve ganglia: herpes simplex virus (HSV) and varicella zoster virus (VZV).²⁴ However, investigations about the role of HSV and VZV in MD have produced inconclusive results. Welling et al²⁵ in 1997 found no viral DNA in the vestibular ganglia of 22 patients. Vrabec, in 2003, with a more sensitive polymerase chain reaction-based approach, reported 100% positive DNA in 25 MD patients undergoing vestibular neurectomy and 80% in controls group.²⁶ More recently Gartner et al²⁷ were unable to find genomic DNA of these viruses in patients with definite MD, stating that reactivation of HSV and VZV in vestibular ganglion does not seem to play a role in the pathogenesis of MD.

Autoimmune mechanisms appear to be associated with the pathophysiology of MD.^{28,29} The evidences that support this hypothesis include the finding of elevated levels of autoantibodies or circulating immune complexes in the serum of some patients,^{29,30} and the association with a functional variant of a lymphoid protein phosphatase, LYP, which inhibits T cell receptors response in patients with bilateral ear involvement.³¹ Moreover, different autoantibodies such as antinuclear antibodies, antiphospholipid antibodies, and antibodies against a 68kD protein have been studied in small series of patients with MD, showing conflicting results.^{28,29,32–34} Recently, a case-control study tested the hypothesis that impaired clearance of immune complexes by innate immune cell receptors may be important in MD. No association between polymorphisms in these receptors or levels of circulating immune

complexes and MD was found. Furthermore, MD displays an elevated prevalence of systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis.³⁵ Finally, recent findings from Chiarella et al^{36,37} seem to confirm the role of inflammatory response in MD pathogenesis, suggesting an intriguing potential role of a set of plasma proteins that could be used as an effective tool for a biomarker-oriented diagnosis and staging of MD.

Rationale for genetic suspicion for MD

There are several characteristics of MD that support a genetic background.

An ethnic susceptibility is well documented in literature. Various reports indicate that women (56%) are more susceptible than men, with nearly identical age of onset for the disease.³⁸ There is an ethnic bias in susceptibility to MD, with the disease being extremely rare in individuals of African ancestry, slightly more prevalent in those individuals of Asian ancestry. A significant disease burden is observed within native Latino American individuals but MD remains primarily a disease of Caucasians (83%),³⁸ with an estimated prevalence of 218 cases per 100,000 persons.³⁹

Inheritance of MD has been described since 1941.⁴⁰ Since then, several further publications supporting a probable autosomal dominant inheritance have followed, with incomplete penetrance estimated at about 60%.^{4,39,41–43} Despite that, recently, in a very large cohort some families with an autosomal recessive inheritance were reported.¹²

The familial form of MD is reported with a frequency between 7% and 15%. Siblings of MD patients display a 10-fold increased risk of developing the disease.^{9,11,43,44} Several MD pedigrees have been reported, mostly in Caucasians. Some Brazilian families with concurrent MD and migraine are also described.⁴⁵

Sometimes, individuals in successive generations manifest the MD phenotype at an earlier age and/or with more severe manifestations, strongly suggesting the presence of anticipation, a phenomenon associated with expanded trinucleotide diseases or dynamic mutations. This has been described in numerous cases of FMD.^{4,41,42,44,46} Although, some authors suggest that this observation could be biased by the difference in health care availability among different generations.⁴⁷

Genetic studies on MD

In Table 1 the reports on genetics studies on MD are summarized.

Linkage studies

Linkage analysis relies on evaluation of genomic markers to identify the region of the genome that segregates with the disease. Genetic markers of MD have not been identified precisely.

HLA

Based on the hypothesis of an autoimmune cause or of a dysfunction in immune function for the production of EH in MD, early investigations focused on analyzing human leukocyte antigens' (HLAs) associations in susceptibility of MD.

Multiple studies have been performed, with different HLA associations or no association documented. Among the earliest studies, Xenellis et al⁴⁸ detected an association between the *Cw07* antigen and MD in 41 British patients and Koyama et al⁴⁹ with the allele *DRB1*1602* in a Japanese population. Only one study provides replication of the *Cw07* association, with a significant increase in the distribution of the *HLA-Cw07* allele in MD patients in comparison to the patients affected by other inner ear diseases or healthy controls, suggesting a predisposing role for the *HLA-Cw07* specificities in MD.⁵⁰ These results were not consistent and not confirmed by successive studies: Lopez-Escamez et al,⁵¹ with a larger sample, failed to demonstrate differences in phenotypic frequencies in *Cw07* and no specific association with allele *DRB1 1602* in a Spanish population, suggesting that the immunological alterations reported are probably epiphenomenon of the inner ear damage. Later, Lopez-Escamez et al⁵² observed an association between *HLA-DRB1 *1101* with bilateral MD.

Because of the observed association between both sporadic and familial cases of MD and HLA class I haplotypes, Morrison et al⁵³ suggested the possibility of an MD locus lying between the *HLA-C* and *HLA-A* loci on the short arm of chromosome 6.

More recently Khorsandi et al⁵⁴ reported the association of definite MD with *HLA-Cw04* allele.

DFNA9

DFNA9 is a type of autosomal dominant nonsyndromic (DFNA) hearing loss. It is localized to chromosome 14q12-13 and the responsible gene is *cochlin (COCH)*. Among the DFNA types of deafness this has unique features, it is the only DFNA type of hearing loss with concomitant vestibular impairment that shares some features with MD, including vertigo, tinnitus, and aural fullness.⁵⁵ Based on these similarities, *COCH* gene has been screened in a large number

Table 1 Reports on genetics studies on Ménière's disease

Author/year	Approach	Study design	Gene	Objective	Subjects	Ancestry	Association
Koyama et al, 1993 ⁴⁹	Genetic	Case-control	<i>HLA-Cw04</i> <i>DRB1*1602</i>	Susceptibility	20/20	Asian	No Yes
Melchiorri et al, 2002 ⁵⁰	Genetic	Case control	<i>HLA-Cw07</i>	Susceptibility	41/34/101	Caucasian	Yes
Lopez-Escamez et al, 2002 ⁵¹	Genetic	Case-control	<i>HLA-</i>	Susceptibility	54/534	Caucasian	No
Lopez-Escamez et al, 2007 ⁵²	Genetic	Case-control	<i>HLA-DRB1*1101</i>	Susceptibility	80/250	Caucasian	Yes
Khorsandi et al, 2011 ⁵⁴	Genetic	Case-control	<i>HLA-Cw04</i>	Susceptibility	22/91	Caucasian	Yes
Klar et al, 2006 ⁶¹	Genomic	Familial	<i>12p12</i> <i>PIK3C2G</i>	Susceptibility	13/8	Caucasian	Yes
Hietikko et al, 2011 ⁴⁷	Genomic	Familial	<i>12p12.3</i>	Susceptibility	16 families	Caucasian	No
Arweiler-Harbeck et al, 2011 ⁴	Genomic	Familial	<i>Chromosome 5</i>	Susceptibility	52/29	Caucasian	Yes
Yazdani et al, 2013 ⁶⁴	Genetic	Case-control	<i>MIF-173</i>	Susceptibility	72/100	Caucasian	Yes
Gazquez et al, 2013 ⁶⁵	Genetic	Case-control	<i>MIF, INFG,</i> <i>TFNA</i>	Susceptibility	580/552	Spanish/ American	No
Mhatre et al, 2002 ⁶⁶	Genetic	Case-control	<i>AQP2</i>	Mutation's analysis	12	American	No
Candreia et al, 2010 ⁶⁷	Genetic	Case-control	<i>AQP3</i>	Mutation's analysis	34/100	Caucasian	No
Maekawa et al, 2010 ⁶⁸	Genetic	Case-control	<i>AQP2</i>	Gene expression study	15/9	Asian	No
Lynch et al, 2002 ⁶⁹	Genetic	Case-control	<i>ATQ1</i>	Mutation's analysis	14	Australian	No
Doi et al, 2005 ⁷²	Genetic	Case-control	<i>KCNE1 – 3</i>	Susceptibility	63/237	Asian	Yes
Campbell et al, 2010 ⁷³	Genetic	Case-control	<i>KCNE1 – 3</i>	Susceptibility	180/180	Caucasian	No
Hietikko et al, 2012 ⁷⁴	Genetic	Case-control	<i>KCNE1</i>	Mutation's analysis	59/98	Caucasian	Yes
Teggi et al, 2008 ⁷⁵	Genetic	Case-control	<i>ADD1</i>	Susceptibility	28/48	Caucasian	Yes
Kawaguchi et al, 2008 ⁷⁶	Genetic	Case-control	<i>HSPA1A</i>	Susceptibility	49/100	Asian	Yes
Vrabec et al, 2008 ⁷⁷	Genetic	Case-control	<i>HCFC1</i>	Susceptibility	21/33	Caucasian	No
Lopez-Escamez et al, 2010 ⁷⁸	Genetic	Case-control	<i>PTPN22</i>	Susceptibility	52/348	Caucasian	Yes
Furuta et al, 2011 ⁷⁹	Genetic	Case-control	<i>IL1A</i>	Susceptibility	68/72/2202	Asian	Yes
Lopez-Escamez et al, 2011 ³¹	Genetic	Case-control	<i>CD16A/CD32</i>	Susceptibility	156/626	Caucasian	No
Gazquez et al, 2011 ³⁵	Genetic	Case-control	<i>NOS1 – NOS2A</i>	Susceptibility	273/550	Caucasian/ American	No
Lopez-Escamez et al, 2009 ⁸⁰	Genetic	Case-control	<i>PARP-1</i>	Susceptibility	80/371	Spanish	No

of MD patients of different ethnicities but no associations have been found.

Considering the studies of SMD form, Sanchez et al⁵⁶ reported that the known mutations in exons 4 and 5 of the *COCH* gene have a low prevalence in MD, not confirming association of *COCH* with MD. Usami et al⁵⁷ concluded that *COCH* mutations may not be a major cause for typical MD. In other studies on FMD, Fransen et al⁵⁸ reported the presence of auditory and vestibular symptoms in a large Belgian family with hereditary hearing loss, designated DFNA9. They described close linkage between the disease and markers surrounding DFNA9 locus. Mutation analysis revealed a missense mutation changing *Pro* to *Ser* (*P51S*). In this study and in other reports it is not clear if DFNA9 patients who suffer from recurrent vertigo represent true cases of MD.^{41,59}

Another experience proposed a unique FMD locus on chromosome 14q distinct from *COCH* (in a region overlapping *COCH*). Mutation analysis did not detect any of the reported *COCH* mutations in DFNA9, or any novel mutations.

The authors concluded that their familial locus is not in *COCH*, without proposing an alternative candidate gene.³⁹

DFNA9 and MD are finally 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 MD are late onset and low frequency at first. Moreover, although some temporal bones from individuals with DFNA9 have shown the presence of EH, the characteristic finding in DFNA9 is microfibrillar deposits in the stria vascularis, a feature not detected in MD.⁶⁰

Chromosome 12

Klar et al⁶¹ studied a large Swedish family segregating for MD for linkage to loci in known familial forms of cochleovestibular dysfunction using a genome wide set of microsatellite markers. This family did show linkage for several markers on chromosome 12. When combined with two additional families, the locus was narrowed to 12p12.3. Within this region only a single known gene is identified, encoding for

phosphatidylinositol 3-kinase class 2 gamma (*PIK3C2G*). Activation of phosphatidylinositol 3-kinase contributes to the differentiation of cells in vestibular epithelia from rats, with a proposed role of these kinases in regeneration of hair cells in mammalian ears.⁶² This finding obtained additional support from a successive work by the same group of researchers⁶³ that refined the region to 1,48 Mb and screened two candidate genes on chromosome 12 (*RERGL* and *PIK3C2G*). Mutation analysis involving the coding regions of the gene did not detect any mutations. Moreover, no linkage with this chromosomal region was observed in a series of 16 Finnish MD families,⁴⁷ suggesting genetic heterogeneity among families affected with MD. Arweiler-Harbeck et al⁴ in their genome-wide linked analysis of 17 German families with 2–4 generations positive for definite MD, documented a weakly positive score for locus on chromosome 12, that in addition appears clearly different from the region identified by Klar et al,⁶¹ and found a probable candidate region for MD on chromosome 5.

Macrophage migration inhibitory factor (MIF)

More recently, again based on the involvement of immune system in MD, Yazdani et al⁶⁴ explored the association between *MIF-173 G/C* polymorphism and MD in an Iranian population. MIF plays a key role in immune-mediated reactions. This study's result indicates the potential role of MIF in definite MD. In the same year, Gázquez et al⁶⁵ found a significant association with the allele containing five repeats of *CATT* within the *MIF* gene in patients with MD in the Spanish cohort but not in the American set of the study.

Candidate genes association studies

In this approach, genes hypothesized to be involved in MD are screened in affected individuals. The selection accuracy of the gene is fundamental for the result. All genes for MD have been selected based on a theory of pathogenesis, but also if some studies found significance for a marker in the candidate gene, none have been replicated in a second population sample.

Genes involved in ionic composition or water transport

Aquaporin

Some authors focused on mutations in aquaporin (AQP), a transmembrane protein expressed in the endolymphatic sac that transports water and other solutes through the cell membrane. *AQP* gene family has a role in fluid transport and *AQP1*, 2, 3, 4, and 5 have been identified within the inner ear.

Mhatre et al,⁶⁶ in unrelated patients, tested the hypothesis that mutations in *AQP2* gene are linked to MD in humans. No sequence alterations in *AQP2* was identified in any of the 12 individuals affected with MD. Two other studies^{67,68} searched for mutations in several AQP genes, *AQP1–AQP4*, in affected individuals; however, no causative mutations were identified.

Antiquitin

Without preliminary linkage study, Lynch et al⁶⁹ selected as candidate gene *antiquin* (*ATQ*) for mutation analysis from a series of FMD cases. The choice was based on a presumed effect in maintenance of fluid balance from the similarity with the pea protein 26 g⁷⁰ that is utilized to counteract water stress in some plant species. No differences were found between affected and unaffected individuals.

KCNE genes

Investigations into the genes *KCNE1* and *KCNE3*, two voltage-gated potassium channel genes expressed in the inner ear,⁷¹ have been similarly inconclusive: on the hypothesis that a dysfunction of these ion transporters may have a role in the development of MD, Doi et al⁷² found that single nucleotide polymorphisms (SNPs) in each gene *KCNE1* (*112G/A – rs1805127*) and *KCNE3* (*198T/C – rs11702354*) showed significant allele frequency differences in a Japanese population affected with MD suggesting that these are susceptibility genes for sporadic forms of MD. Campbell et al⁷³ found no association in the Caucasian population and could not duplicate the Doi results. In a more recent study of Hietikko et al⁷⁴ the genotype with the *A-allele* seemed to protect against SMD. However, they found four novel sequence variations in the *KCNE1* gene in three SMD and one FMD patient, the mutation seems to be disease causing but needs a larger sample to be confirmed.

Adducin

Adducin (ADD) is a heterodimeric cytoskeleton protein consisting of three subunits (alpha, beta, and gamma) coded by three different genes (*ADD1*, *ADD2*, and *ADD3*). *ADD1 Gly460Trp* polymorphism is associated with salt-sensitive hypertension and increased Na-K pump activity in transfected cells. Teggi et al⁷⁵ have not found any significant difference in the distribution of *ADD2* and *ADD3* polymorphism genotypes. The frequency of *ADD1 Trp allele (rs4961)* is significantly increased in patients with MD compared with controls. These data support the possibility that increased Na, K-ATPase activity may be one of the pathologic mechanisms inducing hyperosmolarity in endolymph which may cause hydrops.

Other candidate genes

HSP70

On the observation that MD might be caused or triggered by psychological stress, Kawaguchi et al⁷⁶ examined two SNPs in heat shock 70 kD protein 1A (HSPA1A) which is thought to be involved in the cellular stress response. The SNP 190 G/C was found to be a factor associated with MD: there was significance for one SNP (*rs1043618*) but not for the other (*rs1008438*). Both SNPs have been associated with other diseases like stroke, heart disease, open angle glaucoma, Parkinson's disease, and noise-induced hearing loss. Interestingly no clinical correlation exists between the other diseases associated with these SNPs and MD. Consequently we are in need of future follow-up to establish if the altered function acts as a cause of MD or, more likely, in concert with other still unknown factors to produce it.

Host cell factor C1 (HCFC1)

Vrabec et al⁷⁷ reported a study of a series of SNPs in multiple candidate genes based on a suspected role in MD pathogenesis among patients with MD and selected control individuals. The most significant finding was that the minor allele at each SNP site was significantly more common in controls, suggesting a protective effect of the minor allele in multiple SNPs in the same haplotype block on the X chromosome that includes *HCFC1*. The functional consequences of the SNPs in *HCFC1* are unknown but the documented interaction between *HCFC1* and the HSV viral protein VP16 suggests a model of MD based on HSV reactivation.²⁶ In neurons, *HCFC1* provokes viral reactivation under stress conditions. So, in this model of MD pathophysiology, the reactivation of latent virus infection could be the mechanism underlying the appearance of MD symptoms and herpes virus infection is a necessary cofactor.

PTPN22

MD has also been associated with a polymorphism in the gene *PTPN22* (*rs2476601,1858C/T*), encoding a lymphoid protein phosphatase suggesting that the genotype may confer differential susceptibility to bilateral MD in the Spanish population and supporting an autoimmune etiology for bilateral forms of MD.⁷⁸

Interleukin-1

Furuta et al⁷⁹ documented the association of *interleukin-1 gene (IL1)* polymorphism to both MD and sudden sensorineural hearing loss.

All of the candidate genes examined, could be plausibly linked to MD and each report outlines a verisimilar mechanism of the disease. The accuracy of these reported

associations relies on replication in following studies. The real problem is that most of these studies analyzed familial and sporadic patients together, and principally, that no positive replications of previously described candidate genes have been reported. Actually, a recent study of Hietikko et al⁷⁴ reports on the screening of previously MD associated genes *AQP2*, *KCNE1*, *KCNE3*, *COCH*, *HCFC1*, and *ADD1* on 59 individuals (38 sporadic and 21 independent FMD samples) with a control population of 98 persons. Only *rs1805127 (KCNE1)* remained significant after correction for multiple testing. No association with MD was observed for any of the other genes and no significant haplo/diplotypes were observed.

Conclusion

Based on the published reports analyzed in this review, we can conclude that no convincing evidence for an association with a specific gene has been found, at present.

In fact, all the findings in literature indicate a genetic heterogeneity.

The phenotypic diversity of MD, without available objective tools or measures for certain diagnosis, makes the selection of patients hard, with the adult onset of the disease possibly complicating the assembly of appropriate control groups. Moreover, the predisposing or influencing factors of MD may differ between ethnic groups and even between families affected with FMD.

All these considerations, taken together, illustrate the challenge involved in the candidate gene approach to the study of MD.

A very good consideration⁹ is that MD is a complex disease and, as a consequence, the genetic contribution to MD is also complex. The single gene, or the genes, potentially implicated may not be sufficient to determine the disease by themselves, so, in future research, we have to consider with great attention the combined effect of environmental factors on a susceptible genetic background and the possibility of gene interactions.

On the other hand, the adult onset of MD undermines the regroup of individuals with a common phenotype in association studies. A method to approach adult-onset complex diseases may be carefully selected case-control association studies.

Today, genome-wide studies have gained an elevated level of definition from recent technological advances in sequencing and in sequence analysis. The true problem of genome-wide association is mainly the costs and the evolving methods of statistical analysis.

Undoubtedly, association studies have important limits in defining new disease genes. Inaccurate phenotype definition, as well as difficulties in the interpretation of DNA sequence

alterations can lead to premature claims of association. Confirming the DNA sequence alteration by traditional molecular techniques, linkage analysis in selected pedigrees, and replication of the association in at least a second population is essential to confirm any preliminary finding.

In summary, reports based on a candidate gene's approach provided very little information on the etiology of MD, whereas genetic studies based on linkage with polymorphic traits may provide more information about the development of the disease. These studies will need the collection of larger, well-defined case-control groups affected with FMD for use in genome-wide analyses and/or exome sequencing.

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