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Review

Genetic basis of myasthenia gravis – A comprehensive review

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ABSTRACT

Myasthenia gravis (MG) is a rare autoimmune disease characterized by the production of autoantibodies against proteins of the postsynaptic membrane in the neuromuscular junction. The estimated number of MG patients is steadily increasing, and it had more than doubled in the last 20 years. Monozygotic MG twin concordance is estimated to be about 35% supporting the central role of environmental factors in MG etiology. Epigenetics, presume to be the mechanistic link between environmental and genetic risk factors in disease development, provides support for specific microRNAs associated with MG. Genetic studies have mainly pointed at specific HLA alleles implicated in MG susceptibility, however recently both TNFAIP3-interacting protein 1 (TNIP1) and tyrosine phosphatase non-receptor 22 (PTPN22) were indicated to be associated with MG in a GWAS study. A gender bias was observed for SNPs in the HLA-locus, suggesting female-specific alleles have an increase risk for MG. Moreover, sex hormones play a pivotal role in the gender bias in autoimmunity in general and in MG in particular. Hence the genetic basis of gender bias might be highly pertinent to MG and deserves further characterization. Pathway-based analyses that combine information across multiple genes into a limited number of molecular networks have been found to be a powerful approach. Both regulatory T-cell (Treg) differentiation and NF-κB signaling pathway have been shown to have relevance to MG pathophysiology. Hence studies centered around two pathways might be a fruitful approach to identify additional polymorphisms associated with myasthenia gravis.

1. Autoimmune myasthenia gravis (MG) a rare complex disorder

Myasthenia gravis (MG) is a relatively rare autoimmune neuromuscular disorder, clinically characterized by weakness and fatigability of skeletal and extraocular muscles [1]. MG is a B-cell driven, T-cell dependent, complement and antibody-mediated disease, due to autoantibodies directed against molecules at the neuromuscular junction, including antibodies against the acetylcholine receptor (AChR) (85% of patients), the muscle-specific kinase (MuSK) or the lipoprotein-related protein 4 (LRP4) [2–4]. The binding of anti-AChR antibodies to their target impairs neuromuscular transmission by complement-mediated destruction of the postsynaptic membrane [5]. About 80% of AChR-positive patients have thymic abnormalities (follicular hyperplasia or thymoma). In early onset AChR + MG patient, the thymus is characterized by the presence of anti-AChR autoreactive T cells and autoantibody-producing B cells [4]. While the cause for AChR autosensitization in the thymus is unclear, chronic inflammation, characterized by high expression of inflammatory cytokines which may increase AChR expression [6,7], and impaired regulatory T-cell(Treg)function [8,9], have been suggested to be involved in the pathogenesis. The current hypothesis is that MG is a rare complex disease with numerous genetic polymorphisms, each having a small effect, contributing to MG predisposition. Because of it low prevalence and disease complexity the genetic basis of MG remain largely unknown.

1.1. Geo-epidemiology and prevalence

Current estimates place the MG prevalence at a high value of about 3–30 per 100,000 persons depending on the study and geographic location [10–13]. The estimated number of MG patients is steadily increasing, and it had more than doubled in the last 20

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years in Western countries as well as in Japan and Taiwan [14–16]. This increase is probably due to improved diagnostic accuracy, the improved efficacy of treatment and care, but also by the increasing longevity of the population. MG shows a bimodal distribution with two incidence peaks: Early-onset MG (EOMG) in the third decade (strong female predominance) and late-onset MG (LOMG) in the elderly (slight male predominance). The elderly-onset MG is the major source of the overall increase and showed a 2.3-fold rise in the last 20 years both in Western and in Asian countries [17,18]. The reason for the increase is unclear and might be due to a better awareness of neurologists to discriminate MG symptoms from classical fatigue due to aging. However, the immunological background and the genetic basis are distinct from that in younger patients. In contrast in China, the overall prevalence is similar to the above reports, but with a younger age of onset and a ratio of 1:1 between male and female [19]. This geographic difference in prevalence might reflect difference in the methodology between different studies or might be due to genetic and environmental factors influencing disease frequency.

1.2. Familial autoimmune MG is very rare

Familial autoimmune MG is mostly reported as rare case reports [20–22]. A unique case of a Hungarian family was reported where nine members from two generations develop MG [23,24]. Recently, a sequence variant in the ecto-NADH oxidase 1 gene (ENOX1) was strongly linked to EOMG in an Italian-American kinder with four affected siblings [25]. The variant sequence was not found in 764 controls, in sporadic MG, or in other patients with familial autoimmune MG. The ENOX1 variant decreased ENOX1 levels in a lymphoblastoid cell line in a dose-dependent manner, with a reduction of mRNA levels of up to 80% compared with normal variants. How ENOX1 could predispose to MG is unknown, but immunological function studies could help elucidate its role in MG pathogenesis. Although MG is rarely inherited within a family occurrence of another autoimmune and immune-mediated diseases (AID) among myasthenic patients kin's is relatively common [26]. The most common concomitant AIDs being Rheumatoid Arthritis (RA) and thyroid disorders [27,28]. This suggests that common genetic and environmental factors might predispose to autoimmune disorders and MG being one of them.

2. Genetic susceptibility

2.1. Specific HLA alleles implicated in MG susceptibility

Like most autoimmune diseases, genetic studies have mainly pointed at specific HLA alleles implicated in MG susceptibility. The association of HLA A1-B8-DR3-DQ2 haplotype, also known as AH8.1 [29], with EOMG in the Caucasian population has been reproduced by numerous groups [30–33]. Remarkably, AH8.1 haplotype has been associated with other autoimmune diseases, such as celiac and systemic lupus erythematosus (SLE), supporting the hypothesis of shared genetic risk factors for several autoimmune diseases [34,35]. Other MHC variants have been described in Asiatic MG patients [36], LOMG [37] and anti-MuSK + patients [38]. Childhood-onset of ocular MG in Southern Han Chinese is suggested to be a particular subgroup with distinct genetic background since 90.1% of patients were reported to be positively associated with DQ9 haplotype [36]. In contrast, in a northern Han Chinese population HLA-DRB1(*)09 allele was significantly more prevalent among patients with MG than among healthy controls [39]. DRB1*15:01, DQB1*05:02 and DRB1*16 have been associated with increased risk for LOMG in Norwegian and Italian cohorts [37,40]. Patients with MuSK-MG, a rare and relatively newly described clinical entity, appear to be associated with DQ5 alleles in populations with diverse ancestries both from Southern and Northern Europe [38,41].

Tumor necrosis factor-alpha (TNF-α) is a potent pro-inflammatory cytokine located within the HLA locus that is tightly linked to AH8.1 haplotype. A functional SNP, rs1800629, at −308 nucleotides upstream from the transcription initiation site has been shown to affect TNF-α expression, with the −308A allelic form having a two-fold greater level of transcription than the 308G form [42]. The −308A allelic form was linked with elevated serum levels of TNF-α and with a more severe disease outcome in several diseases [43–46]. The A allele of this functional SNP has been linked to higher expression level and higher serum level of TNF-α in MG by several independent groups [47–49]. In a recently complete EOMG association study rs1800629 was found to be the most significantly associated SNP, increasing the odd ratio (OD) to 2 in males and to over 4 in females (submitted manuscript). All these results suggest a physiological role of TNF-α polymorphism in MG predisposition that needs to be further evaluated.

Table 1
Non-HLA genes associated with MG.

Locus symbol, gene product	Variant or marker	Mechanism	References
Cathepsin L2 (CTSL2)	Association between rs4361859 with EO MG	Unknown	[104]
Cellular tyrosine phosphatase 22 (PTPN22)	Coding (Arg620Trp)	Trp allele impairs binding to Csk kinase	[60,61,65,105]
Cytotoxic T cell late antigen 4 (CTLA4)	Two SNPs in the promoter region	Abnormal alternative splicing	[70,71]
Galectin-1 (LGALS1)	Association with regulatory region (rs4820293, rs4820294)	Unknown	[106]
Fork head/winged-helix transcription factor 3 (FOXP3)	SNP in the intron region IVS9+459 (A/G, rs2280883)	Unknown	[73]
Interleukin receptor 2β (IL2Rβ)	Association with regulatory region (rs743777, rs228941)	Unknown	[106]
Interferon-γ (IFNG)	Noncoding SNP (+874A/T)	Putative NF-κB binding site	[107]
Interleukin-4 receptor a (IL4R)	Coding I75V	Reduced responsiveness to interleukin-4	[108]
Interleukin-10 (IL10)	5′ flanking sequence of the human IL-10 gene (rs45552637 (A/C), rs1800872 (T/C), and rs1800896 (A/G))	Correlated with IL-10 protein production *in vitro*	[109,110]
Muscle nicotinic acetylcholine receptor α-subunit (CHRNA1)	Upstream polymorphism (−478A/G)	Alters binding of IRF8	[79,81]
Muscle nicotinic acetylcholine receptor δ-subunits (CHRND)	Intronic microsatellite	Unknown	[78]
Tumor necrosis factor alpha (TNF)	Rs1800629(-308G<A)	Higher secretion of TNF-alpha	[45,47,48]
TNFAIP3-interacting protein 1 (TNIP1)	rs2233290(Pro151Ala)	Ubiquitin-dependent dysregulation of NF-kappaB signaling	[54]