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A REVIEW OF THE GENOMICS OF MYASTHENIA GRAVIS

Neurology

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ABSTRACT

Advanced age is associated with an increased response to autoantigens, although the implications of MG's age and sex-specific frequency distribution in pathogenesis remain unclear. In the last two decades, the trend has shown a progression in several MG patients, which urges the need to define better prevention and treatment guidelines. Early diagnosis and risk factor screening play a key role in knowing more about MG's pathogenesis and therapeutic modalities. In this article we have reviewed the latest in the genomics of myasthenia gravis.

KEYWORDS

Introduction-

Myasthenia gravis (MG) is an autoimmune disorder due to pathogenic autoantibodies (Abs) against the nicotinic acetylcholine receptor (nAChR) at the neuromuscular junction (NMJ). It is clinically characterized by muscle fatigability manifested by diplopia, ptosis, bulbar and limb weakness (1,2). MG prevalence varies widely between 1.7 and 10.4 per million (3). Epidemiological studies have shown a bimodal incidence pattern, with early-onset cases before 40 years being predominantly in women and late-onset after 50years, mostly in men (4,5). MG is suspected to be underdiagnosed in the elderly population(>80 years) attributed to variability in diagnoses as symptoms are often perceived as stroke or motor neuron disease(6). Advanced age is associated with an increased response to autoantigens, although the implications of MG's age and sex-specific frequency distribution in pathogenesis remain unclear (5). Antibodies typically mediate MG against nicotinic acetylcholine receptors (AChRs) or related proteins located at the NMJ, such as muscle-specific tyrosine kinase (MuSK), lipoprotein receptor-related protein 4, and again (1,2). Up to 20% of patients may suffer from myasthenic crisis leading to acute respiratory failure requiring mechanical ventilation, associated with significant morbidity and mortality (7). Genetic factors have a primary role in the development and progression of MG. Approximately 4% of patients' family members have MG themselves (8), co-occurring with autoimmune diseases, notably autoimmune thyroid disease, rheumatoid arthritis, and type 1 diabetes mellitus (9). This usually follows an autosomal dominant pattern of inheritance (10). Twin studies have shown that MG is more common in monozygotic twins than dizygotic twins, (5) suggesting a genetic predisposition.

Genomics associated with MG-

In contrast to autoimmune MG, congenital Myasthenic Syndromes (CMS) follow Mendelian principles of heredity. MG is a non-inherited disease and is considered to be multifactorial. It is assumed that its pathogenesis is caused by a complex interaction between multiple genotypes of low penetrance and environmental factors, including pathogen exposure, particularly Epstein-Barr virus (11), sex hormones (12), and lifestyle habits such as cigarette smoking (13). The vast majority of genetic factors that have been implicated in autoimmune disease susceptibility are common variants, predominantly single nucleotide polymorphisms (SNPs) rather than insertion/deletion polymorphisms or microsatellites. The human leukocyte antigen (HLA) locus is the most strongly associated risk factor for the disease (4). according to the literature available from a genome-wide association study of 649 patients from the Scandinavian, British, French, Dutch, German, and American populations identified variants in the major histocompatibility complex (MHC) class II locus, protein tyrosine phosphatase nonreceptor type 22 (PTPN22), and TNFAIP3 interacting protein 1 (TNIP1). (14) The cytotoxic T-lymphocyte–associated protein four gene (CTLA4) has also shown susceptibility for MG (15). Various genetic loci, including MHC and non-MHC genes, have demonstrated their Association with MG (8). HLA-A1, B8, and DR3 haplotype genes are genetically associated with the early onset of MG(EOMG) with thymic hyperplasia. The most frequent association is with the HLA-B8 allele. MYAS1, a susceptibility locus, has been mapped to a 1.2 Mb region in the distal MHC III and proximal MHC I, including tumour necrosis factor-alpha (TNFA) and tumour necrosis factor-beta (TNFB) (16). HLA-DR7 is protective in EOMG with thymic hyperplasia and has a significant

negative association in the TNF gene cluster and the HLA-A locus. For late-onset MG (LOMG), HLA-A3, B7, DR2 and HLA-DR4 have a close association. (17) an association with HLA-DR7 has relatively revealed a higher antibody titre against titin. (18) HLA-DR14, DQ5 with MuSK Ab-positive patients have a close association with MG (19). The Fc gamma receptors (FcγR) genes are clustered on the long arm of chromosome 1. MG is associated with functional polymorphisms in FCGR2A (encoding FcγRIIa), FCGR3A (encoding FcγRIIIa) and FCGR3B (encoding FcγRIIIb). There has also been evidence showing a high frequency of FcγRIIa 131H/H genotype in thymoma MG patients. Also, the FcγRIIa 131R/R genotype has been equally prevalent among MG patients (20).

HLA Loci associated MG-

There are many polymorphic genes in this region involved in immune function, and the strong linkage disequilibrium across HLA is challenging to identify specific alleles associated with disease susceptibility.

Thymoma-Related MG-

Thymoma are a heterogeneous epithelial cell neoplasm associated with MG up to 30–45% co-occurring with many other autoimmune diseases (21). The World Health Organization (WHO) classify thymomas into five histological types: A, AB, B1, B2, and B3, in order of increasing malignancy based on their neoplastic (epithelial) and non-neoplastic (lymphocytes) component proportions (22). No reproducible HLA association has been reported in MG with thymoma. A French study found that the HLA-A*25 allele had a higher frequency in paraneoplastic MG occurrence, whereas B2 type thymoma showed a negative association of the HLA-A*02 allele, demonstrating a protective in its development (23). Recent data from northern china state that a Class II HLA-DQA1 and DQB1 genes are associated with thymoma-related particularly the B2 type to have a significant association of HLA-DQA1*0401 DQB1*0604 MG patients with thymoma (24).

Non-thymomatous MG-

The HLA-DRB1 gene role has been studied by many in MG. According to a Caucasian study, MG patients with thymus hyperplasia had an increased frequency of the DR3 allele and a decrease in the DR7 allele frequency. A relative predisposition effect (RPE) analysis of DR alleles, the DR16 and DR9 alleles, shown to have an association with MG and thymus hyperplasia (25). The anti-thymic antibody (ATT)-positive patients were associated with the DR7 allele. In contrast, a negative association was observed for the DR3 allele opposite the ATT negative patients and MG patients with thymus hyperplasia (25). A cohort study of 1,472 SNPs of the MHC region from Sweden determined the Class I HLA locus as the most sensitive in MG (26). The strongest association was rs2523674 SNP mapped 3.5 kb downstream of the HLA complex protein 5 (HCP5) gene, while the imputed HLA-C*0701 allele was also associated independently (26). The greatest association in LOMG found was the DRB1*15:01, DRB1*04 and DQB1*0302 alleles, while EOMG patients demonstrated Association with the HLA-A*01, -B*08, -C*07, and -DRB1*0301 and DQB1*02 alleles of which HLA-B*08 had the strongest risk to MG susceptibility (28,27). A negative association with the DRB1*13: 01 alleles were observed in both EOMG and LOMG patients suggesting its protective role in MG (27). The Chinese population found an increased frequency of the DRB1*09 allele in EOMG patients and a corresponding rise in DRB1*07 allele frequency in LOMG (29). The DRB1*09 was also associated with the negative anti-AChR antibodies subgroup, but the strongest association of this allele in MG patients with the ocular type of the disease (29).

MuSK-MG-

In contrast to AChR-MG, MuSK-MG has distinct clinical patterns of weakness with normal thymic histology. A study conducted among white Dutch patients showed a strong association with the HLA-DR14-DQ5 haplotype, while the B8-DR3 haplotype has been consistently associated with early-onset AChR-MG (30). Another study in the Italian population showed that MuSK-MG patients were strongly associated with DQB1*0502 and DRB1*16 alleles (31). Since the DQB1*0502 allele accounts for serologic DQ5, its Association with DQ5 can be confirmed.

Non-HLA Loci Association with MG-

Protein Tyrosine Phosphatase Non-receptor Type 22 (PTPN22) is a General Autoimmunity Risk Factor located on the 1p13.3–p13.1 chromosomal region encoding specifically for cytoplasmic tyrosine phosphatase in lymphoid cells. Structurally, PTPN22 has two functional domains: the N-terminal catalytic-dephosphorylation domain and the C-terminal binding domain interacting with the SH3 domain of the intracellular C-src tyrosine kinase (CSK), causing T-cell suppression by TCR signalling pathway. A missense rs2476601 (1858C>T) substitutes an arginine with tryptophan (R620W), which leads to multiple autoimmune diseases like rheumatoid arthritis, MG, lupus, type I diabetes, and several other diseases (32). A cohort study among Swedish Caucasian MG patients demonstrated a strong link between minor T allele with the subgroup of MG with thymus hyperplasia and anti-AChR antibodies. (33). At the promoter region of the CHRNA1, rs16862847 SNP has the most common association, which encodes for alpha-subunit of the muscle AChR, which has constant Association with MG (34). Galectin proteins contain a carbohydrate recognition domain which has a high affinity to N-acetyllactosamine oligosaccharide and mediates both intracellular and extracellular immunomodulatory activities, like induction of apoptosis, negative regulation of T-cell response, cell adhesion, and pre-mRNA splicing. The rs2737713 polymorphism causes a substitution of phenylalanine to tyrosine substitution (F19Y) in the LGALS8 locus, encoding galectin-8, which appeared to be moderately associated with MG (35). As per a Hungarian cohort out of three missense of IL4Rα I75V, S503P, and Q576R, a polymorphism of I75V. It had shown to be significantly associated with MG, especially when the 75V allele existed in homozygosity (36). Interleukin-10 (IL-10), an anti-inflammatory cytokine that acts by downregulating TH1-mediated responses, has three SNPs, at positions -1082 (A/G), -819 (T/C), and -592 (A/C) in the 5′ flanking sequence of IL-10. It forms three haplotypes (GCC, ACC, and ATA). A study of the Norwegian population proves to have an association of ACC/ACC and ATA/ATA, respectively, with ATA-positive and EOMG patients (61). Foxp3 is a transcription factor with a specific role in the function of CD4+/CD25+ T regulatory cells. A recent study in Han Chinese MG cases attempted to assess the contribution of two SNPs, rs3761548 (−3279A/C) and rs2280883 (IVS9+459A/G), in the FOXP3 gene to MG susceptibility. IVS9+459G allele showed a Statistically significant protective role in the development of MG, whereas rs3761548 had no association (36).

Conclusion-

In the last two decades, the trend has shown a progression in several MG patients, which urges the need to define better prevention and treatment guidelines. Early diagnosis and risk factor screening play a key role in knowing more about MG's pathogenesis and therapeutic modalities. The detection of MG-specific microRNAs and the study of their functions could provide this information. Additionally, understanding the interaction between genes, gender, and environmental factors may help to reflect its development.

HLA alleles have shown a strong association with MG; moreover, a series of non-HLA loci implicated the same, improving our understanding of the multifaceted autoimmune procedures and thus unravelling the specific role of these genes in immunological pathways.

MG-associated loci exert their effect by upregulation of the immune response, inhibition of immunosuppressive mechanisms, or impaired regulation of the difference between autologous and heterologous molecular conformations via processes such as immune tolerance. SNP frequency in the genome is higher and in more locations than microsatellites. Therefore, SNPs should be focused more by clinicians and researchers as genetic markers. The scope of genetic analysis in autoimmune diseases and its applications in management and prevention relies on the rapid progression of subsequent-generation sequencing platforms in the future, which may attain the sequencing of whole exome, transcriptome or genome with accuracy and cost-effective way.

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