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Review article

Multiple sclerosis genetics: Results from meta-analyses of candidate-gene association studies

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ABSTRACT

As a complex disease, multiple sclerosis (MS) susceptibility implicates many genetic and environmental factors. Usually, individual genetic association studies have several limitations, and results are specific to the population of study. The Meta-analysis approach has been proposed to resolve these limitations and to increase the power of statistical analyses. In this review, we summarize results from meta-analyses of candidate genes of MS. Using the keywords: multiple sclerosis, genetic polymorphism and meta-analysis, we searched electronic databases (PubMed, Embase and Web of Sciences) for published meta-analyses until May 2017. Meta-analyses confirmed the association of polymorphisms in fifteen candidate genes with MS disease. However, polymorphisms in fourteen genes showed none significant association. Results outlined the importance of confirmed genes to understand signaling pathways in MS disease and shed light on their utility to develop new drugs targets.

1. Introduction

Multiple sclerosis (MS) is characterized by inflammation of the central nervous system (CNS), demyelination, axonal and neuronal degeneration [1]. Many hypotheses have been proposed to explain the MS disease, but its etiology remains uncertain. Scientists support an autoimmune origin triggered by a complex combination of environmental and genetic factors [1,2]. Environmental factors include higher latitude which is correlated with increased prevalence of MS [3]. Differences in latitude reflect differences in sunlight exposure and vitamin D levels [4]. In addition, viral agents, specifically Epstein-Barr virus [5] and herpes simplex viruses [6] are suspected as triggers of MS. The strong genetic component in MS disease has been demonstrated by familial, monozygotic and dizygotic twins studies. The major histocompatibility complex (MHC) has been accepted, for several years, as the only universal genetic locus associated to MS. Especially, HLA-DRB1∗1501 class-II allele accounts for less than 50% of MS genetics [7]. As knowledge of MS genetics is progressing, many additional non-HLA susceptibility genes have been identified. Therefore, multiple susceptibility loci, acting in concert, draw a polygenic model for MS. The majority of common variants is located at or near genes having central immunological functions. Most of the validated susceptibility loci such as *IL2RA*, *IL7R*, *CD58*, *CLEC16A*, IRF8, TNFRSF1A, TYK2, have central roles in the immune system, particularly in T cell differentiation, development, activation and regulation [8–13]. A multitude of genes coding for molecules of immunological relevance are related to MS according to the International Multiple Sclerosis Genetics Consortium (IMSGC) [14]. These genes are implicated in cytokines pathways (*CXCR5*, *IL2RA*, *IL7R*, *IL7*, *IL12RB1*, *IL22RA2*, *IL12A*, *IL12B*, *IRF8*, TNFRSF1A, TNFRSF14, TNFSF14), co-stimulation (CD37, CD40, CD58, CD80, CD86, CLECL1), signal transduction (CBLB, GPR65, MALT1, RGS1, STAT3, TAGAP, TYK2) and interactions with environmental risk factors [14]. Candidate gene approach using case–control design, cohort and family based studies is the most commonly used strategy to identify MS associated genes. However, there has been a general lack of reproducibility in genetic association studies which has made conclusions difficult to draw. Meta-analysis, however, combines data of comparable studies, increases sample size, gives greater statistical power and draws more compelling conclusions. The aim of the current review is to update knowledge of MS genetics based on met-analyses of classical candidate-gene association studies.

2. Genetic factors associated with multiple sclerosis, according to meta-analyses of candidate-gene association studies

2.1. HLA genes

The MHC spans a 7.6 Mb region on chromosome 6, and comprises over 400 genes and pseudogenes [15]. HLA genes are key components of the immune system encoding cell surface antigen-presenting proteins. HLA-A, -B and -C class-I molecules present foreign molecules to CD8+ cytotoxic T cells [16]. It has been shown that MHC class-II has a stronger association with MS than class-I [17]. The HLA-DRB1 genetic loci may play the most important role in HLA-DQA1∗0102-

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DQB1∗0602-DRB1∗1501-DRB5∗0101 haplotype, which showed a strong association with MS [18]. HLA genes polymorphisms only make up 20–60% of the genetic predisposition to MS, which means a possible role of non-HLA genetic factors in disease development [19]. Meta-analysis showed that HLA-DR2/DRB1∗15 were more strongly associated with MS risk in Chinese than in Western populations. However, HLA-DR9 alleles were found to confer resistance in Chinese population [21]. Meta-analysis by Zhang et al. [20] showed a protective role of both *HLA-DRB1∗14* and *-DRB1∗07* for MS in Caucasians, but *DRB1∗03* and *DRB1∗15* conferred significant risk to MS.

2.2. ApoE gene

Apolipoprotein E (ApoE) glycoprotein, synthesized in the CNS by glial cells, has an immunomodulatory effect and a crucial role in membrane remodeling and repairs [22]. ApoE protein is associated with cholesterol homeostasis [23], lipid and cholesterol transport, and is involved in brain development [24]. The ApoE gene, at the 19q13 region, is polymorphic with three common allelic forms (E2, E3, E4). The corresponding protein isoforms are distinguishable by having different combinations of the amino-acids arginine and cysteine. Amino-acid changes result in distinctive physical and biochemical properties [25]. In addition, the ApoE gene exists in two minor alleles (E1 and E5) present with less than 0.1% frequency in the population [26]. The allele E4 may speed up neurodegeneration and plays a role in development and progression of MS, Alzheimer's disease and several other disorders [27]. The first meta-analysis performed by Burwick et al. [28] reported no relation between E4 allele and MS susceptibility. Later, meta-analysis performed by Yin et al. [29] suggested that E2 mutation was associated with MS risk, whereas E3 and E4 genotypes had a protective effect in MS. This meta-analysis was based predominantly on European populations. Only two studies included Asian ethnicities, and no studies from other parts of the world were implicated. Authors did not perform subgroup analysis based on the subtype of MS (relapsing remitting MS, primary progressive MS and secondary progressive MS). All these issues develop partial results.

2.3. DPP6 gene

The Dipeptidyl-peptidase-6 (DPP6) gene codes for a dipeptidyl-amino-peptidase-like protein that lacks the enzymatic activity of the other family members. This protein is predominantly expressed in the brain and in the spinal cord [30]. Experiments showed that DPP6 protein is an auxiliary subunit of neuronal Kv4 channels, which are crucial for the excitability of neurons, integrating synaptic input and signal processing in dendrites cord [30]. Martinelli-Boneschi et al. [31] reported increased levels of DPP6, which is predominantly expressed in the brain and in the spinal cord. Earlier studies reported an association between single nucleotide polymorphisms (SNPs) in DPP6 gene and neuro-degenerative disorders, suggesting a relevant role in the CNS [32]. Meta-analysis suggested a possible role of DPP6 in susceptibility to progressive MS in Southern Europeans [33].

2.4. VDR gene

Vitamin D exerts its effects via binding to its nuclear vitamin D receptor (VDR), which is found in most cells immune and non-immune cells. VDR undergoes hetero-dimerization with the retinoid receptor, and then binds to specific DNA-binding sites in the promoter region. This results in depressing or co-activating transcription of lineage-specific genes in calcium metabolism and immune response [34]. The VDR gene, at the 12q 12–14 region, has 5 promoter regions, 8 protein-coding exons and 6 untranslated exons. ApaI, BsmI, FokI and TaqI are the most widely studied VDR polymorphisms. Both ApaI and BsmI locate in the intron separating exons 8 and 9 and are without consequences for the VDR protein structure [35]. Also, TaqI which is located in the exon 9, does not cause any amino acid change in the VDR protein [36]. FokI polymorphism, located in exon 2, leads to the addition of three amino-acids to the VDR protein [37]. Meta-analysis reported that VDR ApaI, BsmI, FokI and TaqI polymorphisms were not associated with MS risk [38]. Similarly, another meta-analysis suggested that FokI and TaqI genotypes were not related to MS disorder [39]. A more recent meta-analysis taking into account subgroup analysis suggested that ApaI and FokI genotypes were significant risk factors for MS. The association between VDR polymorphisms and the risk of MS was significantly affected by exogenous and endogenous factors such as latitude, vitamin D levels, age and gender [40].

2.5. CYP27B1 gene

Cytochrome P450 family 27 subfamily B member (CYP27B1), at the 12q14.1 region, plays a key role in converting vitamin D to its active form 1,25-dihydroxy-vitamin D3. The active form is essential for regulating the level of biologically active vitamin D, calcium homeostasis [41] and is an important immuno-modulator [42]. Given the possible link of vitamin D with MS susceptibility, it is expected that genetic variants in CYP27B1 may have a role in MS disease. Meta-analysis showed that CYP27B1 allele was significantly associated with reduced MS susceptibility. Subgroup analysis by ethnicity showed significant MS risk conferred by rs703842 polymorphism [43]. This meta-analysis was limited by the small sample size, and included studies focused on MS risk only in Caucasians. Furthermore, several important confounding factors were not studied as data for individual studies was not available.

2.6. IL1 gene

IL-1 cytokines (IL-1A, IL-1B and IL-1RA) are key factors in immune regulation and inflammatory processes [44]. Genes coding for these molecules are located close to each other on chromosome 2q13-14 and have several common polymorphisms. IL1A has two variants, both are C to T substitutions in linkage disequilibrium (LD) [45]. It has also a variable number of tandem repeats (VNTR) of 86 base pairs in the second intron [46]. ILB gene has two SNPs at position -511 in the promoter region and in the fifth exon [47]. IL1B and IL1RA co-operatively regulate IL-1RA production, and may be operative in inflammatory responses [48]. Given the existence of strong LD among IL1A, IL1B and IL1RA, it is difficult to determine causal polymorphisms on MS susceptibility [49]. Haplotypes of the IL1 gene should be considered when evaluating genetic effects on MS susceptibility. Meta-analysis did not indicate that IL1A -889 C/T, IL1B -511 C/T and IL1B 3953 C/T polymorphisms affect susceptibility to MS [50]. The value of this meta-analysis is limited by the small number of included studies. IL1A-889, -4845, IL1B -511, -3953 and VNTR polymorphisms did not contribute significantly to MS risk. However, subgroup analysis showed that the VNTR polymorphism increased the risk for both onset relapsing remitting and secondary progressive MS [51].

2.7. IL2RA gene

IL2RA gene, at the 10p15.33 region, has been shown to be related to several autoimmune diseases. Previous studies reported that the T allele of the IL2RA rs2104286 polymorphism and the C allele of the IL2RA rs12104286 were strongly associated with an increased risk of MS [52]. However, other studies reported a weak association. Genetic variants in IL2RA may be involved in MS before the disease onset. The IL2RA rs2104286 and other polymorphisms have been found to affect the expression of IL2RA and modulate the function of lymphocytes [53]. Meta-analysis showed that the IL2RA gene polymorphisms, rs2104286 and rs127224 89, were associated with increased susceptibility to MS [53].