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Genetic determinants of risk and progression in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease that represents a primary cause of neurological disability in the young adult population. Converging evidence supports the importance of genetic determinants for MS etiology. However, with the exception of the major histocompatibility complex, their nature has been elusive for more than 20 years. In the last decade, the advent of large genome-wide association studies has significantly improved our understanding of the disease, leading to the golden era of MS genetic research. To date more than 110 genetic variants have been firmly associated to an increased risk of developing MS. A large part of these variants tag genes involved in the regulation of immune response and several of them are shared with other autoimmune diseases, suggesting a common etiological root for this class of disorders. Despite the impressive body of data obtained in the last years, we are still far from fully decoding MS genetic complexity. For example, we ignore how these genetic factors interact with each other and with the environment. Thus, the biggest challenge for the next era of MS research will consist in identifying and characterizing the molecular mechanisms and the cellular pathways in which these risk variants play a role.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disorder affecting the central nervous system (CNS). MS CNS pathology is characterized by well-demarked inflammation, breakdown of myelin sheaths (demyelination), microglia activation, proliferation of astrocytes with ensuing gliosis, and variable grades of axonal degeneration. Demyelinated lesions are disseminated within the CNS, involving both the white and gray matter, causing axonal and neuronal loss and consequently, a plethora of clinical deficits such as weakness in one or more limbs, sensory disturbances, optic neuritis, ataxia, bladder dysfunction, fatigue and cognitive deficits [1]. MS typically starts as an episodic, relapsing–remitting disease (RR-MS) with complete or partial recovery in between relapses. Over time, it evolves in many of the afflicted individuals into a secondary progressive phase (SP-MS) characterized by irreversible deterioration of both motor and cognitive functions. However, up to 15% of MS patients show a progressive course without relapses and remissions from the onset of clinical signs, which is defined as primary progressive MS (PP-MS) [2]. Ten FDA-approved treatments for MS are now available. However, none convincingly alters the long-term prognosis of the disease. Furthermore, these therapies have very diverse safety and toxicity profiles and no comparative data exist to guide how to select among the available options. No therapy exists for the progressive form of MS, the subtype most responsible for progression of severe disability.

The age of symptom onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present at any time across the lifetime of the individual. Women are affected most frequently than men [3]. Worldwide, over 2.5 million people suffer from MS, making it the most common cause of acquired neurologic disability among young adults. The prevalence of MS varies with geography and ethnicity. Indeed, with some notable exceptions, MS is more frequent in high latitude regions and northern European populations [4,5]. Remarkably, disease incidence has been increasing in the last century as seen for other autoimmune diseases [3]. The etiology of MS is still largely unknown but multiple lines of evidence suggest that the interaction between genetic and environmental factors underlies the risk of developing MS. In recent years, fueled by significant advances in high-throughput genotyping technologies, a considerable effort has been dedicated to the discovery of the genetic determinants of MS susceptibility. We will summarize the major findings of this endeavor and discuss immediate challenges in the field of MS genetics research.

Abbreviations: MS, multiple sclerosis; GWAS, genome wide association study; RR-MS, relapsing–remitting MS; SP-MS, secondary progressive MS; PP-MS, primary progressive MS; CD–CV, common disease–common variant; MAF, minor allele frequency; MHC, major histocompatibility complex; HLA, human leukocyte antigen; OR, odds ratio; SNPs, single nucleotide polymorphisms; IMSGC, International Multiple Sclerosis Consortium; IL2Rα, interleukin-2 receptor; IL7Rα, interleukin-7 receptor; WTCCC2, Wellcome Trust Case Control Consortium 2; TNFRSF1A, tumor necrosis factor 1A; TYK2, tyrosine kinase 2; Th1, T-helper 1; CBLB, Casitas B-lineage lymphoma proto-oncogene b; BMI, body mass index; EAE, experimental autoimmune encephalomyelitis; TCR, T-cell receptor; MBP, myelin basic protein; PLP, proteolipid protein; Batf, basic leucine zipper transcription factor ATF-like; MSGB, MS genetic burden; G × G, genotype by genotype; G × E, genotype by environment; BAC, bacterial artificial chromosome; EBV, Epstein–Barr virus; MRI, magnetic resonance imaging.

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2. MS is a genetic disease

Early evidence that MS holds a genetic component comes from the observation that the disease aggregates within families; first-degree relatives of MS patients are at greater risk for developing the disease compared to the general population [6]. The age-adjusted life-time risk of MS positively correlates with the degree of shared genetic identity, ranging from 0.2% in the general population to 2–4% in siblings and up to 30% in monozygotic twins of MS patients [7,8]. Consistently, adoptees and spouses show risks comparable to the general population, corroborating the idea that shared genetic factors are the main cause of familial disease aggregation [9,10]. However, the fact that even genetically identical individuals (monozygotic twins) are not always concordant for MS, strongly suggests that other risk factors exist. These include environmental factors such as smoking, Epstein–Barr virus (EBV) infection and sun exposure, and epigenetic determinants such as DNA methylation patterns, histone modifications and non-coding RNAs [11,12].

Studies of MS prevalence in ethnic groups residing at the same latitudes support a genetic etiology in MS as well. For instance, the prevalence among non-white population groups in the United States appears to be lower compared to northern European descendants [13,14]. Early estimates suggested that the disease is significantly less prevalent in African Americans than in European Americans (relative risk of 0.64) [15]. In contrast, contemporary incidence studies are challenging the long-held belief that African Americans are at a reduced risk for developing MS [16,17]. Native Americans exhibit significantly lower incidence rates of MS in both the United States and Canada [18,19]. In Europe, emblematic is the case of the genetically divergent Sardinian population that shows higher MS prevalence compared to other southern European groups [20]. The enrichment in specific genetic traits conferring higher risk for MS could explain the discrepancies in MS prevalence among ethnic groups living in the same geographical regions. Interestingly, compared to whites, African Americans are more likely to have a more severe disease course, which at least in part appears to be genetically determined [14,21,22].

The working model for MS heritability that best fits the available genetic and epidemiology data is the so-called common disease–common variant (CD–CV) hypothesis (Fig. 1). According to this model, MS risk is determined by cumulative effects of a large number of allelic variants. Each variant is relatively common within the population (minor allele frequency, MAF > 1%) and contributes small portions of the risk [23]. Moreover, epistatic interactions among some of these risk variants are likely to take place as suggested by the non-linear correlation between familial risk and degree of relatedness [24]. Genetic heterogeneity (different variants might cause identical or similar forms of the disease in different subjects) represents an additional layer of complexity. This multifactorial, non-Mendelian pattern of heritability is not exclusive of MS but it is shared with other common disorders such as type II diabetes and obesity [25].

2.1. MS genetic research before the advent of genome-wide association studies (GWAS)

The landscape of early discovery efforts for MS susceptibility factors was dominated by case–control studies of allelic variants in candidate genes. Candidate genes were defined as genes that have reasonable possibilities to play a role in a disease; for immune-mediated diseases, candidate genes might encode cytokines, immune-receptors, and proteins involved in pathogen clearance. With the notable exception of the human leukocyte antigen (*HLA*) gene cluster within the major histocompatibility complex (MHC) region, the direct testing by association of possibly relevant candidate genes selected based upon concepts of pathogenesis has been in general, unproductive.

2.2. Human leukocyte antigen (HLA) genes in MS

Following the discovery of the MHC in mice in 1936 [26], the human equivalent was subsequently mapped to the short arm of chromosome 6 (6p21.3) and extensively studied for both gene and allelic content variation. The first full sequence of this region was completed and reported in 1999 by the MHC-Sequencing Consortium [27]. Gene density was greater than expected; of the 224 identified loci, approximately 150 were predicted to be expressed and about 40% to have immunological functions. Among these, the highly polymorphic classical *HLA* class I (*HLA-A*, *-B*, *-C*) and class II (*HLA-DPB1*, *-DQB1*, *-DRB1*) gene clusters are now well characterized in terms of structure, diversity, and function. An extraordinary amount of data confirms their central role in the allogeneic response to tissue and hematological transplantation and risk for autoimmunity [28,29].

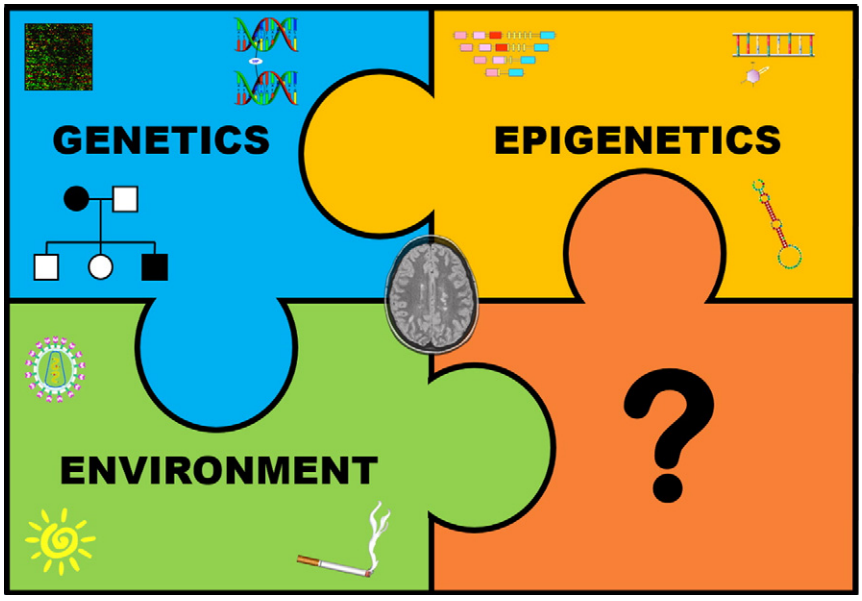

Fig. 1. Working model for multiple sclerosis risk inheritance. Multiple sclerosis is a complex genetic disorder in which multiple common allelic variants interact with non-genetic risk factors to determine disease susceptibility. Such non-genetic determinants can be either epigenetic or environmental. Several environmental risk factors for MS have been convincingly linked to MS risk; these include vitamin D deficiency, exposure to the Epstein–Barr virus (EBV) after early childhood and manifestations of infectious mononucleosis, cigarette smoking and obesity.