



HLA-Genotype in Multiple Sclerosis: The Role in Disease onset, Clinical Course, Cognitive Status and Response to Treatment: A Clear Step Towards Personalized Therapeutics

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Abstract

Multiple Sclerosis (MS) is probably the best studied chronic inflammatory and demyelinating disease of the Central Nervous System (CNS), with a clear impact on patients' quality of life. Many factors have been described to play a role in the initiation and clinical course of the disease, as well as in the response to medication. These factors include age at onset, gender, viral infections, Human Leucocyte Antigen (HLA)-genotype, non-HLA genes, Vitamin D levels and smoking. HLA genetic profile is the most important one, as it not only influences every aspect of the disease, but it also modifies the effect of the other factors.

In this review article we summarize the decisive effect of HLA-genotype on MS initiation, clinical course, cognitive impairment and therapeutical outcome, as well as on other demyelinating diseases of the CNS (including Neuromyelitis Optica and Acute Disseminated Encephalomyelitis). HLA-DRB1*15:01 is the best established allele, both increasing the risk of MS 2-3 times and influencing response to first line medication (including Interferon-beta and Glatiramer Acetate), but neutralizing antibodies' formation against natalizumab, as well. Other Class I and Class II HLA alleles have either a detrimental (DRB1*08:01, 03:01, 13:03, 15:03, 04:05) or a protective (DRB1*14:01, *07, *11, A*02:01) effect on MS. Taking into account their epistatic interactions, we conclude that HLA-genotyping may lead to an individualized approach of MS patients, in different ethnic groups.

Keywords: Multiple Sclerosis, Immunogenetics; Neuroimmunology; Risk factors; Clinical course; Cognitive status; Treatment; Personalized therapeutics

Abbreviations: MS: Multiple Sclerosis; HLA: Human Leucocyte Antigens

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS), affecting around 2 million people worldwide, with Europe considered a high prevalence region for MS (prevalence \geq 30/100,000) containing more than half of the global population of people diagnosed with MS [1]. Its etiology, although not completely understood, is multifactorial, as both genetic and environmental agents can influence the disease risk and clinical course. Vitamin D levels, smoking and Epstein Barr Virus (EBV) (both anti-Epstein Barr Nuclear Antigen-EBNA-IgG seropositivity and infectious mononucleosis) are the best established environmental factors [2], while Human Leucocyte Antigen (HLA)-genotype carries the strongest genetic burden for MS, although non-HLA genes and gene-gene interactions (called epistasis) play a role [3]. Non-HLA genes seem to participate not only in MS initiation, but also in patients' response to treatment.

As far as HLA-genotype (especially class II genes) is concerned, it is not only responsible for up to 30% of the MS risk, but it also crucially participates on almost every aspect of the disease [4]. In other words,

HLA genetic profile modifies the risk of the disease, influences its clinical course and plays a decisive role in patients' response to treatment. Given the inflammatory nature of MS (among others), the role of Major Histocompatibility Complex (MHC) in the disease's pathophysiology cannot be ignored [5]. Supporting evidence is provided by the role of HLA in other demyelinating disorders of CNS, like Neuromyelitis Optica (NMO or Devic's disease) [6] and Acute Disseminated Encephalomyelitis (ADEM) [7].

Of great interest is the observation that HLA alleles seem to modify the influence of environmental factors on MS risk. Smokers have higher risk of developing MS compared to non-smokers [8] and this risk seems to be higher among patients carrying specific HLA alleles. Increasing levels of circulating Vitamin D (25-OH-Vit D) lower the risk of MS [9]. This last observation is of great importance as it can partially explain the well demonstrated latitude-dependence prevalence of MS. Further investigation revealed a close relation between vitamin D and HLA-DR antigen expression and presentation, a finding being described as gene-environment interaction [10]. Epstein-Barr virus has also been found to increase the risk of MS and this is a well-established and unanimously accepted correlation which is stronger among individuals carrying HLA-DRB1*15:01 allele [11]. Other members of Herpesviridae family, including Cytomegalovirus (CMV) [12] and Herpes Simplex Virus (HSV) [13], have also been connected to MS risk.

The HLA genetic background clearly modifies MS clinical characteristics. Age at onset [14], gender of patients [15], clinical

course [16] and cognitive impairment [17], all seem to be more or less influenced by specific HLA alleles, making an individualized prognosis of the disease according to HLA genotype a plausible target. All of the above highlight the importance of HLA, making it inevitable to think that it may also play a key role in response to treatment. This hypothesis has been confirmed for the first line treatment agents, like glatiramer acetate (GA) [18] and interferon-beta (IFN- β) [19], which are the most commonly used disease modifying drugs. Their positive effect on MS differs among patients with different HLA-genotype [18,19], a finding that opens the avenue to personalize our therapeutic decision-making, thus optimizing response to medication.

In conclusion, HLA is by far the best studied factor for over than thirty years now and possibly the most important one. Aim of our review article is to summarize the role of HLA-genotype in every aspect of MS; from pathophysiology to treatment so as to explore its effects in a holistic approach, towards personalized therapeutics.

Multiple Sclerosis and HLA-Genotype

Risk and protection for the disease

Risk evaluation: the role of HLA-Genotype: There are plenty of HLA alleles some of which are referred to predispose for MS, while others to protect from the disease. The best documented HLA allele is DRB1*15:01, which is the strongest risk factor for MS. Human Genome Epidemiology review of 72 papers published from 1993 to 2004 found that in all but a very few studies, the frequency of DRB1*15:01 was greater in cases than controls [4]. The studies where DRB1*15:01 was not associated with MS were, in nearly every instance, conducted in non-European populations. More recently, GWAS (Genome Wide Association Studies) have pointed out HLA-DRB1 gene, in the class II region of the MHC, as the main susceptibility locus, explaining up to 10.5% of the genetic variance underlying risk. HLA-DRB1*15:01 has the strongest effect with an average odds ratios (OR) of 3.08, and all additional DRB1 associations appear to account for less than 2% of the remaining variance [20]. These findings have been confirmed by a meta-analysis of GWAS studies. (DRB1*15:01 OR=2:92) [3].

Another meta-analysis (including studies in Caucasian populations, published from 1994 to 2010) confirms the above mentioned data, concerning the role of HLA-DRB1*15:01. HLA-DRB1*15 frequencies were significantly higher (OR=2:59) in MS patients compared with controls in both allele and phenotype groups [21].

Interestingly, the risk associated with HLA-DRB1*15:01 seems to be additive, depending on the copies of the risk allele with a clear dose response to 0, 1 or 2 copies. A similar pattern of dose effect of HLA-Genotype has been observed in other autoimmune diseases as well, including rheumatoid arthritis, narcolepsy, and celiac disease and Type-1 diabetes.

An independent association for DRB1*08:01 has been observed in an Ashkenazi cohort when patients were subdivided into clinical subgroups, with a weak but significant association reported for primary progressive MS patients only [22].

A well established, although not very strong (OR=1:7), association has been found for DRB1*03:01, a very common allele worldwide. HLA-DRB1*13:03 is a well-studied gene, although its association with MS risk is neither as strong nor as clear as that of HLA-DRB1*15:01. A possible explanation for the inconsistent identification of DRB1*13:03 in MS risk is the low power due to its worldwide rarity. Where it is seen

at higher frequencies, such as in the Israeli population [23], in Sardinia [24,25], or in studies with thousands of individuals, DRB1*13:03 is revealed clearly as a risk allele.

As far as African Americans are concerned, DRB1*15:03 seems to be the predominant DR2 allele in this population [26]. Importantly, this DRB1*15 subtype is also associated with MS (OR=1:6). HLA-DRB1*15:01 also plays a role, but it is not so common among African Americans (frequency 7.3%, in contrast to around 50% among white Americans population with MS) and its effect seems weaker, too (OR=1:7). Similar results arise from case-control studies in Martinique [27], Iran [28] and Brazil [29].

Another risk allele for MS is DRB1*04:05. DRB1*04:05 was recognized as a risk variant for "Asian" MS [16] (OR=2:23), but with a clinically distinct disease course characterized by earlier age at onset, reduced severity and fewer brain lesions, while DRB1*04:05 negative Japanese patients have features similar to Western-type MS, characterized by an association with EBV infection as well as presence of DRB1*15:01. These results have been partly reproduced in another Asian cohort [30].

HLA-DRB1*04:05 has also been found to be associated with MS in Sardinia, where the incidence of MS is quite high [31], among African Americans [32] as well as Sicilians [33]. This allele is relatively common in both the Japanese and Sardinian populations, but much less so in other Europeans. Thus, limited statistical power may explain a lack of clear association of DRB1*04:05 in other populations [20].

As far as the protective alleles for MS are concerned, DRB1*14 and DRB1*07 showed protective effects against MS in a meta-analysis of 37 case control studies, all in Caucasian populations [21].

The class II allele, which is most consistently associated with protection from MS in European populations, is DRB1*14:01. Protection mediated by DRB1*14 appears to be dominant, reducing the predisposing effect of DRB1*15:01 [34]. HLA-DRB1*15/14 demonstrates strong evidence for a protective effect when contrasted with HLA-DRB1*15/X genotypes (where X stands for any other HLA allele, except DRB1*15) (OR=0:2) [34].

HLA-DRB1*11 was also found to be protective in Brazilian [35], Canadian [36] as well as Greek [37] populations. The protective role of HLA-A*02:01 has been confirmed among many different populations and it remains the best studied HLA-Class-I allele, independently associated with MS [38].

Except for HLA genes, there are also other genes outside the MHC region (non-HLA genes), which have been found to predispose for MS and in some cases to be able to influence the therapeutical outcome. Candidate gene studies, as well as genome wide association studies (GWAS) provide evidence concerning the role of non-HLA genes. Cytokines play a core role in MS pathophysiology. Dysregulation of cytokines, like Interleukins and Tumour Necrosis Factor (TNF) may be one of the early events that contribute to the onset and further cascade of inflammation, not only in MS patients, but also among patients with other autoimmune diseases. Not surprisingly, the genes coding TNF are located within chromosome 6, at the MHC region [39]. Genes coding for interleukin receptors (IL7RA and IL2RA) have been proved to confer a moderate risk for MS in many studies [39]. De Jager et al. point out in their meta-analysis specific susceptibility loci (with a modest effect) at *TNFRSF1A*, *IRF8* and *CD6* genes [40]. Recently, Lopez de Lapuente et al. highlighted the detrimental effect of ANKRD 55 not only on MS risk, but also on neuroinflammation procedures

[41]. Interestingly, a CD58 variant (rs2300747) has been established as a protective allele, as its expression seems to boost the function of a CD4 subpopulation which is defective among MS individuals [42]. On the other hand, rs12044852 allele has been proved to increase MS risk [43].

To conclude at this point, various non-HLA genes have a well-established, but much weaker than HLA genes, effect on MS risk. However, their contribution is rather important as they may represent the missing genetic link of MS, taking into account their epistatic interactions with HLA alleles.

Epistasis: Epistasis refers to the combinatorial effect of one or more factors, which seem to influence the risk of a disease. These factors may be both genetic (gene-gene interactions) and environmental (gene-environment interactions) [44]. Via epistasis we try to interpret interactions found to be statistically relevant in order to get closer to their biological definition and to understand the underlying functional mechanisms [45]. Given the great number of factors implicated in MS, epistasis is a really useful tool in our aim not only to study those factors but also to explore their possible interactions.

Gene-gene interactions

As mentioned above, the role of many HLA and non-HLA alleles and their contributions to MS is almost clear. However, the possible interaction between those genes, along with the extent of these interactions still remains rather obscure. The epistatic interactions between HLA and non-HLA genes have been thoroughly examined in a meta-analysis by Moutsianas et al. [46].

After analyzing high-density Single Nucleotide Polymorphisms (SNPs) data on 17,465 cases and 30,385 controls from 11 cohorts of European ancestry, the authors found evidence for two interactions involving pairs of class II alleles: HLA-DQA1*01:01-HLA-DRB1*15:01 and HLA-DQB1*03:01-HLA-DQB1*03:02.

HLA-DQA1*01:01 plays a protective role only in the presence of HLA-DRB1*15:01, which replicated in meta-analysis (OR=0.65). A second allelic interaction involving HLA-DQB1*03:02 and HLA-DQB1*03:01 was also identified such that the latter abolished the risk associated with the former (OR in the presence of HLA-DQB1*03:02=0.60).

No evidence for interactions between HLA and non-HLA risk loci has been found among MS patients, although such interactions have been described for other autoimmune diseases (including psoriasis, ankylosing spondylitis and Behçet's disease) [46].

Besides these findings, the authors suppose that it is nevertheless possible that the effects of individual classical alleles are modulated by many weak effects at many loci across the genome, a phenomenon called polygenic epistasis.

Another case control study of a Spanish population (380 unrelated patients diagnosed with MS and 1088 healthy controls) [47] found DRB1*07 allele to exert an epistatic effect along with the DRB1*15 but in an opposite direction which neutralizes this genotype, but this hypothesis still needs to be verified.

In a family-based investigation of a Canadian population 48 HLA-DQA1*01:02 was also found to interact strongly with HLA-DRB1*15, increasing MS risk in the presence of HLA-DRB1*15 and playing a protective role in its absence. To assess this allele for interaction with HLA-DRB1*15, transmission of HLA-DQA1*01:02 from HLA-DRB1*15-negative parents was stratified by the presence

(overtransmission) or absence (undertransmission) of HLA-DRB1*15 (transmitted from the other parent) in affected offspring. HLA-DQA1*01:02 is overtransmitted (OR=2.1) when HLA-DRB1*15:01 is also present in affected offspring, but when HLA-DRB1*15:01 is absent, HLA-DQA1*01:02 is undertransmitted (OR=0.64).

Gene-environmental interactions

The role of vitamin D: Hypovitaminosis D has long been established as a risk factor for MS probably explaining the epidemiological evidence which correlate MS risk to latitude and subsequently exposure to sunlight [48,49] (MS prevalence increases with distance from the equator in both hemispheres). Ramagopalan et al. [50] have identified a vitamin D response element (VDRE) in the HLA-DRB1 promoter region, a finding of great importance, as it indicates a direct biological interaction between the main MS risk allele (HLA-DRB1) and one of the best established environmental risk factors (Vitamin D). This interaction when studied to its full extent may explain the so-called missing genetic risk for MS. Ongoing randomized controlled trials have to find out if Vitamin D supplementation reduces the risk of MS, as current data implicate a protective role of high serum levels, proposing Vitamin D intake as a primary prevention measure against MS [9,51,52].

Smoking: Both ever-smokers and current-smokers have a higher MS risk and this is a well-established correlation by numerous retrospective and prospective studies. The influence of smoking on MS natural history remains controversial, although smoking seems to deteriorate disease's clinical course, accelerating conversion to secondary progressive MS [8,53]. Smoking interferes with the HLA-Genotype, thus modifying the risk of MS among patients carrying specific risk or protective alleles. Hedström et al. have found that the odds ratio associated with a profoundly susceptible genotype (carriage of HLA-DRB1*15 but not HLA-A*02) in smokers was 13.5, whereas in non-smokers was 4.9, compared with non-smokers without these genetic risk factors [54]. The same authors expanded the above mentioned findings among passive-smokers, although this correlation is weaker [55].

The role of viruses in MS initiation and HLA-Genotype: A number of viral agents have been investigated and Epstein-Barr virus has been the most consistently associated with increased MS risk.

Epstein Barr virus

The role of EBV in autoimmune diseases and especially its contribution in MS pathogenesis is thoroughly examined, but not yet fully understood. EBV is a human gamma-herpes virus that specifically infects nasopharyngeal epithelial cells and resting B-lymphocytes, hiding in a latent form in memory B-cells in the majority of the world population. As infected memory B-cells differentiate into plasma cells EBV switches to lytic reproductive phase to produce new EBV particles. Enhanced lytic replication results in new infection events and EBV-associated transformation events, and seems to be a risk factor both for malignant transformation and the development of autoimmune diseases [13].

There is a persuasive body of evidence linking EBV infection to MS risk and several hypotheses have been proposed to explain the role of EBV in the development of MS [56].

Epidemiologic evidence of its involvement include higher prevalences of anti-EBV seropositivity (virtually 100%) in MS patients compared with matched controls, higher concentrations of serum antibodies against both the EBV viral capsid antigen (VCA) and

nuclear antigens (EBNA-1) and more frequent history of infectious mononucleosis, a marker of late age at infection with EBV. A systematic review of eight published case-control studies comparing EBV serology in MS patients and controls included a total of 1,005 cases and 1,060 controls. The summary odds ratio of MS comparing EBV seropositive individuals with EBV seronegative individuals was 13.5 (95% CI =6.3-31.4). These findings support a role of EBV in the etiology of MS [57].

A similar correlation has been established in paediatric populations [58-60]. Moreover, infectious mononucleosis (manifestation during adolescence or early adulthood) is identified as a clear risk factor for MS later in adulthood [61].

Considering this association and the close relationship (both epidemiological and aetiological) between HLA genes and MS, it is inevitable to suppose that HLA genotype may interfere with the effect of EBV infection to MS pathogenesis, clinical course and response to treatment.

A meta-analysis calculated the additive (S) and multiplicative interaction indexes (OR) between EBV infection and HLA-DRB1*. EBV infection was significantly associated with MS (OR=2.60). HLA-DRB1*15:01 was associated with a significantly increased risk of MS (OR, 3.06). An additive interaction effect between EBV infection and HLA-DRB1*15:01 on MS was observed (S, 1.43; 95% CI, 1.05-1.95, P=0.023), but no interaction effect was observed on the multiplicative scale. HLA-DRB1*15:01 was associated with a 3-fold elevation in MS risk, and EBV infection was associated with a 2.6-fold elevation in MS risk. The combined effects of HLA-DRB1*15:01 positivity and EBV infection result in an up to six-fold increased risk of MS. These findings highlight the importance of the interaction effects between HLA-DRB1*15:01 and EBV infection on the occurrence of MS [11]. Another study population reproduced the additive interaction of HLA-DRB1*15:01 status and EBV infection (expressed by antibodies against EBNA1 or EBNA1 fragments). All EBNA1 fragment IgGs were associated with MS risk. However, EBNA1 fragment 385-420 IgG levels were more strongly associated to MS than total EBNA1 IgG, OR=3.60 (2.75-4.72 95% CI), and also interacted with both HLA-DRB1*15 and absence of HLA-A*02. These observations suggest that the mechanism through which HLA genes influence the risk of MS may, at least in part, involve the immune control of EBV infection [62].

Similar results were found in a paediatric population (189 MS patients and 38 controls), as DRB1 positivity seemed to be associated with higher EBNA-1 antibody response among those who were EBNA-1 positive. In contrast, DRB1 positivity was not associated with higher VCA, EBNA, CMV or HSV-1 antibody response among those who were positive for seroconversion against the virus [12].

On the other hand, the above mentioned correlation was not confirmed in a Kuwaiti MS cohort (including 141 patients and 40 controls) [63].

Herpes simplex virus (HSV)

As far as the role of HSV is concerned, Waubant et al. have found no significant association between HSV infection and MS risk [59]. However, it is of great importance the notice that HSV-1 does appear to have a strong role in predicting MS or Clinically Isolated Syndrome (CIS) when evaluated separately in HLA-DRB1*15-positive and HLA-DRB1*15-negative individuals.

HSV-1 positivity seems to be associated with greater MS risk in DRB1-negative patients (OR=4:1) but reduced risk in HLA-DRB1-positive patients (OR=0:7).

Cytomegalovirus (CMV)

As far as CMV is concerned, there is no definite evidence regarding its role in MS, as both a protective and a harmful effect have been reported. However, during the last years there is a growing amount of evidence supporting its protective role. CMV, another virus from the Herpesviridae family, is a common virus with a seroprevalence ranging from 45% to 100% worldwide, and slightly higher in women compared to men [64].

Both a case control study and a meta-analysis published by Sundqvist et al. [65] found CMV to be associated with a decreased MS risk (OR=0.73 and 0.77, respectively).

Interestingly, the authors describe an interaction on the additive scale between CMV seropositivity and HLA-DRB1*15. Some additional evidence for a protective role of CMV on MS risk was found in a meta-analysis of only prospective studies [66].

CMV infection is also associated with better clinical and MRI outcomes in MS patients [67] and with a lower risk of developing MS or CIS (OR 0.37, 95% CI 0.16-0.84, p=0.02) among a paediatric population [59]. Supporting evidence come from a pilot study which studied whether underlying murine CMV (MCMV) infection affects the course of the Theiler's murine encephalitis virus (TMEV) induced murine model of MS [68].

Age at onset and HLA-Genotype: Although MS has been traditionally recognized as a disease of early adult life, it is nowadays well-established the fact that the disease can begin in childhood or adolescence, despite the rarity of this condition. Approximately 2-5% of MS patients experience their first symptoms before the age of 18, thus having an early-onset MS. When disease begins before the age of 16 we are talking about pediatric onset MS, while disease onset between 16-19 years is called adolescent onset MS [37]. An initial attack of demyelination in childhood, named acute demyelinating syndrome (ADS), is not always a prelude to MS appearance, as in some cases it remains a monophasic illness [14]. The correlation of HLA genotype with ADEM (another demyelinating disease of childhood) is further analysed in next sections.

There is evidence that genetic background between paediatric and adult MS is similar, while children with ADS seem to have a different and still not well-defined genetic profile [69].

Data from large Canadian prospective studies proved that children with HLA DRB1*15 alleles have increased risk of developing MS after an ADS (OR=2.32-2.7) [70,71]. Interestingly, this association has been established only in children of European ancestry. HLA-DRB1*15 has been described as a risk factor for early-onset MS in a Scandinavian population [72], while in an Australian cohort it seems to be associated with a reduced age at onset only when combined with HLA-DRB1*04:01. The same authors found that HLA-DRB1*04:01 may delay age at onset when combined with HLA-DRB1*08:01, highlighting the effect of possible epistatic interactions on MS onset [73]. In a Korean population, close linkage of DRB3*02, DRB1*13 and DQB1*03 was also associated with the risk of childhood MS, but the sample size is not sufficient to establish those associations [74].

Part of the above mentioned findings were also confirmed in the Hellenic population [37]. Patients with early-onset MS had

significantly higher frequencies of the DRB1*15 allele (OR=2.653) and significantly lower of the DRB1*11 allele (OR=0.448). HLA-DRB1*16 allele was found significantly absent in the paediatric group (p=0.011), while HLA-DRB1*11 allele was significantly lower in the adolescent group (OR=0.204). Adult-onset MS (above 20-years-old) was characterized by significantly higher HLA-DRB1*15 allele frequency (OR=2.653) and significantly lower DRB1*11 allele frequency (OR=0.462).

Patients with adult-onset disease onset had a significant increased frequency of DRB1*16 allele versus patients with paediatric onset (p=0.004).

Patients with adolescent onset MS showed increased frequency of the DRB1*16 allele than the paediatric group (p=0.009).

Gender and HLA-Genotype: It is common knowledge that MS affects more women than men, with a female to male ratio as high as 3:1 [75], with an increasing trend established in many prospective studies [15]. However, when examining each type of MS ratios are quite different: in Relapsing Remitting (RR)/Secondary Progressive (SP) MS patients sex ratio is similar to the overall ratio (2.5:1), while in the Primary Progressive (PP) MS group distribution among sexes is almost equal (ratio 1.2:1). Concerning RRMS, men seem to experience a more malignant form of the disease compared to women, as they have a more rapid accumulation of disability and a poorer recovery after relapses [76]. Interesting data correlate HLA genotype to gender, suggesting that HLA-DRB1*15:01 haplotype seems to be female specific, meaning that among affected individuals, the female-to-male ratio was significantly higher in the presence of HLA-DRB1*15 [77-79]. A maternal parent of origin effect has also been established; in other words, a significant over-transmission of the maternal HLA-DRB1*15 allele.

Epitope spreading and HLA-Genotype: Multiple Sclerosis, as an autoimmune disease, is caused by an inappropriate T-cell response against various autoantigens (Myelin Basic Protein, Myelin Oligodendrocyte Protein and Proteolipid Proteins are the most pronounced ones), which leads to the initial attack of demyelination. As the inflammatory process goes on, T-cell activation spreads to other epitopes of the same antigen (intramolecular epitope spreading) or to other antigens (intermolecular epitope spreading), possibly sharing similar physicochemical features to the initial (trigger) autoantigen, a phenomenon called molecular mimicry. Epitope spreading has been found to play a role in MS pathophysiology both in animal models and among MS patients [80]. There is plenty of data from animal MS like models supporting the hypothesis that specific HLA risk alleles hold a vital role in the immunological processes of autoantigen presentation and epitope spreading, which guide the inflammatory procedure in MS [5]. HLA-DQB1*06:02 along with DRB1*15:01 are the best studied alleles which seem to boost pathogenic autoimmunity via targeting the above mentioned autoantigens. Despite really intriguing, these data still remain to be confirmed in studies among human populations so as to explore if epitope spreading is a crucial link of HLA's contribution to MS pathogenesis.

Clinical course and HLA-Genotype

The clinical course of MS is diverse. Most patients (around 85%) experience a chronic disease with relapses and remissions (RRMS), which after an unpredictable period of time changes to a progressive type (SPMS) in about 75% of patients. In only 15% of patients the disease may follow a progressive course from the onset (PPMS) [81].

One of the main problems when facing MS patients is our difficulty to predict the disease course; in other words to personalize prognosis. HLA genotype may play a key role in identifying those patients prone to a better or worse clinical outcome.

HLA genotype and especially HLA-DRB1*15:01 has frequently been associated with markers of disease severity, acting as a disease modifier [37,82]. MS patients carrying the HLA-DRB1*15:01 haplotype are more likely to be female and have earlier age at onset [83,84], while disease course [85] (as expressed by Expanded Disability Status Scale-EDSS- score), spinal cord pathology [17] (in terms of demyelination and inflammation), motor cortical demyelination [86], loss of brain volume and cognitive decline all seem to be more severe [87].

However, a big family based, case-control study by Barcellos et al. [34] failed to reproduce the above mentioned findings.

Two case control studies [88,89] suggest that disease course of MS may be influenced by the presence of alleles encoding HLA-DR molecules containing specific amino-acids in positions important for antigen binding. These alleles have been found to protect against the development of a relapsing-remitting course or increases the susceptibility to a primary progressive course of disease, or both.

These findings have been partially confirmed from a molecular point of view by Kumar et al. [90], as they found that in a Sardinian population protective allele HLA- DRB1*16:01 (in contrast to predisposing one DRB1*15:01) may discriminate between self and non-self-peptides, thus modifying the inflammatory procedure and as a result the disease course.

Cognitive impairment and HLA-Genotype

Multiple sclerosis is a progressive disease of the CNS characterised by widespread lesions in the brain and spinal cord. The common cognitive impairment includes deficits in complex attention, efficiency of information processing, executive functioning, processing speed and long-term memory [91]. Although cognitive impairment in MS is well established, less is known about the effect of HLA. Only DRB1*15:01 has been proved to deteriorate cognitive function measured by neuropsychological tests [87]. HLA-genotype seems to influence cognitive status and its decline over years not only in MS patients, but also among healthy populations and in other neurodegenerative diseases. Payton et al. have found in a healthy population HLA-DRB1*11:01 to be associated with improved vocabulary ability, while HLA-DRB1*08:01 was associated with impaired vocabulary ability and faster rate of decline in addition to impaired memory ability [92]. Furthermore, there is evidence of shared immunopathological mechanisms between MS and Alzheimer's disease, as Lambert et al. have identified HLA-DRB5-DRB1 region as a possible susceptibility genetic locus for Alzheimer's disease (OR=1.11) [93]. However, the authors did not accurately define the gene(s) responsible for this correlation, due to the complex genetic organization of HLA region on chromosome [6].

Only few studies have provided evidence connecting cognitive decline among MS patients with the presence of Oligoclonal Bands (OCB) in their Cerebrospinal Fluid (CSF).

Patients with OCB seem to perform significantly worse on both visual and verbal memory compared to patients without OCB [94], but studies with big sample size are needed to establish this finding, given the rarity of OCB-negative MS. These data may indicate an indirect connection of HLA with cognitive impairment, if we take into account

the quite clear association between OCB status and HLA-genotype (analyzed below).

Brain volume: As far as the characteristic radiological findings of MS are concerned, these include T2 lesions, postcontrast enhanced lesions, T1 hypo intensive lesions and global or regional atrophy or brain volume reduction [95].

HLA-DRB1*15:01 not only deteriorates cognitive function (as mentioned in the previous section) but also increases radiological burden, expressed by the above mentioned MRI findings [87]. This correlation between HLA-DRB1*15:01 genotype and neuroradiological findings has been reproduced in a prospective study of a PPMS population [96].

As Healey et al. have proven, HLA-B*44 is associated with higher Brain Parenchymal Fraction(BPF) and lower T2 lesion volume, what in other words means that this allele seems to have a protective effect (in contrast to DRB1*15:01) in terms of MRI disease burden [97].

Except for the brain lesions, HLA-DRB1*15 seems to increase the extent of both demyelination and inflammation in the spinal cord of MS patients [17,98].

Oligoclonal bands and HLA-Genotype

Only few studies have provided evidence connecting cognitive decline among MS patients with the presence of OCB in their CSF.

Patients with OCB performed significantly worse on visual memory compared to patients without OCB. Evaluation of verbal memory in MS patients supported a main deficit in information retrieval, followed by encoding as disability increased, with infrequent storage deficit [94].

The presence of OCB has been also connected with HLA genotype of MS patients. Mero et al. have shown in a Scandinavian population that DRB1*15:01 is associated with presence of OCBs in the CSF of MS patients, while HLA-DRB1*04:04 is associated with increased risk of OCB negative MS and reduced risk of OCB positive MS [20]. The above mentioned correlation of HLA-DRB1*15:01 gene with OCB has been reproduced in Spanish [47], Italian [99] and Japanese (where also a negative association of HLA-DRB1*04:05 with OCB status has been found) [16,100] cohorts and confirmed by Goris et al. [101], through a large study based on data collected from nine countries. The same authors concluded that patients with MS and high CSF antibody levels, as characterized by OCB-positive status and/or high IgG index, more often are female and seem to have a lower age at onset and higher Multiple Sclerosis Severity Score (MSSS). OCB-status and IgG index are highly correlated probably reflecting the same immunological process [102]. Both measurements are useful in the diagnosis and management of MS, as OCB is the most sensitive method to detect abnormal antibody production in CSF, while quantitative assessment of IgG in CSF is much easier and quicker and thus can be used as an additional diagnostic tool [103].

Other Demyelinating Diseases and HLA Association Studies

Neuromyelitis optica (NMO)

Neuromyelitis optica represents <1% of demyelinating diseases of the CNS in Caucasians and it is certainly more common in Asians. NMO was for many years considered as an opticospinal subtype of MS, but today a broader disease spectrum (NMO spectrum disorder,

NMOSD) is recognised with standard diagnostic criteria [6]. Studies regarding NMO and its HLA genetic background have been conducted mainly in Japanese populations, given the greater frequency of NMO in Asia.

Researches among Asian populations have found that NMO is associated with the HLA-DPB1*05:01 allele [104-106] HLA-DPB1*05:01 is the most common DPB1 allele in Japanese, which may explain the frequent occurrence of anti-aquaporin-4 antibody (anti-AQP-4) in Japanese Opticospinal MS (OSMS- subtype of MS in Asians that shows a selective involvement of the optic nerve and the spinal cord). However this association has not been reproduced in a Caucasian population [107], while HLA-DRB1*03 allele is highly frequent in the NMO-IgG positive patients [108]. On the other hand, frequency of HLA-DRB1*15:01 was reduced among NMO patients compared to MS patients fact that indicates a possible protective role of this allele [109]. This is of great importance, given the role of this allele in MS risk.

As a conclusion, it is clear that quite different HLA alleles are correlated to NMO compared to MS patients, resulting to a distinguished ethnic distribution of these two diseases. The above mentioned ethnic and consequently genetic discrepancy possibly reflects different underlying immunopathogenic mechanisms [6].

Acute disseminated encephalomyelitis (ADEM)

ADEM is an inflammatory disorder of the CNS characterized by a widespread demyelination, predominantly involving the white matter of the brain and spinal cord. The condition is usually precipitated by a viral infection or vaccination. The presenting features include an acute monophasic encephalopathy with multifocal neurologic signs and deficits. Children are preferentially affected. As specific biological markers have not been established, the diagnosis of ADEM is still based on the clinical and radiological findings. Recurrent or multiphasic forms have been reported, raising diagnostic difficulties in distinguishing these cases from MS [110,111].

Given the rarity of this condition, no big studies examining its connection to HLA genotype have been conducted.

Studies on peripheral immunocytes and CSF revealed the presence of cytokine-mediated responses in ADEM [112]. As the cytokines profiles are mediated by HLA, it can be speculated a possible association between ADEM and HLA alleles. Possibly, a T-cell mediated autoimmune response to myelin basic protein, triggered by an infection or vaccination, underlies its pathogenesis, as well as the possible role of HLA-genotype [113].

Still, there is evidence proposing a role of HLA-genotype in the risk of ADEM. More specifically, ADEM seems to be associated with HLA-DRB1*01 and HLA-DRB1*17 in the Russian population [7].

Leon et al. [113] found in a Brazilian population significant association of HLA- DQB1*06:02, HLA-DRB1*15:01 and HLA-DRB1*15:03 alleles with ADEM monophasic patients. Italian cohorts provided some further evidence, regarding the role of HLA. Frequencies of HLA-DRB1*16 and HLA-DQB1*05, as well as the association of HLA-DRB1*16/HLA-DQB1*05 were significantly increased in ADEM population compared to the control group [114].

Response to Treatment

The studies so far show that HLA-genotype plays a vital role in response to treatment of MS patients. As a result it is of great importance to study and evaluate every possible aspect of this correlation, as that would allow us to target and personalize our therapeutical approaches, thus leading to better outcome.

Interferon-beta (IFN- β) and Glatiramer acetate (GA) are called Disease Modifying Treatments (DMTs), as they have been clearly found to reduce relapse rate and delay progression of disability [115,116]. No significant difference has been found between these two agents, concerning both the clinical and the neuroradiological outcome [117-119]. Other agents (including alemtuzumab, natalizumab, and fingolimod) have been proved to be equally or even more effective, but these data remain yet to be confirmed in long term trials, regarding not only their efficacy, but also their safety [120,121].

A number of studies have shown a modest positive correlation between HLA- DRB1*15:01 genotype and response to GA [122,123]. Furthermore, Gross et al. have identified the additive model of that association, meaning that individuals homozygous for HLA-DRB1*15:01 appear to have a longer event-free time when compared to heterozygous subjects [18].

These findings are of great importance, given the known mechanism of action of GA [124,125]. As the drug binds to MHC class II molecules, different HLA alleles (which indicate structural variations of the MHC molecule) may favor this binding, thus leading to a better pharmacological and clinical response through a switch in patients' neuroimmunological profile (Table 1) [126-128].

Drugs	HLA ^a allele	Response to treatment	Pathophysiology	References
Glatiramer Acetate	DRB1*15:01	Positive	Favors binding of GA ^b to MHC ^c molecules	[122] [123] [18]
IFN β^d (Regardless of preparation used)	DRB1*15:01	Negative	Anti-IFN antibodies	[19]
	DRB1*04:01 DRB1*04:08	Negative	Anti-IFN antibodies	[139] [140]
	DRB1*07:01	Negative	Anti-IFN antibodies	[141]
IFN β -1b	DRB1*04	Negative	Anti-IFN antibodies	[19]
IFN β -1a i.m. ^e	DRB1*04	Negative	Reduces relapses	[144]
	B*15	Positive	Delays EDSS ^f progression	
IFN β -1a s.c. ^g	DRB1*03	Positive	Reduces relapses	[145]
	DQB1*02	Positive	Delays EDSS progression	
	DQB1*03	Positive		
Natalizumab	DRB1*13	Negative	Anaphylactic/anaphylactoid reactions	[148]
	DRB1*14	Negative		
	DRB1*15	Positive		

^aHLA: Human Leucocyte Antigen; ^bGA: Glatiramer Acetate; ^cMHC: Major Histocompatibility Complex; ^dIFN β : Interferon beta; ^ei.m.: intramuscular; ^fEDSS: Expanded Disability Status Scale; ^gs.c.: subcutaneous

Table 1: Summary of the effect of HLA alleles on response to treatment.

IFN- β has long been identified as a DMT in MS with a well-established safety and efficacy profile. It is a fact however that around 40% of the patients is poor- or even non-responders to the drug [129]. The exact mechanism of action remains obscure, although immunomodulatory effects on B- and T- cells, along with an effect on Blood Brain Barrier (BBB) are identified. Antibodies against IFN- β have been largely studied as possible inhibitors of drug action, while their production seems to be influenced by HLA genotype. Antibodies prevent IFN- β from effectively binding to or activating its receptor, thereby blocking its biological effects and inhibiting its favourable therapeutic outcome, as expressed by relapses and MRI activity [130-136]. Not surprisingly, antibody development depends on the

IFN- β preparation, as IFN β -1a i.m seems to be by far the less immunogenic, whereas IFN β -1b and IFN β -1a s.c. seem to be related with higher percentage of neutralizing antibodies [137, 138].

As Link et al. [19] have shown, HLA-DRB1*15:01 carriers are associated with increased risk of developing antibodies (OR=1.43, Pc=0.036) and especially high or so-called biologically relevant titers (OR=1.58; Pc=0.01), which more effectively block IFN- β efficacy. That risk seems to follow the above mentioned pattern of IFN preparations' immunogenicity. In addition, HLA-DRB1*04 carriage was associated with development of biologically relevant titres (OR 3.53; P=0.029; AR=28.2%) in patients receiving IFN β -1b. HLA-DRB1*04 (including *04:01 and *04:08) has been found to increase the risk of developing

antibodies in two further studies, although the correlation with specific IFN preparation was not studied [139,140]. Barbosa et al. [141] have identified HLA-DRB1*07:01 as a risk allele for antibody development, but this finding has not been reproduced.

Nevertheless, the above mentioned findings have not been reproduced in two other studies. [142,143].

Lately, HLA-genotype has been proved to directly influence clinical efficacy of IFN- β , in terms of relapses and progression in the EDSS during follow up. Mazdeh et al. have found increased frequency of HLA-DRB1*04 and decreased frequency of HLA-B*15 to be associated with better response to IFN β -1a (intramuscular preparation) [144].

Furthermore, HLA-DRB1*03, HLA-DQB1*03 and HLA-DQB1*02 alleles have been found to contribute to better response to IFN β -1a (subcutaneous preparation) in an Israeli group consisting of 17 RRMS patients [145].

Recent studies have identified a possible role of non-HLA genes, too. Homozygotes for a CD58 variant (rs12044852) which as mentioned above has been proved to increase MS risk, seem to have a poor response to IFN- β therapy [43].

Warabi et al. have shown that patients carrying the NMO-specific HLA-DPB1*05:01 allele showed a poor prognosis following IFN-1b treatment [146].

Natalizumab is a humanized monoclonal antibody against integrin α 4 and its biological action is based on blocking migration of T and B cells into the CNS with a well-established clinical efficacy [147]. Not only the efficacy, but also the safety of a drug must be taken into account before choosing the appropriate agent. HLA genotype seems to influence the possibility of adverse effects among MS patients treated with Natalizumab. Individuals carrying HLA-DRB1*13 and HLA-DRB1*14 alleles seem to have higher risk for developing natalizumab-related anaphylactic/anaphylactoid reactions, while on the other hand, HLA-DRB1*15 allele, has a rather protective effect [148]. Another aspect that we should not ignore is the risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML). Positive anti-JC virus antibody status (among other factors, including prior use of immunosuppressants and duration of treatment) clearly increases the possibility of PML during or after the treatment with Natalizumab. Consequently, the stratification of patients regarding their anti-JC antibody status is a measure that allows us to individualize our therapeutic approach [149].

McKay et al. have identified that transcription factors EOMES and TBX21 (ET) can be used as clinical biomarkers to predict response to Natalizumab, as their expression significantly increases during the treatment with this drug reflecting its efficacy [150].

Towards personalized therapeutics in MS

For over 30 years now HLA genotype has been established as a key risk factor for MS. HLA-DRB1*15:01 is the best studied allele (from animal model studies to big MS-case control studies) and it seems to influence every aspect of the disease: its role is crucial in MS initiation and pathophysiology, clinical course and, last but not least, response to treatment. During the last 15 years it has become possible to widely use the methods of molecular biology, so as to perform population based studies (GWAS), which have revealed not only the differential distribution of HLA alleles among different populations, but also more HLA alleles (other than HLA-DRB1-15:01) closely correlated to MS.

Using GWAS studies we are capable to know the HLA background of every population studied. These data combined with clinical and radiological findings make the stratification of MS patients a plausible goal and the individualized therapeutic approach the main clinical challenge nowadays.

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