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The HLA-DRB1 Alleles Effects on Multiple Sclerosis: a Systematic Review

REVIEW

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Abstract

Background: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects sensitive and motor functions. Many population studies were made with the intent of knowing better the most affected groups and the disease manifestations. These review analyses some of those studies, evaluating risk factors, especially genetic relations of Human Leukocyte Antigen DRB1 (HLA-DRB1) gens, for developing clinical disease.

Method: We have analyzed 57 articles, published between 2009 and 2014, with the key words "multiple sclerosis", "genetic association studies" and "HLA-DRB1 chains", through the Scopus database. Only 18 articles were eligible for our study; they were read entirely and included in the final analysis.

Results: Most studies imply genetic and environmental factors for the incidence of MS, its age of starting and prognosis. Previous studies have shown that many gens are related in MS pathogenesis and that interactions between them are important in determining clinical manifestations.

Limitations: Different results were observed when different populations were targeted in the studies.

Conclusion: There is an important relation between HLA-DRB1 and MS in diverse population groups. Complementary studies are needed to know better the importance of environmental factors and its interaction with gens in the development of MS.

Keywords
Multiple Sclerosis, HLA-DRB1 Alleles, Genetic Association Studies.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease of the Central Nervous System (CNS) [1, 2]. It presents with a variety of pathological process, such as demyelination, axonal injury and inflammation, with auto-reactive T cells [3, 4, 2]. The autoimmune response is directed against myelin proteins, such as myelin associate glycoprotein and myelin oligodendrocyte protein [5, 6].

The disease usually begins between 20 and 40 years of age, though it can occur, less frequently, in children and older individuals. Women are affected approximately twice as often as men [7, 6]. Its etiology remains unknown, but the current theories points towards an association between genetic an environmental factors in MS pathogenesis [8, 2].

Some studies have shown consistent and strong genetic relations between Human Leukocyte Antigen (HLA) class II and MS (Ramagopalan et al, 2009 [9]; Lincoln et al, 2005 [10]) [11]. Some alleles of the HLA DRB1 gen have been associated to higher the risk of MS, meanwhile, others may be considered as protective factors for the disease [12, 13, 11]. The HLA DRB1*15 allele is the most implicated for the developing of MS, being well correlated to its occurrence [11], and may imply worst prognosis [14-16, 11]. HLA DRB1*15 frequently interacts with other alleles, which is crucial to influence the course of MS [17, 18]. Other alleles associated to greater risk of developing MS are HLA DRB1*0405 [1] and HLA DRB1*03 [11]. HLA DRB1*11 [17, 22, 11] and HLA DRB1*1001 [2] are considered protective alleles against MS.

Furthermore, interactions between alleles or haplotypes of the HLA may occur, modulating the susceptibility risk of MS, and determining the global risk of the disease for each individual genotype [12, 13, 19, 20, 21]. Due to MS prevalence and clinical relevance, it is important to understand its possible causes. In this article, we performed a systematic review aiming to understand the relation between HLA-DRB1 and MS development.

Methods

The present study is a systematic review of literature, performed at the Scopus database in October 2014, with the keywords "multiple sclerosis", "HLA-DRB1 chains" and "genetic studies association", including articles published between 2009 and 2014. Five researchers (TL, LB, SA, GS and JS) conducted, independently and blind to each other, a literature survey, aiming articles for a possible inclusion. Any discrepancies between the five reviewers about the analysis of the articles were resolved through consultations with a senior author (MR).

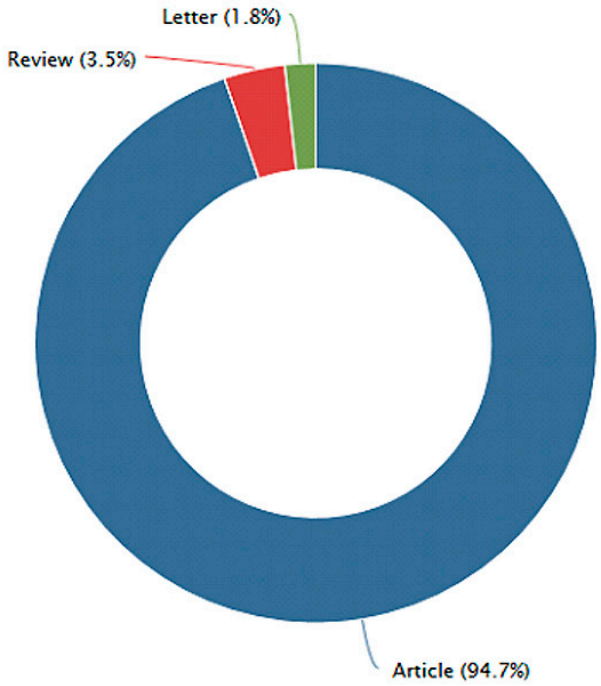
The selection of articles to compose this review followed the previously determined eligibility criteria: (1) manuscripts written in English; (2) original articles with full text available for online assess at Coordination of Improvement of Higher Educational Personnel (CAPES) Journal Portal; (3) articles about the HLA-DRB1 alleles acting on multiple sclerosis; (4) case-control and cohort studies, besides clinical trials **(Figure 1)**.

The exclusion criteria adopted was: (1) non-original studies, including letters to the editor, reviews, and editorials; (2) other designs, such as reviews of literature, pilot studies, short communications and meta-analysis; (3) Out of the context; (4) full text not available at CAPES Journal Portal.

Thereafter, the selected articles through eligibility criteria were entirely read by all five authors. The extracted data were organized into a matrix, which presented authors, sample characteristics, study design, journal, category, main findings, limitations and conclusion. A few studies approached not only the HLA-DRB1 chains as a risk factor for MS but also explored the role of other gens increasing MS susceptibility.

Later, we compared the selected studies' findings and categorized them in three groups, according to

Figure 1: A chart produced by Scopus database which represents the total of documents rated by document type.



Document Type	Documents
Article	54
Review	2
Letter	1
Total	57

the article subject, aiming to facilitate our analysis: (1) Articles about how HLA-DRB1 haplotypes affects the multiple sclerosis, (2) Articles about how the non-HLA polymorphisms affects the HLA effects on MS and (3) Articles about how the HLA-DRB1 alleles affects the multiple sclerosis.

We have adopted for this present study 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis' (PRISMA) guidelines to reach a high pattern of reporting. The PRISMA statement consists of a 27-item checklist and a four-phase flow diagram, which are used for development of systematic reviews and meta-analyses. This statement is useful for ensure a complete and transparent reporting of the studies that was analyzed. Beyond that, the eligibility criteria of this review were based in PICO (Patient, Problem, Population; Intervention; Comparison, Control, Comparator; Outcomes) process.

Results

First of all, the foregoing search strategies resulted in 57 studies. After analyzing tittle and abstract of all 57 references, 18 articles reached inclusion criteria and were included in the final sample. In this regard, all manuscripts were found at the Scopus database **(Figure 2)**.

Table 1 summarizes the 18 included studies in final sample as well as all data elements that were used in the data analysis process. The selected articles were later separated in three categories: (1) how the HLA polymorphisms affect the multiple sclerosis, (2) how the non-HLA polymorphisms affect the HLA effects on MS and (3) how the HLA-DRB1 alleles affect the multiple sclerosis **(Table 1)**.

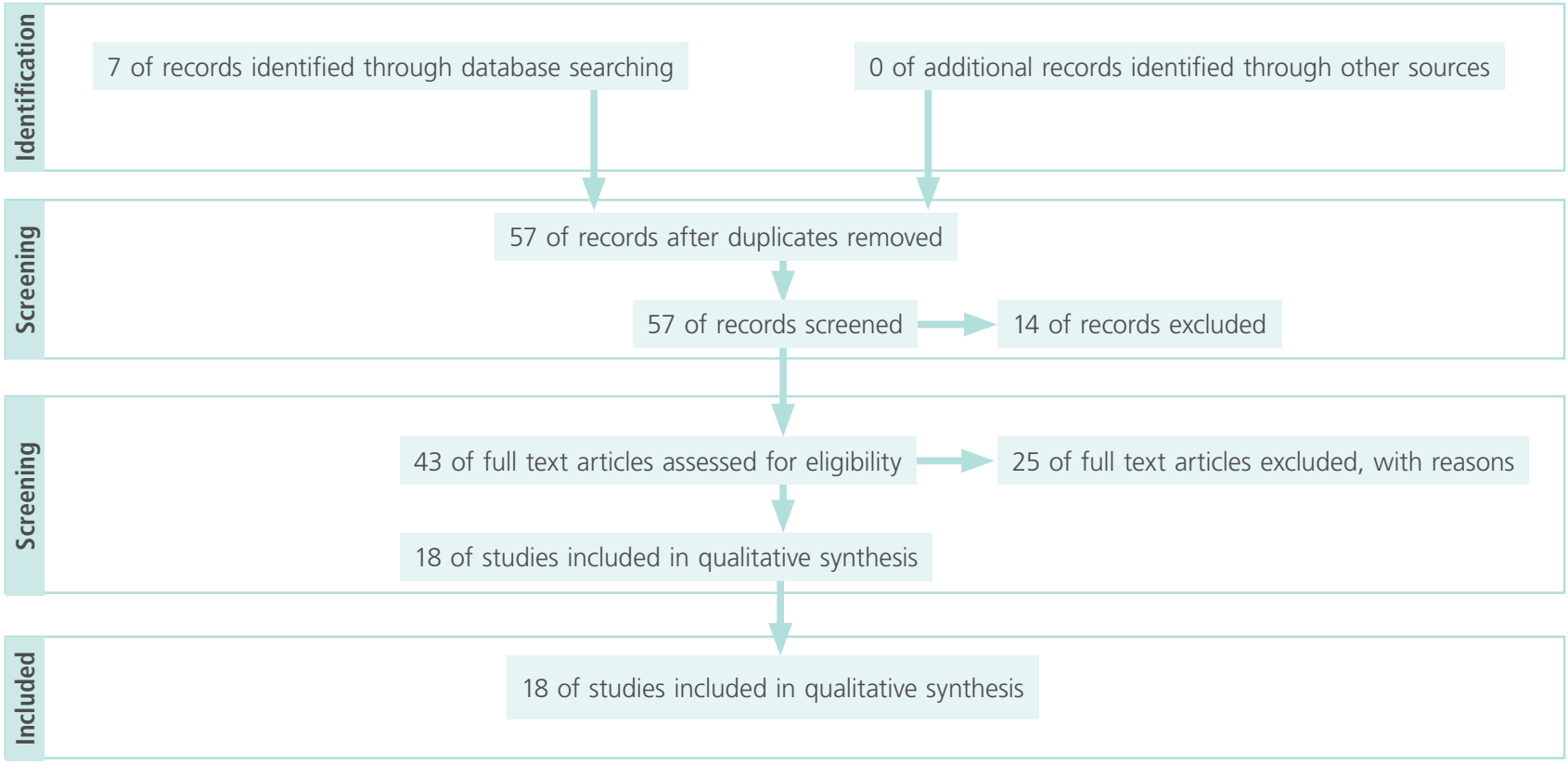
Discussion

The influence of hla drb1*1501 allele in ms

In population studies, high MS prevalence areas were analyzed, as Lithuania [22]. In that population, the HLA DRB1*1501 allele were frequently found in patients with progressive MS, being associated with the beginning of the disease, female gender and worst prognosis [11-18, 23-26]. Smestad et al. (2007) [23], Hensiek et al. (2002) [25], Van der Walt et al. (2011) [27], Cree et al. (2009) [28] e Wu et al. (2010) [29] have previously suggested that this allele may be strongly associated to the rising of MS, its first symptoms in younger individuals and more aggressive manifestations of the disease [31].

Balnyte et al. (2013) [30] reported that, in more than 80% of Lithuanian patients with MS, Oligoclo-

Figure 2: PRISMA 2009 Flow Diagram.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Table 1. HLA-DRB1 affects multiple sclerosis: Studies and main findings.

Authors	Sample characteristics	Study Design	Journal	Category	Main Findings	Limitations	Conclusions
Balnyte R, Rastenyte D, Vaitkus A, et al. [30]	120 multiple sclerosis patients, older than 18 years age	Cross-sectional	BMC Neurology	How the HLA-DRB1 alleles affects the multiple sclerosis	HLA-DRB1 was more found in patients with the progressive form of the disease. There is a genetic association between the HLA-DRB1 genotype and MS susceptibility. People with the progressive form of the disease showed that HLA-DRB1*15 is the most prevalent allelic group in this patients, specially the younger ones. Further, the HLA-DRB1 genotype was associated with worse prognosis. Besides, HLA-DRB1*8 was related to a lower degree of disability.	Small sample of MS patients. Some clinical data was gathered retrospectively from the medical records. Further a large scale studies are needed.	There is an association between HLA-DRB1 alleles and the disease's prognosis. The HLA-DRB1*15 was related to a lower degree of disability. Therefore, HLA-DRB1 allelic may have an influence on MS manifestation.
Mowry EM, Carey RF, Blasco MR, et al. [100]	503 white subjects evaluated within a year of Multiple Sclerosis onset.	Cross-sectional	PLoS ONE	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	There are an association among HLA-DRB1 and EVI5. HLA-DRB1 positive groups presents more severe attacks by EVI5. EVI5 was associated with an unimportant risk of severe attacks. That gene was related to a greater possibility of worse recovery. Also this study evaluated the interaction between HLA-DRB1 and CD226A. Those associations were related to a susceptibility studies.	Analysis was reduced to white persons, which does that study is not able to represent others racial groups	There are an association among HLA-DRB1 and EVI5. HLA-DRB1 positive groups presents more severe attacks by EVI5. EVI5 was associated with an unimportant risk of severe attacks. That gene was related to a greater possibility of worse recovery. Also, this study evaluated the interaction between HLA-DRB1 and CD226A.

Huang J, Yoshi-mura S, Isobe N, et al. [54]	118 multiple sclerosis patients and 152 healthy controls for rs422951.	Case-control study	Multiple Sclerosis J.	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	G allele of NOTCH 4 rs422951 was negatively associated with only MS, but not with non-NMO/NMOSD. This allele was also significantly related to Multiple Sclerosis as an independent resistant allele for this disease in Japanese. Moreover, the analysis identified two susceptible an three resistant haplotypes produced from HLA-DRB1*0405, HLA-DRB1*0901 andrs422951. Besides, G allele was not associated with any clinical parameters. HLA-DRB1*0405 was positively associated with Multiple Sclerosis.	Some genotyping results were not validated by DNA sequencing. Remains unclear if the association among NOTCH4 an NMO/NMOSD and non-NMO/NMOSD Multiple Sclerosis is distinct because the sample included both MS and NMO patients. The NOTCH 4 mutation protects against the developing Multiple Sclerosis.	G allele of NOTCH 4 rs422951was negatively associated with only MS, but not with non-NMO/NMOSD. This allele was also significantly related to Multiple Sclerosis as an independent resistant allele for this disease in Japanese. Moreover, the analysis identified two susceptible an three resistant haplotypes produced from HLA-DRB1*0405, HLA-DRB1*0901 and rs422951. Besides, G allele was not associated with any clinical parameters. HLA-DRB1*0405 was positively associated with Multiple Sclerosis.
Cocco E, Murru R, Costa G, et al. [21]	2,555 multiple sclerosis (MS) Sardinian patients and 1,365 healthy ethnically matched controls.	Case-control study	PLoS ONE	How HLA-DRB1 haplotypes affects the multiple sclerosis	Interactions between HLA-DRB1-DQB1 haplotypes were analyzed and haplotypes were found to confer susceptibility and protection to multiple sclerosis	Not disclosed	Interactions between HLA-DRB1-DQB1 haplotypes were analyzed and haplotypes were found to confer susceptibility and protection to multiple sclerosis
Yoshimura S, Isobe N, Yonekawa T, et al. [1]	145 patients with multiple sclerosis and 376 healthy from Japan.	Case-control study	PLoS ONE	How the HLA-DRB1 alleles affects the multiple sclerosis	Multiple Sclerosis patients without DRB1*0405, the frequency of DRB1*1501 allele was higher, while the DRB1*0901 allele was lower compared with healthy patients. Furthermore, Multiple Sclerosis patients DRB1*0405 negative were significantly more likely to be positive for antibodies to the Epstein-Barr virus nuclear antigen compared to healthy patients.	Few number of patients enrolled in the study	The DRB1*0405 is related to multiple sclerosis in younger age and causes a benign course of the disease, the detection of this gene accounts for the largest number of young Japanese Multiple Sclerosis patients. Multiple Sclerosis patients without this gene, has multiple sclerosis and similar Western sclerosis.

Kollaee A, Ghaffarpor M, Ghlichnia HA, et al. [2]	120 Iranian patients with Multiple Sclerosis and 120 controls.	Case-control study	Interna-tional Journal of Imuno-genetics	How HLA-DRB1 haplotypes affects the multiple sclerosis	The findings indicate that the DRB1*1501 allele, the DRB1*1501-DQB1*0602 haplotype and the DRB1*1501/0701- genotype and amino acid Leu26 and Phe9 on the DQβ1 chain are significantly associated with Multiple Sclerosis susceptibility. DRB1*1001 was the only allele that had a protective effect against Multiple Sclerosis. Thus, that the DQB1*0303 allele was significantly associated with disease severity. However, protective effect of the DRB1*1001 against Multiple Sclerosis and also association of DQB1*0303 allele with Multiple Sclerosis severity.	Sample size	Findings indicate that the DRB1*1501 allele, the DRB1*1501-DQB1*0602 haplotype and the DRB1*1501/0701- genotype and amino acid Leu26 and Phe9 on the DQβ1 chain are significantly associated with Multiple Sclerosis susceptibility. DRB1*1001 was the only allele that had a protective effect against Multiple Sclerosis. Thus, that the DQB1*0303 allele was significantly associated with disease severity. However, protective effect of the DRB1*1001 against Multiple Sclerosis and also association of DQB1*0303 allele with Multiple Sclerosis severity.
Link J, Kockum I, Lorentzen ÅR, et al. [65]	1.784 Multiple Sclerosis patients and 1.660 healthy controls.	Case-control study	PLoS ONE	How HLA-DRB1 haplotypes affects the multiple sclerosis	Haplotype analysis showed that almost all DRB1*15 haplotypes were risk bearing, and that all A*02 haplotypes were protective bearings if they did not carry DRB1*15 In addition, was found a class I haplotypes, the carrying *C-02*05 B*12, which abolished the risk of DRB1*15.	Not disclosed	Confirmed the role of HLA class I and II, in addition to DRB1*15 and A*02 in susceptibility to multiple sclerosis by the inclusion of all three HLA genes class I classical and their functional interaction with DRB1*15 and various DRB1 alleles of class I genes.

Irizar H, Muñoz-Culla M, Zuriarrain O, et al. [46]	364 multiple sclerosis patients and 513 healthy controls.	Case-control study	Multiple Sclerosis	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	It was confirmed that *15:01 haplotype gives a greater risk of suffering from multiple sclerosis. There was no association between Vitamin D Receptor (VDR) gen variants of Multiple Sclerosis, but they modulate moderately the risk conferred by *15:01. Sex confers a much stronger modulation at *15:01-MS, being more remarkable in females the risk conferred by *15:01. Sex confers a much stronger modulation at *15:01-MS, being more remarkable in females.	Not disclosed	It was confirmed that *15:01 membership is female specific. The HLA-DRB1*15:01 appears to be related consistently linked to a haplotype expression of HLA II high gene.
Cocco E, Sardu C, Pieroni E, et al. [89]	943 Multiple Sclerosis families consisting of one affected sibling and both healthy parents (trio), and 362 healthy siblings (one from each family) of patients coming from the same families from Sardinia.	Case-control study	PLoS ONE	How HLA-DRB1 haplotypes affects the multiple sclerosis	The test of haplotype DRB1*DQB1* confirmed a higher transmission rate than expected *13:03-*03:01, *04:05-*03:01 and *03:01-*02:01 haplotypes. In contrast the *16:01-*05:02 and *15:02-*06:01 haplotypes showed a lower than expected rate of transmission. The independence of the transmission of each haplotype was confirmed for all the haplotypes associated positively and negatively related to *16:01-*05:02 haplotype. The study of DRB1 and DQB1, chain protein residues showed that the Val / Gly at position 86 of the DRB1 chain was the only difference between the protector *16:01-*15:02 alleles and predisposition *15:01 one. As well, the Ala / Val residue at position 38 of the DQB1 chain differentiated positively associated *06:02 and the negatively associated allele *05:02, *06:01 alleles	Not disclosed	The study showed that the association of specific, independent DRB1*-DQB1* haplotypes confer susceptibility or resistance to multiple sclerosis the population. The data also points to the functional role of specific residues of DRB1 and DQB1 in protein predisposing to multiple sclerosis

Alcina A, Abad-Grau MdM., Fedetz M, et al. [96]	Case samples comprised 1049 Caucasian individuals obtained from four public hospitals in the South of Spain. Controls were 972 blood donors with no history of inflammatory disease.	Case-control Study	PLoS ONE	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	It was been found that the tag of DRB1*1501, rs3135388 A allele, correlated with high expression of DRB1, DRB5 and DQB1 genes in a Caucasian population. In quantitative terms, the MS-risk AA genotype carriers of rs3135388 were associated with 15.7-, 5.2- and 8.3-fold higher expression of DQB1, DRB5 and DRB1, respectively, than the non-risk GG carriers. The haplotype analysis of expression-associated variants in a Spanish Multiple Sclerosis cohort revealed that high expression of DRB1 and DQB1 alone did not contribute to the disease. However, in Caucasian, Asian and African American populations, the DRB1*1501 allele was always highly expressed.	The nature of the HLA, which is highly polymorphic.	It is concluded that the DR/DQ expression levels, together with specific structural properties of alleles, seem to be the causual effect in multiple sclerosis and in other immunopathologies rather than specific presentation alone.
Kouri I, Papa-konstantinou S, Bempes V, et al. [18]	126 Greek patients born or living long in the northwest Greece and 93 healthy controls individuals.	Case-control study	Journal of the Neuro-logical Sciences	How the HLA-DRB1 alleles affects the multiple sclerosis	The results revealed that HLA-DRB*1501 allele was significantly more frequent among patients with Multiple Sclerosis compared to the control group.	Sample size	The results revealed that HLA-DRB1*1501 allele was significantly more frequent among patients with Multiple Sclerosis compared to the control group.
Romero-Pinel L, Pujal JM, Martínez-Yélamos S, et al. [11]	380 unrelated patients with the diagnosis of MS and 1088 unrelated healthy controls from Spanish.	Case-control study	European Journal of Neurology	How the HLA-DRB1 alleles affects the multiple sclerosis	Statistically, the HLA-DRB1*15 allele had a much higher frequency in patients diagnosed with multiple sclerosis when compared with the control group.	Not disclosed	Statistically, the HLA-DRB1*15 allele had a much higher frequency in patients diagnosed with multiple sclerosis when compared with the control group.

Romero-Pinel L, Martínez-Yélamos S, Bau L, et al. [32]	268 unrelated patients diagnosed with MS and 1088 unrelated healthy controls from Spanish.	Case-control study	European Journal of Neurology	How the HLA-DRB1 alleles affects the multiple sclerosis	Was founded 206 OCB-positive and 62 OCB-negative patients. The HLADRB1*15 allele in OCB-positive patients had a higher frequency when compared with OCB-negative patients	Not disclosed	HLA-DRB1*15 allele is associated with OCB-positive patients with MS when studying a Spanish Multiple Sclerosis population.
Deschamps R, Paturel L, Jeannin S, et al. [73]	42 NMO patients, 163 Multiple Sclerosis patients and 150 healthy controls. All cases and controls were of Afro-Caribbean ethnic origin (four Caribbean grandparents) and resided in the French West Indies (Martinique and Guadeloupe)	Case-control study	Multiple Sclerosis Journal	How the HLA-DRB1 alleles affects the multiple sclerosis	The study confirms that the French population has distinct Afro-Caribbeans susceptibility allele HLA involved in Multiple Sclerosis and Devic's disease. The first is positively associated with HLA-DRB1*15, whereas the risk for the latter is correlated to HLA-DRB1*03 allele.	Few relatively number of NMO patients.	The study confirms that the French population has distinct Afro-Caribbeans susceptibility allele HLA involved in Multiple Sclerosis and Devic's disease; The first is positively associated with HLA-DRB1*15, whereas the risk for the latter is correlated to HLA-DRB1*03 allele.
Kaimen-Maciel RD, Reiche EMV, Borelli SD, et al. [6]	119 Multiple Sclerosis patients and 305 healthy blood donors to control in a Brazilian Caucasian population from Londrina, Southern Brazil.	Case-Control Study	Molecular Medicine Reports	How the HLA-DRB1 alleles affects the multiple sclerosis	The results showed that the HLA-DRB1*15 was positively associated with Multiple Sclerosis. The frequency of allele HLA-DRB1*11 was reduced in the MS patients when compared to the control group.	Homozygosis for HLA-DRB1*15 allele failed to show any association with Multiple Sclerosis susceptibility.	The HLA-DRB1*15 may be considered a risk of susceptibility a Multiple Sclerosis. However the HLA-DRB1*11 may be considered a marker of resistance to Multiple Sclerosis in Brazilian population.

Fernández O, R-Anti-güedad A, Pinto-Medel MJ, et al. [68]	197 patients and 200 regionaly matcheds controls from Basque Country, northern Spain	Case-control study	Journal of Neurology	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	Several alleles are over represented in Multiple Sclerosis patients: DRB1*0402, DRB1*1303, DRB1*1501, DQA1*0102, DQB1*0302 and DQB1*0602. DRB1*0101, DQA1*0101, DQB1*0303, and DQB1*0501 showed lower frequencies in Multiple Sclerosis patients, but only DRB1*0101 and DQB1*0303 maintained a negative association with the disease.	Not disclosed	The results confirm the positive association of the DR2 haplotype. DRB1*0402-DQA1*0301-DQB1* showed a possible association with Multiple Sclerosis. DRB1*0101 allele may be a possible protective factor to Multiple Sclerosis.
Živković M, Stanković A, Dinčić E, et al. [99]	Subjected group consisted of 164 females and 105 males, 36,3 ± 10,5 years age. The control group consisted of 106 female and 117 males, 43,2 ± 11,6 years age.	Case-control study	Clinica Chimica Acta	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	It was identifying high frequency of the tag single nucleotide polymorphism (SNP) for HLA-DRB1β1501, rs3135388, in Multiple Sclerosis patients.	Not disclosed	The tag single nucleotide polymorphism (SNP) for HLA-DRB1*1501, rs3135388 has significant association with MS in patients from Serbia.
Ghabaee M., Bayati A, Saroukolaei SA, et al. [48]	183 Iranians patients with multiple sclerosis compared with 100 healthy individuals	Case-control study	Cellular and Molecular Neuro-biology	How the non-HLA polymorphisms affects the HLA effects on multiple sclerosis	HLA-DRB1*1501 was significantly more frequent among Multiple Sclerosis patients. DQA1*0102 haplotype was negatively associated with Multiple Sclerosis. No significant association was found with DQB1*0602 and Multiple Sclerosis patients in comparison with control group. No significant correlation was observed among these alleles with sex, type of disease; initial symptoms, expanded disability status scale (EDSS), as well as age at onset and familial multiple sclerosis.	Examining patients from different parts of the country that may have variable ethnic backgrounds.	There is no association of above HLA haplotypes with clinical presentation, disease duration, and disability in Iranian patients with MS which is in line with other previous studies in different ethnic groups.

nal Bands (OCBs) were detected in their cerebrospinal fluid (CSF) [30]. Other studies came to the similar conclusions, in Australia (Wu et al., 2011) [29], Turkey (Idiman et al., 2009) [31], and Spain (Romero-Pinel et al., 2011) [32, 30] OCBs were more frequently found in those patients with HLA DRB1*15 allele. Balnyte et al. (2013) [30] suggested that this association produces immunological disturbances that may affect MS prognosis, with possible regulation of other genetic factors may. [30]

The study of Romero-Pinel et al. (2011) [32] also demonstrated the association between HLA DRB1*15 and OCBs in MS, in the Spanish population - as the studies of Kikuchi et al. (2003) [33], Wu et al. (2010) [34], Imrel et al. (2006) [35] e Idiman et al. (2009) [31,.32] Although, other cohort studies have shown that the DRB1*15 predisposes MS, regardless the positivity of OCBs in the CSF. However, when both factors are positive, the predisposition seems to be more significant [31, 34, 36, 32].

Back to the Lithuanian population, there is no consensus on the role of HLA DRB1*15 in determining the severity of MS. Kouri et al. (2011) [18] concluded that it may be associated with a better prognosis18. On the other hand, Van der Walt et al. (2011) [27] reported that HLA DRB1*15 have no influence on the disease's severity, except when determining earlier beginning of symptoms. [30].

In Sardinia, where MS also have a high incidence, [37, 38] a genomic association study of the International Multiple Sclerosis Genetic Consortium, in 2011 [39], confirmed that DRB1*1501 is the most significant genetic factor for developing MS, and its interactions with other alleles influences the disease. [21].

However, a small number of studies in non-european populations, as chinese, iranians, african-americans and african-brazilians, have found a lower prevalence of DRB1*1501 allele in MS patients (Kelly et al., 1995 [40]; Caballero et al., 1999 [41]). [18] Furthermore, Wu et al. (2010) [29] in Western Australia reported that the positivity of HLA DRB1*1501 has no significant influence in the age of MS beginning. [18]

Romero-Pinel et al. (2011) [11] haven't found any significant association between age of MS development and the different HLA alleles in the Spanish population. On the contrary, several studies found a significant association between a lower age at onset and the HLA-DR15 haplotype, the DRB1*15 allele (Masterman et al., 2000 [42]; Smestad et al., 2007 [23]; Hensiek et al., 2002 [25]; Cree et al., 2009 [28]) and other DRB1 alleles (Wu et al., 2010 [29]). [11].

In addiction, other studies haven't found any association between DRB1*15 allele and the severity of the disease (Masterman et al., 2000 [42]; Barcellos et al., 2006 [20]; Hensiek et al., 2002 [25]; Weinshenker et al., 1998 [43] and Runmarker et al., 1994 [44]).[11] Meanwhile, Vasconcelos et al. (2009) [14], Cornu-Rebeix et al. (2008) [15] and Wu et al. (2010) [16], in desagreement with the study of Silva et al. (Portugal, 2007) [45], have reported that patients with positive HLA DRB1*15 were related to a worst prognosis, not a better one. [11]

In Irish patients, positive DR15 were associated with earlier beginning of MS and to female gender [25, 42, 11] And Irizar et al. (2012) [46], studying the Japanese population, concluded that DRB1*15 allele confers greater risk of MS only for women [46].

Kollaee et al. (2012) [2] have compared the alleles of HLA-DRB1*15 (DRB1*1501, DRB1*1502, DRB1*1506, DRB1*1508, DRB1*1511 e DRB1*1515) in the Iranian population, and concluded that the DRB1*1501 allele is associated with relapsing–remitting multiple sclerosis (RRMS), compared to the control group. [2] This finding is consistent with some other studies conducted in Iranian relapsing–remitting and primary progressive MS patients (Kalanie et al., 2000 [47]; Ghabaee et al., 2009 [48]), but it is inconsistent with the study conducted by Amirzargar et al. (1998) [49], which was performed on chronic progressive patients with MS in Iran. [2]

Although DRB1*1501 was shown to be associated with MS in many ethnic groups, especially in Caucasians (Fernandez et al., 2004) [50], a few studies in European populations, such as Sardinians, and non- European populations, such as Afro Brazilians and Chinese, show that the frequency of the HLADR*1501 allele was slightly lower in the patient group compared to the controls (Kelly et al., 1995 [51]; Caballero et al., 1999 [41]; Oksenberg et al., 2004 [52]) [2].

According to Kankokar et al. (2003) [17], most population studies about HLA and MS have focused in Europeans, Caucasian Americans, Australians, Chinese, Japanese, Jewish and Turkish, in which MS predisposition has been frequently associated with DRB1*15 and its related alleles (DRB1*1501, DQA1*0102, DQB1*0602). [18] Other studies, from North Europe, have found a strong relation between the haplotype DR15 (DRB1*1501-DQA1*0102-DQB1*0602) and its alleles and MS. [53, 54].

The majority studies associating alleles and MS took place in North Europe [55, 42], but Mediterranean populations [56-58], as north and south Americans, have also been the subject of large studies [59-61, 11] Australian patients with MS have also been strongly associated to the allele [62]. [11]

Other drb1 alleles that affect ms

There are another isolated alleles that can be related to MS. For example, HLA DRB1*04 and HLA DRB1*01 have been associated to a worst prognosis in MS patients [11, 23, 25, 62, 30].

The HLA DRB1*04 allele, further than being related to rapidly progressive disease [63, 30] –as the HLA DRB1*01 allele [11] –, may also be associated with more Magnetic Resonance Imaging (MRI) abnormalities, along with HLA DRB1*09 [63, 30]. However, these alleles, especially the DRB1*09, are rarely seen and appeared to be no influence on clinical signs of MS [64, 30].

Balnyte et al. (2013) [30] reported that HLA DRB1*01 allele is related with shorter time to reach and Kurtze Expanded Disability Status Scale (EDSS) of 6, this likely to be related to a worse prognosis [30]. Meanwhile, Link et al. (2012) [65] reported that the HLA DRB1*01 allele has a protective effect in MS patients when they are also positive for DRB1*15 allele [65].

Studies in the Northern Spain populations have also demonstrated a protective effect of HLA DRB1*01 allele in MS patients, which had a significant higher level of positivity compared to control groups (Fernández-Morera et al., 2008 [66]; Pina et al., 1999 [67]) [68]. In addiction, Brynedal et al. (2007) [69] reported that the HLA DRB1*01 may be a protective factor alone [68]. DeLuca et al. (2007) [70] have also reported that the DRB1*01 allele segregates with both disease resistance and favorable outcome, were founded some sporadic MS cases that the DRB1*01 is significantly underrepresented in malignant compared with benign MS. Adding to it, the control groups indicated that the DRB1*01 allele seems to diminish the progressive disability that characterizes MS in the long term and hypothesized that the protective effect of DRB1*01 in a replication cohort of affected sibling pairs may result from a specific epistatic interaction with DRB1*1501. [68].

Yoshimura et al (2012) [1] reported that the HLA DRB1*0405 allele may be a significant risk in Japanese patients with MS. In their study, the DRB1*0405-positive subgroup had significant differences compared to the DRB1*0405-negative subgroup, as: younger age at disease onset, lower EDSS scores, a lower Progression Index (PI), and a lower frequency of MS-like brain lesions [1]. As there is an earlier age of onset and a lower PI compared with patients without DRB1*0405, the authors suggested that the DRB1*0405-positive subgroup may be the only one with a relatively benign disease course and a premature age of onset [1].

Also, a tendency of lower positivity of oligoclonal IgG bands (OB)/increased IgG index in the CSF has been demonstrated, compared to DRB1*0405-ne-

gative MS patients [1], which agrees with studies in Swedish [35] and Japanese [33] populations, which have shown that the DRB1*04 is related to OB-Negative MS patients [1].

On the other hand, in DRB1*0405-negative MS Patients a higher frequency of positivity of HLA DRB1*1501 has been observed, as of brain lesions and increased CSF OB/increased IgG index (Yoshimura et al., 2012) [1].

Yoshimura et al. (2012) [1] have also reported that the DRB1*0901 allele has a significant protective effect against MS, regardless HLA DRB1*0405 is positive or not. This event was demonstrated in a meta-analysis performed with Chinese patients, in which the DRB1*0901 allele showed its protective effects against MS (Qiu et al., 2010). [71] Fujisao et al. (1996) [72] reported that the DRB1*0901 allele is more frequently found in Asians than in any other ethnical group [1], which could reasonably explain the lower incidence of MS in Japan and other Asiatic countries (Yoshimura et al., 2012). [1].

A Lithuanian study evinced that the HLA DRB1*08 and *15 alleles were strongly related to the risk of MS in the population (Balnytė et al., 2012). [64, 30] However, the HLA DRB1*08 allele was more commonly found in patients with relapsing-remitting MS, which has a lower degree of disability. Furthermore, lower IgG index was documented in the patients with the HLA DRB1*08 allele than in those without it. [30].

Another gene associated to risk of MS is the HLA-DR*17 gen, an allele of DRB1 that, according to large study of Dyment et al. (2005) [12] with Canadian MS patients, is also associated to higher susceptibility of MS [2].

Wu et al. (2010) [29] reported a relation between HLA DRB1*0801 allele and an older age of onset [30]. And Balnytė et al. (2013) [30] reported that this allele is also related to more benign course and less severe disability in MS patients [30]. Meanwhile, HLA DRB1*13 allele was associated with a younger age of onset of MS. [64, 30].

An Iranian study of Kollaee et al. (2012) [2] demonstrated that the DRB1*1001 allele was the only one with a negative relation with MS, playing a protective role against the disease. In addition, 15 patients in the control group were positive for DRB1*1001 allele, meanwhile none of the 120 sick patients had it. The authors have also evinced that the absence of DRB1*0701 allele, in any genotype containing the DRB1*1501 gen, may increase the individual risk of MS [2].

Deschamps et al. (2011) [73] discussed about a minor protective effect of DRB1*1101 allele in the risk of MS, independently of the occurrence of DRB1*15 and DQB1*06 alleles. Similar results were reported in Malta [58], Italy [56, 74], in Caucasian Brazilians (but not in mulattos) [60], Canada [13] and in a French Caucasian population [75]. [73].

Kaimen-Maciel et al. (2009) [6] evinced that the presence of DRB1*11 allele in MS patients is related to resistance in disease development, what shows a tendency of a protective role. These authors demonstrated that, in homozygosis, the allele may confers protection against MS onset [6].

Another studies observed the possible protective effect of DRB1*11 allele for MS (Ramagopalan et al., 2007 [13]; DeLuca et al., 2007 [70]). [11]. The inference results of the high positivity of this allele in control groups, meaning it is rather a protective factor alone or because of its interactions with other alleles implicated in the appearance of MS. [20, 11].

Romero-Pinel et al. (2011) [11] reported that the HLA DRB1*03 allele is the second in frequency to be associated with MS, though the comparison is already obsolete [11].

Furthermore, according to Deschamps et al. (2011) [73], the HLA DRB1*03 is also related to neuromyelitis optical (NMO), agreeing with the conclusions of previous studies in French Caucasians Zéphir et al., 2009) [75] and Brazilian Mulatto (Brum et al., 2010) [76] with NMO that were positive for this allele [73]. On the other hand, HLA DRB1*15 seems to have no significant effect on the risk of NMO

(Deschamps et al., 2011) [73]. Moreover, there are consistent evidences that the HLA-DRB1*01 allele is strongly associated with risk of numerous autoimmune diseases [77, 78]. [73].

According to Kouri et al. (2011) [18], DRB1 is not the only susceptibility locus to MS in the MHC region – another examples are DQB1*0602 and DQA1*0102 alleles [18]. The authors reported a higher positivity frequency of the DQB1*0602 in MS patients, compared to control groups [18]. Studies with Europeans (Dunne et al., 2006) [79] and Caucasian (Fernández et al., 2004) [50] and certain non-Caucasian populations, including African Americans (Oksenberg et al., 2004) [52] and Martinicans (Quelvennec et al., 2003) [80] came to the same conclusions. [48]

Fernández et al. (2004) [50] reported the DQB1*0602 allele as the only one that kept the association with MS in a logistic regression model [18]. Fernández et al. (2009) [68] have also reported that the DQB1*0602 allele had a consistent positivity frequency in MS patients [68].

Kollaee et al. (2012) [2] have also evinced that DQB1*0602 was slightly higher in patients with MS than in healthy individuals, which, however, had no statistical meaning [2]. Nevertheless, Dyment et al. (2004) [81], studying the Northern European population, reported a high frequency of DQB1*0602 in MS patients, but the intense linkage disequilibrium of the DRB1*15-DQB1*0602 haplotype made it hard to define the particular susceptibility factor [2].

However, Ghabaee et al. (2009) [48] haven't find any significant associations between DQB1*0602 and MS [48]. Sardinian studies (as the one of Marrosu et al., 1993) [82] and in northeastern Italy (Zivadinov et al., 2003) [83] corroborates the absence of that association [48].

Kouri et al (2011) [18] reported a positive association between the HLA DQA1*0102 allele with MS [18]. Marrosu et al. (2006) [84] also reported an elevated prevalence of DQA1*0102 allele in MS cases. Still, Marrosu et al (1993) [82] and Haegert et al (1993) [86] reported that, in Sardinians, the DQA1*0102 allele were less common in MS patients than in control groups [48]. Similar results were obtained by Kalanie et al (2000) [47], with a negative association between HLA DQA1*0102 and MS [48].

The DQB1*0303 have shown to confers a protective effect against MS, being strongly negatively associated with the disease in Caucasian patients of Basque Country, in northern Spain (Fernández, et al. 2009). [68] But in Iranian patients, Kollaee et al. (2012) [2] reported no significant differences in the DQB1*0303 allele prevalence in MS patients and healthy control groups. [2].

Yoshimura et al. (2012) [1] discussed the risk conferred by the DPB1*0301 allele for MS, highlighting that positive and negative patients for the allele had no significant clinical differences. [1] However, there have been reports of the association of this allele with MS in inhabitants of Hokkaido, North Japan [86] and in other populations, with different ethnics, like Australians [87] and Sardinians [88]. [1].

Fernandez et al. (2009) [68] evinced that DRB1*0101, DQA1*0101 and DQB1*0501 alleles had protective effects against MS, with significantly higher phenotypic frequencies in control groups than in sick patients [68].

Haplotypes of drb1 alleles influencing ms

There are many associations between the locus of the HLA-DRB1*-DQB1* alleles related in MS, already described in different populations. According to The International Multiple Sclerosis Genetics Consortium (2011) [39], the haplotype *15:01-*06:02 is responsible for the elevated risk of MS in populations with northern European ancestry [89]. However, some populations differs on which alleles predisposes MS and presents different DRB1 alleles. [89].

The studies of The International Multiple Sclerosis Genetics Consortium (2011)39 associated the elevation of MS susceptibility to the presence of another alleles beyond DRB1*1501, as DRB1*03:01, DQB1*02:01 and *13:03. [89].

The results of Celius et al. (2000) [90], the DRB1*1501 gen containing the HLA-DR2,DQ6 haplotype, which is also associated to higher risk of MS, was found more often in women [46].

Kollae et al. (2012) [2], in a study with the Iranian population, reported that the HLA DRB1*1501 allele is not the only predisposing factor to MS. In MS patients, the odds ratio (OR = 7.792) for the DRB1*1501-DQB1*0602 haplotype have shown to be more frequent in the patients that present the DRB1*1501 allele alone (OR = 3.203)2. Thus, the haplotype must have a more significant influence in MS susceptibility. Moreover, those studies indicated that, in genotypes containing DRB1*1501 allele alone, the absence of DRB1*07 allele increases the susceptibility of MS. [2]. The evidences were based in the higher prevalence of the DRB1*1501-*0701 haplotype in MS patients, compared to control group in that study. [2].

Moreover, the DRB1*1501-DQB1*0602 haplotype has been pointed as one the risk factors for MS in Northern Europe [39] and Mediterranean populations [91, 92, 89]. Analysis performed by Cocco et al (2012) [89] in the Sardinian population have confirmed that a higher MS susceptibility is associated with the*13:03-*03:01 (OR = 2.9), *04:05-*03:01 (OR = 2.4) and *03:01-*02:01 (OR = 2.1) haplotypes. Besides, the *03:01-*02:01 haplotype presented the and additive effect as a predisposing allele for MS. [89].

On the other hand, the *16:01-*05:02 haplotype, presenting in its recessive form in Sardinian patients besides the *15:02-*06:01 haplotype, are negatively associated to MS susceptibility. [21].

Jones et al. (2006) reported that the associations between the DRB1 and DQB1 alleles may influence the severity of the disease through unknown mechanisms. [93, 2].

According to Dyment et al. (2005) [12], Ramagopalan et al. (2007) [13], Barcellos et al. (2003) [19] and Barcellos et al. (2006) [20], some alleles may influence the effect of DRB1*1501 in MS susceptibility. [89] The presence of two copies of *1501 represents a higher risk of MS; meanwhile, the association of the *14 and *15 alleles induces a diminished risk for the disease. [89].

The conclusions of Cocco et al. (2012) [89] have pointed towards a protective effect of the *16:01-*05:02 haplotype, compared to homozygotes and heterozygotes patients (OR = 01). However, while the association of the *16:01-*05:02/*16:01-*05:02 haplotypes contributes for diminishing MS risk (OR = 0.2), the *16:01-*05:02 haplotype when alone is ineffective in providing protection in genotype where it is combined with other predisposing haplotypes. [89]

According to Link et al. (2012) [65], groups of Class I HLA alleles may interact with Class II HLA-DRB1*15, neutralizing its negative effect as a predisposing factor of MS. That mechanism may have altered results when different populations are considered.65

Neuromyelitis Optical (NMO) is an autoimmune antibody-mediated disease, commonly associated with other immune disturbance [94, 73]. According to Pittock et al (2008)94, French Caucasian and Brazilian mullatos probably presented a relation between DRB1*03 and NMOs. The presence of these alleles in the groups of patients with NMO in the targeted population of the study was significantly higher. [73] Moreover, the DRB1*03 allele was also related to increased risk of other autoimmune disturbances, including MS [77, 78], which makes NMO an associated manifestation of MS in patients positive for the DRB1*03 allele. [73] However, the findings of Matsushita et al (2009) [95] does not point, in the Japanese population, towards an increased frequency of HLA-DRB1*0301 in patients with NMO and demyelinating diseases like MS. [73]

According to Alcina et al. (2012) [96], in the Class II HLA, the single nucleotide polymorphisms (SNPs) are considered the main signs to be related with MS. Those polymorphisms are associated with a higher expression of the DRB5, DRB1 and DQB1

genes. However, in African-Americans and Spanish populations, the altered expression of these genes is no significant. [96] The conclusions of Irizar et al. (2012) [46} have indicated that the DRB1, DRB5 and DQA1 genes are expressed significantly in the samples positives for DRB1*1501 in their genotypes, with no distinctions in the expression between MS patients and control groups. Thereto, the expression of DRB5 gene have been shown to be specific of the DRB1*1501 allele, once the super expression of that gen have shown to be significantly higher in the individuals with positive allele. [46]

The EVI5 polymorphisms influence the disease severity according to the patient's HLA DRB1 statuses. For DRB1 negative patients, the disease is less severe; on the other hand, in DRB1 positive patients, MS manifestations are severe. The patients with HLA DRB1 also presented worse recovery. [97-99, 100].

Zivkovic et al. (2009) [99] reported an association between DRB1*15 and the rs3135388 polymorphism. The rs3135388 is useful as marker for the DRB1*1501 allele, helping in the detection of this polymorphism in clinical tests with MS patients. [99] According to Huang et al. (2013) [54], the haplotypes formed by rs422951 and HLA-DRB1*15 influences MS pathogenesis. [54]

CD58 and CD6 are gens related with MS. The most convincing relation is the one of CD58 gen, a CD2 binder expressed in T cells. [101, 102, 100] According to Kofler et al. (2011) [103], the CD6 gen tends to be related with a worse illness recovery, but it is known to be involved in the maintenance of T cells activation. [100]

Conclusion

Multiple Sclerosis is an inflammatory autoimmune disease that affects the central nervous system and is determined by genetic and environmental factors. There is a clear association between Human Leukocyte Antigen (HLA) and MS. The disease affects often more women, appearing earlier or later, in higher or lowers severity degrees. We have performed a review about MS presentation in different population groups.

A limitation of our study is due to the different outcomes the disease presents in different populations. Thus, more studies are still in need to understand better the genetic and environmental factors that may affect MS course. Our review highlighted important previous knowledge about MS and compiled results from many different studies, in the hope being useful to direct new assays on the disease.

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