Multiple sclerosis and human leukocyte antigen genotypes: Focus on the Middle East and North Africa region

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Abstract

Recent reports have demonstrated that the prevalence of multiple sclerosis (MS) is increasing in the Middle East and North Africa region. There is also emerging evidence regarding the genetic components of MS risk. This review provides an overview of the role of genetic factors in MS susceptibility by examining human leukocyte antigen loci in patients within the Middle East and North Africa region. Most of the genetic studies conducted in the Middle East and North Africa region have been based on case–control designs, which cannot confirm direct causality of genetic variants on MS susceptibility. Moreover, there are very limited and inconsistent studies on human leukocyte antigen class I and II (DQA and DQB) in MS patients of the Middle East and North Africa region. To identify common risk haplotypes in the Middle East and North Africa region or its sub-populations, further longitudinal studies will be required.

Keywords: Multiple sclerosis, disease susceptibility, genetic factor, major histocompatibility complex, human leukocyte antigen, Middle East and North Africa.

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Introduction

Multiple sclerosis (MS) (OMIM 126200), a common inflammatory demyelinating disorder of the central nervous system, is an autoimmune disease that causes a high rate of disability in young adults. Among the neurological disorders, MS is associated with a particularly low life expectancy and represents one of the more major public health concerns.

The prevalence of MS varies with respect to geographical location and ethnicity. Epidemiological studies have demonstrated a North–South gradient, with the highest prevalence of MS among individuals of northern European ancestry. Based on the atlas of MS in 2013, the countries of the Middle East and North Africa (MENA) are located in a low- to moderate-intensity risk zone for MS (20.01–60/100,000); however, the prevalence of MS seems to have increased significantly in this region. Although the prevalence and incidence of MS is not well-documented in many of the MENA countries, recent studies have suggested an increase in the number of MS cases in areas within this region, with an increasing ratio of females to males. A recent meta-analysis on the epidemiology of MS in the MENA region has illustrated that the overall prevalence of MS is 51.52/100,000. The increased prevalence of MS in MENA countries cannot simply be explained by a prevalence–latitude relationship. The exact etiology of the increase is unknown, but the most likely explanations include the interaction of changing environmental factors with genetic factors, increased availability of neurologists and magnetic resonance imaging machines, and a better knowledge of the disease due to increased public awareness and education.

Some environmental factors that could be related to the increase in MS prevalence in MENA countries include changing nutritional patterns, vitamin D
deficiency and tobacco status. During the past few decades, a significant shift in nutritional pattern from a healthy high consumption of vegetables towards a more western dietary pattern has been accompanied by an increase in metabolic-related disorders in the MENA region. This loss of traditional diet, along with a lack of fortification programs, and restrictions due to religious habits, has led to a high frequency of vitamin D deficiency (VDD) in the MENA region. The prevalence of VDD (defined as less than 20 ng/ml) in the MENA region ranges 12–97% in children and adolescents, and 34–90% in adults, with a higher prevalence in females. VDD is officially a global health problem, and the high prevalence of VDD in MENA countries is known to contribute to other health problems, such as autoimmune disorders.

Regarding tobacco status, a multinational study of 60,622 subjects from 11 MENA countries demonstrated that the age-adjusted smoking rate was 48.0% in males and 13.8% in females. It was similar to worldwide smoking rates that had been reported by the World Health Organization in 2008: 47% of men and 12% of women.

In addition to environmental factors, genetic factors also play a significant role in the pathogenesis of MS. As a common disease, there are many single nucleotide polymorphisms that have been associated with MS. However, recent evidence has led to the proposal that genetic susceptibility to MS is mainly regulated by polygenic effects. Under such a polygenic model, many of the individual single nucleotide polymorphisms would be expected to have only a minor effect on susceptibility. However, as MS is a multifactorial disorder, it is proposed that the interaction between the various genetic alterations and the environment gives rise to the distribution of disease risk in a given population. Therefore, the combined effects of environmental and genetic factors have resulted in the heterogeneity in the etiology of the disease.

Among the causal loci, the genetic effect of the human leukocyte antigen (HLA) has been particularly highlighted as potentially changing and defining the relationship between environmental factors and autoimmune disorders, such as MS. It is noteworthy that the set of HLA alleles related to various autoimmune disorders may vary between, and even within, populations, and that different alleles might be related to different autoimmune disorders. This review presents the results of searching the PubMed, ISI and Scopus databases for English-language studies focusing on MS susceptibility and HLA genes in the following MENA countries: Iran, Algeria, Bahrain, Egypt, Iraq, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, Turkey, Palestine, United Arab Emirates, Western Sahara, and Yemen. The databases were searched for all relevant studies published before July 2019.

Genetic variants of HLA genes and multiple sclerosis risk

As mentioned above, emerging evidence regarding the genetic component of MS risk has indicated its association with polygenic effects. The set of alleles related to MS may vary from one population to another, and even within the same population. Studies on genetic linkage using monozygotic and dizygotic twins have shown that the most relevant genetic factors for MS are located in the major histocompatibility complex (MHC), and in particular, the HLA class I and class II. Among different populations, and even within the same population, HLA genes are highly polymorphic, with more than 21,000 alleles observed so far (http://hla.alleles.org/nomenclature/index.html). The HLA complex contains more than 220 genes regulating various functions, which are grouped into six classical subfamilies, comprising the class I genes HLA-A, HLA-B and HLA-C, and the class II genes HLA-DPB1, HLA-DQB1 and HLA-DRB1. These genes encode at least 132 proteins with various functions in immune system modulation, such as presenting antigenic peptides to CD4+ and CD8+ T lymphocytes.

HLA class I

HLA class I epitopes serve as key components in MS pathogenesis. The earliest relationship between MS and HLA was demonstrated in the 1970s for the class I alleles A3 and B7 using serological-based measurements. Initial HLA typing studies suggested that HLA-A*02 is negatively related to the risk of MS, being associated with protection or reduced susceptibility independent of the presence of the DRB1*15 allele. Studies have reported that the haplotypes HLA-A*02-HLA-B*12-HLA-Cw*05 and HLA-A*02-HLA-B*44-HLA-Cw*05 reduce MS risk. The presence of the Cw*05 allele in the haplotype has been reported to play a protective role by suppression of HLA-B*12 and DRB1*15 expression. HLA-B*52 has also been reported to reduce susceptibility to MS.

In the MENA region, there are a limited number of studies reporting inconsistent results on HLA class I
allele associations in MS patients for the following countries: Iran,19–24 Tunisia,25 Kuwait,26 Bahrain27 and Iraq28 (Table 1).19–24,26–38 With regard to HLA-A, an increased frequency of -A3, -A9, -A19, -A24 and -A33,19,20,23,26,27 and a lower frequency of -A2, -A11, -A28 and -A2320–23,27 have been reported in MS patients of the MENA region. Although there is consistency in the results reported by some of the studies, the allele frequencies of HLA-A2, -A3 and -A10 reportedly differ between populations, and even within the same population in the MENA region. For example, Ghabaee et al. reported a protective role of the HLA-A11 antigen against MS in the Iranian population,22 inconsistent with the results of the study conducted by Lotfi et al.19 In addition, Al-Shammri et al. reported that a higher frequency of HLA-A10 was associated with MS in the Arab Kuwaiti population, whereas a lower frequency of the same antigen was reported to be associated with MS in the Bahraini26 and Iranian populations.21,22

There have also been differing results relating HLA-B to MS risk. A higher risk of MS related to allele frequency was reported for HLA-B719 and -B2723 in Iran, -B5, -B35 and -B40 in Kuwait,27 and -B5 and -B44 in Iraq.28 Meanwhile, a lower frequency of HLA-B38,21,27 -B55,23 -B51,21 -B14, -B15 and -B4020 in Iranian MS patients, and -B35 in Iraqi MS patients,28 was reportedly associated with a reduced susceptibility to MS.

Table 1. Human leukocyte antigen class I and class II typing in multiple sclerosis patients compared with healthy controls in the Middle East and North Africa region.

| Authors                  | Year | Population         | Sample size (MS/control) | HLA class I | HLA typing method | HLA class II | HLA typing method |
|--------------------------|------|---------------------|--------------------------|-------------|-------------------|-------------|-------------------|
| Lotfi et al.19           | 1978 | Iranian             | 35/100                   | A, B        | Lymphocytotoxicity| –           | –                 |
| Kalanie et al.20         | 2000 | Iranian             | 79/100                   | A, B, C     | Microlymphocytotoxicity | DR, DQ    | –                 |
| Amirzargar et al.21      | 2005 | Iranian             | 12–15/75–100             | A, B        | Lymphocytotoxicity | DRB1, DQA, DQB | –                 |
| Ghabaee et al.22         | 2009 | Iranian             | 183/100                  | –           | –                 | DRB1, DQA1, DQB1 | Microlymphocytotoxicity |
| Kollaee et al.37         | 2012 | Iranian             | 120/100                  | –           | –                 | DRB1, DQB1, DQB1*0602 | PCR-SSP |
| Zabibi et al.38          | 2015 | Iranian             | 200/200                  | –           | –                 | DRB1, DQB1 | PCR-SSP |
| Mazdeh et al.39          | 2016 | Iranian             | 231/180                  | A, B        | PCR-SSP           | DRB1, DQ2, DQB8, DQB1*02 | PCR-SSP |
| Almadabadi et al.40      | 2018 | Iranian             | –                       | –           | –                 | –           | –                 |
| Alsahebofsoul et al.41   | 2015 | Iranian             | 205/205                  | G           | ELISA             | –           | –                 |
| Ben Fredj et al.42       | 2016 | Tunisian            | 60/112                   | G (sHLA-G)  | ELISA, PCR and PCR-RFLP | – | – |
| Al-Din et al.43          | 1990 | Kuwait              | 121 (72 Palestinian, 51 Kuwaiti MS), Control: 50 | –           | DR1 to DR9, DQW1, DQW3 | – | Microlymphocytotoxicity |
| Al-Din et al.44          | 1996 | Jordanian           | 30/45                    | –           | –                 | HDR, DQ    | Microlymphocytotoxicity |
| Al-Shammi et al.45       | 2004 | Kuwaiti             | 67/145                   | A, B, C     | Microlymphocytotoxicity | DR, DQ    | Microlymphocytotoxicity |
| Messadi et al.46         | 2010 | Tunisian            | 58/105                   | –           | –                 | HLA-DRB1 and -DQB1 | PCR/SSP |
| Saleem et al.47          | 2007 | Iraqi               | 44/62                    | A, B, C     | Microlymphocytotoxicity | DR, DQ    | Microlymphocytotoxicity |
| Al-Nashmi et al.48       | 2018 | Bahraini            | 50/50                    | A, B        | PCR/SSP           | DR, DQ     | PCR/SSP |
| Ouadghiri et al.49       | 2013 | Moroccan            | 57/172                   | –           | –                 | DRB1 and DQB1 | PCR/SSP |
| Saruhan-Direskeneli et al.50 | 1997 | Turkish             | 103/101                  | –           | –                 | DRB, DQA, DQB | PCR/SSO |
| Al Jumah et al.51        | 2018 | Saudi Arabian       | 133/158                  | A, B, C     | Next generation sequencing | DQB1, DRB1 | Next generation sequencing |

MS: multiple sclerosis; HLA: human leukocyte antigen; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; SSP: sequence-specific primers; RFLP: restriction fragment length polymorphism

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Similar to the HLA-A typing results, there are inconsistencies in the association between HLA-B-loci and MS risk between populations. For example, HLA-B5 was reported to have a protective role against MS in the Iranian population,\(^\text{20}\) while it was reported as a risk allele in the Iraqi population.\(^\text{28}\)

The role of HLA-C in MS patients within the MENA region has been reported in only three studies.\(^\text{20,26,28}\) In the Iranian population, a lower frequency of CW2 was reported in MS patients.\(^\text{20}\) Al-Shammri et al. reported that a higher frequency of CW4 antigen was associated with MS in the Arab Kuwaiti population.\(^\text{26}\) Meanwhile, Saleem et al. did not find any significant association between HLA-Cw alleles and risk of MS in the Iraqi population.\(^\text{28}\)

Only a few studies have been conducted on the role of HLA-G in MS patients within the MENA region. Ben Fredj et al. investigated two polymorphisms (+3142 G and 14 bp INS/DEL) as well as serological levels of HLA-G in the Tunisian population.\(^\text{29}\) They found no difference in serum levels of HLA-G between the two groups, consistent with the results obtained by Alsahebfosoul et al. on the Iranian population.\(^\text{24}\) However, they did find a significantly increased frequency of the +3142 G allele in patients with MS compared with healthy controls.\(^\text{29}\)

Regarding the clinical course of the disease, only two studies have investigated the association between HLA class I and MS severity. Neither study found any significant relationship between HLA class I antigen distribution and the severity or course of the disease.\(^\text{20,22}\)

**HLA class II**

Although the initial relationship between MS and HLA was related to class I HLA-A and HLA-B alleles, the HLA Class II-group leukocyte antigen -DQ (HLA-DQA1, DQB1) also plays a significant role in the immune system by presenting peptides derived from extracellular proteins to immunocompetent cells. More recently, a genome-wide association study found that the main MS susceptibility signal maps to the HLA-DRB1 gene in the class II region of the MHC, explaining up to 10.5% of the genetic variance underlying the risk.\(^\text{30}\) As expected, the strongest relationship with MS susceptibility was observed in HLA-DRB1*15:01, with an average odds ratio (OR) of 3.08.

Recently, our research group conducted a systematic review and meta-analysis on HLA-DRB1 in the MENA region. The results showed a significant relationship between total HLA-DRB1*1501 allele frequency and MS prevalence.\(^\text{40}\) DRB1*15 displayed a significant relationship with MS HLA-DRB1 alleles and the -DRB1 phenotype (OR = 1.6 and OR = 2.51, respectively). Moreover, DRB1*03 and DRB1*04 were shown to have a predisposing role (OR = 1.8 and OR = 1.9, respectively), while DRB1*07 and DRB1*11 had a protective role (OR = 0.56 and OR = 0.67, respectively).

**HLA-DQ**

There are inconsistent reports regarding the allele frequency of HLA-DQA1 and -DQB in the populations of MENA countries. Notably, these inconsistencies are not only between different populations, but occur even within the same population.

Based on serological techniques, Al-Din et al. investigated the HLA-DQ epitopes in MS patients who were originally from Kuwait, Palestine and Tunisia.\(^\text{31}\) This revealed that HLA-DQW1 was significantly higher only in Palestinian MS patients.\(^\text{30}\) Notably, the frequency of DQW3 was lower in Palestinian MS patients and higher in Kuwaiti MS patients.\(^\text{30}\) Furthermore, the frequency of HLA-DQ2 was significantly higher in Palestinian MS patients but lower in Jordanian MS patients.\(^\text{31}\)

Al-Shammri et al. conducted a study on another sample of the Kuwaiti population.\(^\text{26}\) They reported that the haplotype frequencies of HLA-DQ5, -DQ6, -DQ7 and -DQ8 antigens were higher in MS patients. They also suggested that HLA-DQ1 was lower in MS patients, indicating that it may be associated with reduced susceptibility. The authors also reported that there were not relationships between the clinical course of MS and any of the HLA-class I or II antigens. Meanwhile, Saleem et al. reported that HLA-DQ1 and -DQ3 are risk factors for MS in the Iraqi population.\(^\text{28}\)

Based on molecular techniques investigating the HLA-DQA and -DQB loci in the Iranian population, DQA1*0101, DQA1*0103 and DQB1*0602 were identified as susceptibility alleles,\(^\text{21}\) and DQA1*0102 was identified as a protective allele for MS.\(^\text{22}\) Meanwhile, Ahmadabadi et al. reported no difference in the HLA typing of DQB1 and DQA1 between two groups of the Iranian population.\(^\text{32}\) In the Turkish population, Saruhan-Direskeneli et al. reported that DQA1*0101, DQA1*0103, DQB1*0302, DQB1*0602 and
DQB1*0501 were more frequent in patients with MS.33

In Saudi MS patients, HLA-DQB1*06:02, HLA-DQB1*06:03 and HLA-DQB1*02:01 were shown to be more frequent (OR = 3.52, OR = 2.42 and OR = 1.76, respectively).34 In the Tunisian population, Messadi et al. showed that the most frequent alleles in MS patients were DQB1*03, DQB1*06 and DQB1*02, and the least frequent were DQB1*03, DQB1*02 and DQB1*06; however, these results were not statistically significant.35 However, Ouadghiri et al. did not find any association between DQB1* allele frequencies and MS risk in the Moroccan population.36

Based on this evidence, DQB1*06, DQB1*03 and DQA1*01 were reported as risk alleles in MS patients in some populations of the MENA region.

Haplotypic associations
The HLA-DQ loci have close genetic linkage to HLA-DR, and the distribution of the DQ–DR haplotypes has been compared between autoimmune disorders patients and control groups. Regarding MS, there is inconsistency in the results reported by studies on whether HLA class I is related to MS risk mainly via its association to HLA class II (DR and DQ). Analysis of haplotype transmission in disorders patients and control groups. Regarding MS, there is inconsistency in the results reported by studies on whether HLA class I is related to MS risk mainly via its association to HLA class II (DR and DQ). Analysis of haplotype transmission in

Few studies have investigated the haplotype risk association of HLA class I in the MENA region, and the results have shown that HLA class I is related to MS risk via its contribution to HLA class II (DR and DQ), similar to the results in other regions. Mazdeh et al. performed haplotype analyses on Iranian MS patients compared with healthy controls.23 They reported A*01-B*51-DRB1*04 (OR = 8.62) and A*03-B*44-DRB*04 (OR = 7.95) as susceptibility haplotypes for MS, and A*01-B*35-DRB1*13 (OR = 0.11) and A*11-B*35-DRB1*11 (OR = 0.26) as protective haplotypes for MS. Meanwhile, Al-Nashmi et al. reported HLA-A2-B40-DR2 as a susceptibility haplotype for MS compared with control subjects in the Bahraini population.27 They also reported that the HLA-A2-B15-DR3, HLA-A2-B15-DR7 and HLA-A19-B15-DR1 haplotypes were not presented in Bahraini MS patients. Based on these studies, we could not find any agreement regarding a particular risk haplotype for HLA class I in populations of the MENA region.

Discussion
Several studies have investigated the association of HLA allele frequencies and haplotypes with MS susceptibility in the MENA region. Most of these studies have been conducted in Middle Eastern countries, including Lebanon, Kuwait, Turkey, Bahrain, Iran, Saudi Arabia and, to a lesser extent, North African countries, including Jordan and Tunisia.

So far, the results of HLA-typing in the MENA region show inconsistencies from one population to another, and even within the same population. It should be noted that some of the HLA associations in the MENA region have been identified in a small number of MS patients, and it is known that sample size can affect the robustness of results. In such cases, the p-value of associations needs to be corrected by robust statistical analysis methods such as Bonferroni correction. Considering the low number and unequal distribution of studies in the MENA region, combined with the small sample sizes, the obtained results may not be representative of the whole MENA population; therefore, they have only limited power to detect the genetic susceptibility of MS.
As all the studies have been based on case–control designs, gene variants should be confirmed in other populations, or other study groups in the same population, using larger sample sizes. Case–control studies cannot confirm direct causality of genetic variants on MS susceptibility. Therefore, more longitudinal studies will be needed to robustly investigate the effect of variants on MS susceptibility. Recently, a three-year longitudinal cohort study was initiated in the Multiple Sclerosis Center of Tehran University of Medical Sciences, with the participation of approximately 400 MS patients. Comprehensive approaches such as this cohort study will enable us to study the genotype–phenotype relationship of MS more efficiently.

In addition, as different populations of MENA countries show varying patterns of linkage disequilibrium in the HLA region, cross-population analysis could be particularly informative in identifying the causal locus in a multilocus association. If a consortium of MS patients and unrelated healthy controls could be created, high throughput technologies could then be used to detect the genetic architecture underlying MS in the MENA region.

Moreover, most of the studies performed so far have focused on MS risk rather than MS severity. However, investigating the link between MS phenotype and severity is highly dependent on the individual patient history of other diseases and drug usage.

The vast majority of studies in the MENA region have addressed MS susceptibility rather than genotype–phenotype associations. In addition to genetic factors contributing to MS susceptibility, specific variants also influence the clinical manifestation and course of the disease. It is important to assess the role of variants in responses to anti-inflammatory, immunomodulatory or immunosuppressive drugs, whose mechanism of action involves cytokine signaling. To achieve this goal, more longitudinal studies need to be designed.

**Conclusion**

Increasing our knowledge about the etiology related to MS could lead to the development of control strategies for this disease. Insight into the etiology of MS, as well as identification of possible causative roles of different region-related environmental factors, is facilitated by studying genetic heterogeneity. For effective risk identification, we will need to effectively integrate genetic and epigenetic factors with environmental effects.

**Declaration of conflicting interests**

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