MSJ Experimental Translational Clinical

MS in the Middle East

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

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January-March 2020, 1–7

DOI: 10.1177/2055217319881775

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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.

Date received: 30 March 2019; Revised received 5 August 2019; accepted: 18 September 2019

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.[1] 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.[1] 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);[2] 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.[3] 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.[3] The increased prevalence of MS in MENA countries cannot simply be explained by a prevalence–latitude relationship.[4] 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,[5] vitamin D

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deficiency[6] and tobacco status.[7] 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.[5] 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.[6] 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,[8] 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.[9] 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.[10] 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,[11] 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.[12] 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,[13] 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[14] and B7[15] 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.[16] 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.[16,17] 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.[16] *HLA-B*52* has also been reported to reduce susceptibility to MS.[18]

In the MENA region, there are a limited number of studies reporting inconsistent results on HLA class I

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	Microlymphocytotoxicity
Amirzargar et al.[21]	2005	Iranian	12–15/75–100	A, B	Lymphocytotoxicity	DRB1, DQA, DQB	PCR-SSP
Ghabaee et al.[22]	2009	Iranian	183/100	–	–	DRB1, DQA1, DQB1	PCR-SSP
Kollaee et al.[37]	2012	Iranian	120/100	–	–	DRB1, DQB1	PCR-SSP
Zabihi et al.[38]	2015	Iranian	200/200			DQB1*0602	PCR-SSP
Mazdeh et al.[23]	2016	Iranian	231/180	A, B	PCR-SSP	DRB1	PCR-SSP
Ahmadabadi et al.[32]	2018	Iranian		–	–	DQ2, DQ8, DQB1*02	PCR-SSP
Alsahebfosoul et al.[24]	2015	Iranian	205/205	G	ELISA	–	–
Ben Fredj et al.[29]	2016	Tunisian	60/112	G (sHLA-G) (14bp insertion/ deletion (INS/DEL) and +3142 C>G)	ELISA, PCR and PCR-RFLP	–	–
Al-Din et al.[30]	1990	Kuwaiti	121 (72 Palestinian, 51 Kuwaiti MS), Control: 50			DR1 to DR9, DQW1, DQW3	Microlymphocytotoxicity
Al-Din et al.[31]	1996	Jordanian	30/45	–	–	HDR, DQ	Microlymphocytotoxicity
Al-Shammri et al.[26]	2004	Kuwaiti	67/145	A, B, C	Microlymphocytotoxicity	DR, DQ	Microlymphocytotoxicity
Messadi et al.[35]	2010	Tunisian	58/105	–	–	HLA-DRB1 and -DQB1	PCR/SSP
Saleem et al.[28]	2007	Iraqi	44/62	A, B, C	Microlymphocytotoxicity	DR, DQ	Microlymphocytotoxicity
Al-Nashmi et al.[27]	2018	Bahraini	50/50	A, B	PCR/SSP	DR	PCR/SSP
Ouadghiri et al.[36]	2013	Moroccan	57/172	–	–	DRB1 and DQB1	PCR-SSP
Saruhan-Direskeneli et al.[33]	1997	Turkish	103/101	–	–	DRB, DQA, DQB	PCR/SSO
Al Jumah et al.[34]	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

allele associations in MS patients for the following countries: Iran,[19–24] Tunisia,[25] Kuwait,[26] Bahrain[27] and Iraq[28] (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 *-A23*[20–23,27] 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*, *-A10* and -A11 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 Bahraini[26] 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-B7*[19] and *-B27*[23] 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 *-B40*[20] in Iranian MS patients, and -B35 in Iraqi MS patients,[28] was reportedly associated with a reduced susceptibility to MS.

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,[20] while it was reported as a risk allele in the Iraqi population.[28]

The role of *HLA-C* in MS patients within the MENA region has been reported in only three studies.[20,26,28] In the Iranian population, a lower frequency of CW2 was reported in MS patients.[20] Al-Shammri et al. reported that a higher frequency of CW4 antigen was associated with MS in the Arab Kuwaiti population.[26] Meanwhile, Saleem et al. did not find any significant association between *HLA-Cw* alleles and risk of MS in the Iraqi population.[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.[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.[24] However, they did find a significantly increased frequency of the +3142 G allele in patients with MS compared with healthy controls.[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.[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.[39] 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.[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-DQA* 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,[30] Palestine[30,31] and Tunisia.[31] This revealed that *HLA-DQW1* was significantly higher only in Palestinian MS patients.[30] Notably, the frequency of *DQW3* was lower in Palestinian MS patients and higher in Kuwaiti MS patients.[30] Furthermore, the frequency of *HLA-DQ2* was significantly higher in Palestinian MS patients but lower in Jordanian MS patients.[31]

Al-Shammri et al. conducted a study on another sample of the Kuwaiti population.[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.[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,[21] and *DQA1*0102* was identified as a protective allele for MS.[22] Meanwhile, Ahmadabadi et al. reported no difference in the HLA typing of *DQB1* and *DQA1* between two groups of the Iranian population.[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 Canadian families has suggested that associations observed between *HLA-B7* and MS risk are secondary due to linkage disequilibrium with the *DRB1*15:01-DQB1*06:02* haplotype.[41]

The *DRB1*15:01-DQA1*01:02-DQB1*06:02* HLA haplotype is commonly found in MS patients and is related to MS risk. *HLA-DRB1*15:01* has been identified as the key allele for increased risk within this haplotype, with the other alleles being secondary due to their linkage disequilibrium with *HLA-DRB1*15:01*.[39,42]

In the MENA region, the association of *HLA-DRB1* with *-DQB1* and *-DQA1* has been investigated. *RB1*1501-DQB1*0602* has been reported as a risk haplotype in Iranian MS patients (OR = 7.792).[37] However, *DQB1*0602* was not confirmed as a risk allele in another Iranian MS population.[38] In Morocco, the *HLA-DRB1*15-DQB1*06* haplotype was also found to be more frequent in MS patients (OR = 2.78).[36] In the Turkish population, the *DRB1*1501-DQA1*0102-DQB1*0602* and *DRB1*04-DQA1*03-DQB1*0302* haplotypes were also related to MS risk (OR = 3.7 and OR = 2.9, respectively).[35] Based on these studies, it can be concluded that the *DRB1*1501-DQB1*0602* haplotype is more frequent in MS patients in the Iranian and Turkish populations.

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-DRB*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 causative 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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by The Neuroscience Research Institute of Tehran University of Medical Sciences (grant number 97-01-186-38707).

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