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Research Article

HLA Association with Multiple Sclerosis in South-Eastern of Iran

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Abstract

Introduction: Investigation of the HLA_DRB1 alleles frequency between Multiple Sclerosis (MS) patients in Kerman city, south-eastern of Iran, the association of rs3135388, tagging gene polymorphism of HLA_DRB1*15, with multiple sclerosis and comparing HLA_DRB1*11, the most frequent allele in this population, with HLA_DRB1*15, the most related allele to MS disease.

Methods: DNA samples were extracted and amplified by PCR with sequence-specific primers (PCR-SSP) for the HLA-DRB genes, using HLA SSP DRB Typing Kit. Based on HLA typing results, Samples having HLA_DRB1*15 were amplified with (PCR-SSP); rs3135388 primers, tagging gene for HLA_DRB1 *15 polymorphism, then PCR product was digested by specific restriction enzyme for rs3135388, Cla I,

Results: Our findings indicated that HLA_DRB1*11 was the most frequent allele followed by HLA_DRB1*15. HLA_DRB1*15 allele was more frequent in females compared to the males, while there was no significant correlation between HLA_DRB1*11 and gender. Also, HLA_DRB1*15 was more related to disease severity based on Extended Disability Status Scale (EDSS) results. The rs3135388 T allele was more frequent in the MS group compared to the controls.

Conclusion: HLA_DRB1*15 is most probably related to MS disease with T allele as the most common polymorphism among the MS patients.

Keywords: Multiple Sclerosis; HLA_DRB1 Alleles; HLA Typing; rs3135388; Cla I Restriction Enzyme; Kerman-Iran Population

Abbreviations

MS: Multiple Sclerosis; RRMS: Relapsing-remitting Multiple Sclerosis; PPMS: Primary-progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; EDSS: Expanded Disability Status Scale; NA: Not Applicable

Introduction

Multiple Sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system which causes progressive and relapsing neurological handicaps [1]. The disease is the most common human demyelinating illness [2,3] which afflicts twice as many women as men [4]. It is the first reason of non-traumatic neurological disabilities in young people [5]. The onset of MS typically is in young adults, thus it is associated with long term physical effects. It's prevalence is 57.3 in 100000 populations in Kerman city, southern-east of Iran [6]. MS is a multifactorial disorder whose pathogenesis seems to involve interactions between genetic and environmental factors, which vary in different populations, ethnic groups and geographic locations [7,8]. Among the potential genetic factors, the Human Leukocyte Antigen (HLA) class II, the human form of MHC molecules on the 6p21 chromosome, has been identified as the main region associated with MS [9,10].

A main feature of HLAs is allelic polymorphism. Such polymorphism apparently enhances the probability of increasing an immune response by a subset of individuals among a population [11]. Various investigations have been done on HLA class II genes in different ethnic groups. Between these alleles, the HLA-DRB1*15 was found more frequent in most of patients in Caucasia [5], Greece [12], Latin American [13], Western Australia [7], Brazil [9], Moroccan [5], Portugal [14], Europe [15,16,17,18,19,20,21], Arabs [22] and African Americans [23].

So at present study we aimed to investigate the frequency and genetic polymorphisms of HLA class II alleles in Kerman province, southern-east of Iran, which has been postulated to suffer from high prevalence of MS, and to compare the findings with other populations worldwide.

Materials and Methods

Patients

Kerman university of Medical Sciences ethics committee approved the study. The subjects provided a written consent before the initiation of the study. The study included 50 unrelated MS patients (33 women and 17 men) introduced by the neurological clinic of Shafa hospital at Kerman University of Medical Sciences, Kerman-Iran. Diagnosis was based on the revised Mc-Donald criteria, which were registered at the Iranian MS society, Kerman branch. Ten healthy individuals from the same community entered the study as controls. Through medical evaluation, it was ensured that the control individuals were free of acute or chronic internal and neurological diseases

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Table 1: Demographic and clinical characteristics of MS patients and controls.

Clinical information		MS patients	Controls
Total number of individuals		50	10
Gender	male	16	3
	female	34	7
Mean age (y)		33.78	28.8
Mean age at onset (y) (S.D.)		27.9 ± (8.8)	NA
Mean disease duration(y)(S.D)		7.4 (4.8)	NA
Type of initial symptoms, n (%)			NA
Optic neuritis		18 (36%)	NA
Long motor tracts		33 (66%)	NA
Long sensory tracts		10 (20%)	NA
Brainstem-Cerebellum		17 (34%)	NA
Disease course, n (%)			NA
RRMS		28 (56%)	NA
PPMS		3 (6%)	NA
SPMS		14 (28%)	NA
NEW CASE		5 (10%)	NA
EDSS, n (%)			NA
<3		19 (38%)	NA
3≤EDSS≤6		17 (34%)	NA
>6		14 (28%)	NA
Symptoms at enrollment time, n (%)	Optic neuritis	21 (42%)	NA
	Long motor tracts	34 (68%)	NA
	Long sensory tracts	10 (20%)	NA
	Brainstem-Cerebellum	17 (34%)	NA
Family history, n (%)	With MS	4 (8%)	NA
	Without MS	46 (92%)	

RRMS, Relapsing-remitting MS; PPMS, Primary-progressive MS; SPMS, Secondary progressive MS; EDSS, Expanded Disability Status Scale; NA, not applicable.

Sample collections

Peripheral blood samples (10 ml) from MS patients and controls were collected in EDTA. Each subject was informed about the study and provided a written informed consent for the genetic analysis.

DNA extraction and HLA typing

Genomic DNA was obtained by manual techniques.

1000 µl RBC lysis buffer was added to 500 µl of peripheral blood and centrifuged at 7000 rpm for 2 minutes. The step was repeated 2-3 times and the supernatants were discarded each time. 400 µl nuclear lysis buffer, 100 µl Nacl solution and 600 µl chloroform were added and centrifuged at 7000 rpm for 2 minutes.

800 µl cold absolute ethanol was then added to 400 µl of supernatant and centrifuged at 12000 rpm for 1 minute. The supernatants were finally discarded and 50 µl elution buffer was added to the tube.

The test requires DNA with a ratio (A260/A280) of >1.6 and at least a concentration of 75 ng per reaction.

Table 2: Associations of HLA-DRB1 alleles with MS and carriage frequencies in the MS and control groups of subjects.

HLA_ DRB1	Case carriage frequency% (n)	Control carriage frequency% (n)	Odds ratio	p-value
*01	9 (7.5%)	2 (1.6%)	0.89	0.05
*03	10 (8.3%)	2 (1.6%)	1	0.05
*04	11 (9.1%)	0	0	0.05
*07	8 (6.6%)	2 (1.6%)	0.78	0.05
*08	1 (0.8%)	0	0	0.05
*10	1 (0.8%)	0	0	0.05
*11	23 (19.1%)	1 (1.6%)	5.67	0.05
*12	1 (1.6%)	0	0	0.05
*13	7 (5.8%)	4 (3.3%)	0.3	0.05
*14	6 (5%)	4 (3.3%)	0.2	0.05
*15	12 (10%)	4 (3.3%)	0.54	0.05
*16	11 (9.1%)	1 (1.6%)	2.34	0.05

DNA was amplified by PCR with Sequence-Specific Primers (PCR-SSP) for the HLA-DRB genes, using MorganTM HLA SSP DRB Typing Kit. PCR products were visualized under UV illuminator after electrophoretic separation on 2% agarose gel containing ethidium bromide. Genotypes were deduced from the amplification patterns using the worksheet provided in kit in the special software.

Restriction enzyme digestion

Based on HLA typing results, Samples having HLA_DRB1*15 were amplified with Polymerase Chain Reaction using Sequence-Specific Primers (PCR-SSP); rs3135388 primers, tagging gene for HLA_DRB1*15 polymorphism. The data showing primer, PCR and digestion information are presented elsewhere [24].

PCR product was digested by Cla I, specific restriction enzyme for rs3135388 provided from Thermo fisher scientific company, after electrophoresis the results were compared in order to examine the genotype differences between the samples.

Statistical analysis

HLA-DRB1 allele results were set up using the Excel software, and allelic frequency was obtained using SPSS version 16.1.

Results

Demographic and clinical data

To determine the association of HLA-DRB1 and MS disease, a total of 50 MS patients and 10 controls were analyzed. The original city of birth of the patients and control group were recorded. They all were from the same ethnicity and regional location; Kerman province, southeastern Iran.

Among 50 patients with MS and 10 controls there were 35 females and 15 males in MS and 7 females and 3 males in the control group.

Mean age was 33.78 years in MS and 28.8 years in the control group. Mean age at onset was 27.9 years, mean disease duration was 7.4 years. Other clinical features are recorded in Table 1.

HLA typing parameters

Allele frequencies in MS and control group: As the results show in Table 2, HLA_DRB1*11 was significantly the most frequent

Table 3: Distribution of homozygote and heterozygote HLA_DRB1 alleles in MS group.

HLA_DRB1 alleles in case group	*01	*03	*04	*07	*08	*10	*11	*12	*13	*14	*15	*16
*01	.	.					…					.
*03			.						..		.	
*04		.	..	.			.	.	.			
*07				.			..				.	
*08										.		
*10											.	
*11	.		.	.			….			..	.	.
*12												
*13		.								..		
*14											.	
*15	.	.		.			..				.	
*16		..							.			…

Table 4: Distribution of homozygote and heterozygote HLA_DRB1 alleles in control group.

HLA_DRB1 alleles in control group	*01	*03	*04	*07	*08	*10	*11	*12	*13	*14	*15	*16
*01												
*03	.			.								
*04												
*07												
*08												
*10												
*11	.											
*12												
*13										…	.	
*14												
*15				.							.	
*16										.		

allele in MS patients and after that alleles *15, *04 and *16 are more frequent among the others. Also, HLA_DRB1*08, *10 and *12 have the least frequency in MS group.

Genotype frequencies in MS and control group: The HLA_DRB1*11/11 and 11/01 genotypes were the most frequent in MS group followed by HLA_DRB1*16/16, 11/07, 11/15 and 13/03. Among the control samples HLA_DRB1*13/14 had the highest frequency (Tables 3,4).

Genotype characteristics: According to other studies HLA_DRB1*15 is the most related allele to multiple sclerosis. Our results also showed high frequency in this allele (Table 5). So we decided to study the allele frequencies of HLA-DRB1*1501 rs3135388 gene polymorphism, a tagging polymorphism for HLA_DRB1*15, in MS patients who had had this allele based on the HLA typing results. Among all, 11 samples in MS and 3 samples in control group had HLA_DRB1*15 allele.

The homozygotes TT and heterozygotes TC were more frequent in MS patients and a higher frequency of the rs3135388 T allele was found in MS group compared to the controls.

Comparing HLA_DRB1*11 and *15 features: As the frequency of HLA_DRB1*11 is so high among MS patients in this study and also in Iranian population and HLA_DRB1*15 is reported to be severely associated to MS disease we compared some features of these two allele carriers.

According to Table 6 among 50 MS patients 19 of them carried HLA_DRB1*11 and 11 patients carried HLA_DRB1*15 allele in either homozygote or heterozygote forms.

In HLA_DRB1*11 group there were 9 (47.3%) female and 10 (52.6%) male carriers and in HLA_DRB1*15 group there were 8 (72.7%) female and 3 (27.2%) male carriers and it shows that HLA_DRB1*15 allele is more frequent in females compare to the males. Although there is no significant relationship between HLA_DRB1*11 and gender, there is no significant difference in disease duration between these two groups.

Based on comparing EDSS in these two groups we could see that 15.7% of HLA_DRB1*11 carriers showed EDSS >6 but this ratio was 45.4 in HLA_DRB1*15 group and it shows that HLA_DRB1*15 allele can affect disease severity even though HLA_DRB1*11 was more frequent.

Table 5: Genotype differences of rs3135388 Polymorphism.

Polymorphism	Genotype	Genotype	Genotype	Allele	Allele
rs3135388	TT (%)	TC (%)	CC (%)	T	C
MS (N=11)	4/11 (36.3%)	1/11/2019 -9%	6/11 (54%)	9/22(40.9%)	13/22(59%)
Control (N=3)	0/3	2/3/2019 (66.6%)	1/3/2019 (33.3%)	2/6 (33.3%)	4/6 (66.6%)

Table 6: HLA_DRB1*11 and 15 comparison.

HLA_DRB1		*11	*15
gender		9 female (47.3%)	8 female (72.7%)
		10 male (52.6%)	3 male (27.2%)
Mean disease duration		6.9 y	6.6 y
Disease course, n (%)	RRMS	12 (63.1%)	4 (36.3%)
	PPMS	2 (10.5%)	2 (18.1%)
	SPMS	5 (26.3%)	4 (36.3%)
NEW CASE		0	1 (9%)
EDSS, n (%)	<3	9 (47.3%)	2 (18.1%)
	3≤EDSS≤6	7 (36.8%)	4 (36.3%)
	>6	3 (15.7%)	5 (45.4%)

Discussion

Multiple sclerosis is a multi-factorial autoimmune disease which its genetic association to MHC class II genes has been described by Jersild C et al in 1973 [25]. HLA is the human form of MHC gene and the relationship between HLA_DRB1*15 and MS susceptibility has been noted in many populations[15,22,16,23,17,18,19,20,21,13,7,12, 14,5] . However, some studies have reported other alleles like HLA_ DRB1*03 and *04 are related to MS in some populations [26] and in some researches it has been reported that HLA_DRB1*15 shows low frequency in non-European populations like Iranians and also in MS patients compared with controls [27, 28].

The aim of this study was to investigate HLA_DRB1 allele's frequency in Kerman city, Iran, and their relationship to MS disease. A recent study among Iranian population in Tehran showed that HLA_DRB1*15/11 genotype has high frequency and HLA_DRB1*15 is related to MS disease [1]. Our study shows that HLA_DRB1*11 allele has the highest frequency followed by HLA_DRB1*15. Marrosu et al have also shown an exception of Sardinian population where HLA_DRB1*03 and *04 were more frequent among MS patients [26]. Our results also show high frequency of HLA_DRB1*04, *03, *16 and *01 in MS patients. In some Mediterranean regions like Spain (29%) [21], France (26%) and Turkey (21%) [18] HLA_DRB1*15 showed higher frequency among control group in comparison with Tunisian controls (3.8%).

Our results also show higher frequency of HLA_DRB1*15 (3.3%) compared with other alleles but a higher sample size is required to verify the results.

This study shows low frequency of HLA_DRB1*12 in the target population, (1.6%) in MS group and (0%) in controls, our results are in agreement with another study which has shown nearly the same frequencies in Iranian population; (1.4%) in patients and (0%) in the controls [1], however some other studies indicated that HLA_ DRB1*12 is related to lower MS disease risk [29,16] but another study is noting to HLA_DRB1*12 as a MS associated allele and the believe that interactions between HLA_DRB1*15 and other DRB1 alleles might have a modifying effect on MS risk and severity [7] and these interactions may also have some effects on other autoimmune diseases such as diabetes mellitus [30]. Wu et al have proposed that HLA_DRB1 polymorphisms may have different binding properties based on their protein sequences which has some effects on disease risk and severity, and as (when) the two alleles are both expressed, they may present t antigenic epitopes to immune system. Besides the genetics some environmental factors may also affect the process and modify the disease risk and severity [7].

Our findings show that HLA_DRB1*11 allele and HLA_ DRB1*11/11 genotype are the most frequent in this population, mostly in MS patients and HLA_DRB1*15/11 genotype and HLA_ DRB1*15 allele are also frequent as reported in another study having been carried out in Iran [1]. However, HLA_DRB1*11 has been reported to have disease resistance effects in MS patients (Lublin and Reingold 1996).

Our results show an agreement with the report that HLA_ DRB1*15 is related to MS disease and it shows higher frequency of rs3135388 T allele in MS patients, as reported in a Serbian population [31] and Czechs population [24].

So many researches have been done to find out the relationship between HLA_DRB1*15 and gender, some of them have found no relations [32] while others have found a relationship between this allele and females [33,34] or males [35] . a study has revealed higher frequency of rs3135388 polymorphism in females suffering from MS [24].

Our results also show higher frequency of HLA_DRB1*15 in females compared with males, while no significant difference were found in HLA_DRB1*11 frequency between males and females.

There are many controversial information on the association of HLA_DRB1*15 and disease severity and course. Many researches indicate that there is no relationship between these two [35,34,36,24] however some others have found some degrees of relationship between this allele and disease risk and severity [37,38,7]. Also, Kwon et al showed that HLA_DRb1*15 is related to RR- or SPMS among the non-Ashkenazi MS patients [39,40].

According to our results the Extended Disability Status Scale (EDSS) score was >6 in 45.4% of patients who had HLA_DRB1*15 allele while it was just 15% in patients with HLA_DRB1*11 allele so based on our results HLA_DRB1*15 might be related to disease severity.

Conclusion

The present study confirmed that HLA_DRB1*11 and HLA_ DRB1*15 alleles are the most frequent in our study population. HLA_ DRB1*15 is most probably related to MS disease with T allele as the

most common polymorphism among the MS patients.

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