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ARTICLE

The *CIITA* genetic polymorphism rs4774*C in combination with the *HLA-DRB1*15:01* allele as a putative susceptibility factor to multiple sclerosis in Brazilian females

O polimorfismo rs4774*C no gene *CIITA* em conjunção com o alelo *HLA-DRB1*15:01* é um possível fator de susceptibilidade a esclerose múltipla em mulheres brasileiras

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ABSTRACT

The objective of this study was to investigate the association between the HLA alleles at the *DQA1, DQB1* and *DRB1 loci*, the *CIITA* genetic polymorphisms -168A/G and +1614G/C, and susceptibility to multiple sclerosis (MS) in a sample from Rio de Janeiro State, Brazil. Furthermore, we wished to determine whether any of these associations might be more significant in women compared with men. DNA samples from 52 relapsing-remitting MS (RRMS) patients and 126 healthy controls matched for sex and age were analyzed. We identified a significant *HLA-DRB1*15:01*-MS association that was female-specific (Odds Ratio (OR) = 4.78; p = .001). Furthermore, we observed that the +1614G/C mutation in combination with the *HLA-DRB1*15:01* allele increased susceptibility to MS in females (OR = 4.55; p = .01). Together, these findings highlight the polygenic nature of MS.

Keywords: *CIITA* gene, HLA, rs4774*C, *HLA-DRB1*15:01*, multiple sclerosis.

RESUMO

O objetivo deste estudo foi investigar a associação entre alelos HLA, *loci DQA1, DQB1* e *DRB1*, polimorfismos -168A/G e +1614G/C no gene *CIITA*, e suscetibilidade à esclerose múltipla (EM) em uma amostra de Rio de Janeiro, Brasil. Além disso, buscou-se determinar se alguma dessas associações pode ser gênero-dependente. Foram analisadas amostras de DNA de 52 pacientes com EM reincidente-remitente (EMRR) e 126 controles saudáveis pareados por sexo e idade. Foi identificada associação significativa *HLA-DRB1*15:01*-EMRR, que foi específica para o gênero feminino (Odds Ratio (OR) = 4,78, p = 0,001). Além disso, observou-se que o polimorfismo +1614 G/C, em combinação com o alelo *HLA-DRB1*15:01* provoca o aumento da susceptibilidade à EM em pacientes do sexo feminino (OR = 4,55, p = 0,01). Juntos, estes resultados destacam a natureza poligênica da EM.

Palavras-chave: gene *CIITA*, HLA, rs4774*C, *HLA-DRB1*15:01*, esclerose múltipla.

Multiple sclerosis is one of the most common causes of chronic neurological disability among young adults in economically productive societies[1]. Although MS affects approximately one million people worldwide, it has historically been more common in cold or temperate climates. However, recent reports have suggested that this latitude gradient is disappearing[2]. Among the highly admixed Brazilian population, which is the result of interbreeding between European

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Caucasians, Africans and Amerindians[3], the prevalence of MS is less than 15 cases per 100,000 inhabitants in Sao Paulo City[4] and about 20,100,000 inhabitants in Rio de Janeiro City[5].

The genetic components of MS pathogenesis are quite complex[6], and the human leukocyte antigen (HLA) class II genes (6p21.3) appear to play an important role in determining the risk for MS. For example, the *HLA-DRB1*15:01* allele is consistently associated with MS[6]. Studies performed on North American and European populations revealed an association between the *HLA-DRB1*15:01, -DQA1*01:02* and *-DQB1*06:02* alleles and the development of MS[7], and these alleles have also been linked to MS in the Brazilian population[8,9,10]. In particular, a previous Brazilian study showed that the *DRB1*15:01* allele confers ethnicity-dependent MS susceptibility in Caucasian patients, whereas that the *DQB1*06:02* allele confers genetic susceptibility regardless of ethnicity[8]. In addition, the *HLA-DRB1*15* allelic group has been associated with MS in samples from Brazil[9] and Portugal[11,12], the European country that originally colonized Brazil.

Studies have also searched for non-MHC genetic risk factors for MS, and *CIITA* (also called *MHC2TA, loci* 16p13) polymorphisms have been reported as putative susceptibility factors[13,14]. In fact, *CIITA* is an attractive candidate molecule in studies involving a variety of autoimmune diseases and inflammatory HLA-associated conditions[13,14,15]. Furthermore, expression of MHC II is tightly controlled by the class II transactivator, which is a master regulator of both constitutive and inducible MHC II expression[16].

The goal of this study was to investigate the association between a large number of polymorphic alleles and MS in a sample from Rio de Janeiro State, Brazil. In particular, we analyzed 84 polymorphic alleles, including the HLA *DQA1, DQB1* and *DRB1 loci*, as well as the *CIITA* polymorphisms -168A/G and +1614 G/C. In addition, we searched for gender-related differences in the associations between MS and these polymorphisms.

METHOD

Patients and controls

Peripheral blood samples were taken from 52 relapsing-remitting MS (RRMS) patients [35 females (67.3%); 17 males (32.7%)] who had been diagnosed with MS and were registered with the outpatient clinic of neurology at the University Hospital Clementino Fraga Filho (UFRJ). All the patients fulfill magnetic resonance imaging (MRI) criteria for distribution in space and time[17]. Blood samples were also taken from 126 healthy control subjects [85 females (67.46%); 41 males (32.54%)] who had been matched with the MS patient group for ancestry [patient group: 22 Afro-Brazilians (42.30%); 30 non-Afro-Brazilians (57.30%); control group: 52 Afro-Brazilians (41.26%); 74 non Afro-Brazilians (58.74%)], sex and age. Patients were classified according to the criteria laid out by McDonalds et al.[17]. The Afro-Brazilians were classified in this ethnic group if they could not identify White ancestry for up to three generations time period. This criteria was accepted in our previous studies ethnicity-dependent[8].

DNA Typing

DNA was extracted from the blood samples using the organic method, and the *HLA-DRB1* (Table 1), *HLA-DQB1* (Table 2) and *HLA-DQA1* (Table 3) alleles were identified by PCR amplification with sequence-specific primers using the One Lambda (Canoga Park, CA, USA) kit, according to the manufacturer's recommendations. Sequencing of the single nucleotide polymorphisms (SNPs) +1614G/C (rs4774*C; G500A) and -168A/G (rs3087456) within *CIITA* was performed using PCR, as described by Patarroyo et al.[18], followed by capillary electrophoresis on the ABI PRISM® 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA) platform to identify the genetic profiles in the patient and control groups.

Statistical analysis

The relative frequencies of the alleles were manually calculated. The p-values and odds ratio (OR) were calculated using the Epi Info, a public-domain software program created by the CDC (Centers for Disease Control and Prevention), and SPSS Statistics software.

Ethics

All patients were duly informed with respect to the use of their clinical and genetic data in accordance with the study protocol, which was approved by the institution's Internal Review Board. The project was approved by CONEP (National Council for Ethics in Research; #1265) on May 29th, 2000.

RESULTS

We investigated the association between MS susceptibility and 84 alleles of the polymorphic *HLA-Class II* genes: 49 from the *DRB1 locus*, 25 from the *DQB1 locus* and 10 from the *DQA1 locus* (Tables 1, 2 and 3). To the best of our knowledge, this is the most comprehensive survey of the association between genetic polymorphisms and MS that has been conducted on a Brazilian population.

We observed that the OR related to MS associated with *HLA-DRB1*15:01* was 3.52. In addition, the association between MS and *HLA-DRB1*15:01* was only significant in female patients: 31.43% of female patients had the allele (OR = 4.78; p = .001), whereas only 23.53% of male patients had the allele (OR = 2.05; p = .16) (Table 4).

We did not find a significant association between the *CIITA* polymorphism rs3087456 and susceptibility to MS. The data related to the rs4774 *CIITA* polymorphism are shown in Table 4. We observed that the *CIITA* polymorphism rs4774 (+1614G/C) in combination with *HLA-DRB1*15:01* increased the OR to 2.65 (p = .005). Table 5 shows our gender analyses. In particular, females carrying both the rs4774*C and *DRB1*15:01* alleles had an OR of 4.55 (p = .02).

Table 1. Frequencies of the HLA-DRB1 polymorphic alleles.

Allele	P	C	p-value	OR	Allele	P	C	p-value	OR
**01:01*	6	9	0.5	1.6	**10:01*	0	1	0.47	1.1
**01:02*	3	4	0.24	1.7	**11:01*	3	9	0.32	0.72
**01:03*	5	8	0.54	1.43	**11:02*	1	9	0.02	0.23
**03:01*	5	13	0.37	0.8	**11:03*	1	2	0.46	1.1
**03:02*	2	4	0.44	1.11	**11:04*	1	1	0.57	2.2
**03:05*	2	4	0.44	1.11	**12:01*	1	2	0.46	1.1
**03:08*	0	3	0.24	0.32	**12:02*	1	2	0.46	1.1
**03:11*	2	3	0.32	1.5	**13:01*	3	10	0.26	0.64
**04:01*	1	2	0.46	1.1	**13:02*	0	3	0.24	0.32
**04:02*	2	3	0.32	1.5	**13:03*	1	8	0.09	0.26
**04:03*	2	3	0.32	1.5	**13:04*	0	0	NA	NA
**04:04*	0	1	0.47	1.1	**13:05*	0	0	NA	NA
**04:05*	2	3	0.32	1.5	**13:06*	1	3	0.39	0.72
**04:06*	0	1	0.47	1.1	**13:09*	0	2	0.35	0.54
**04:07*	1	3	0.39	1.1	**14:01*	1	2	0.46	1.1
**04:08*	0	1	0.47	1.1	**14:02*	2	4	0.44	1.1
**04:09*	2	3	0.32	1.5	**14:05*	1	1	0.27	1.1
**04:10*	2	4	0.44	1.1	**14:06*	1	2	0.46	1.1
**04:11*	3	7	0.47	0.95	**15:01*	15	13	0.002	3.2
**07:01*	3	9	0.32	0.72	**15:02*	4	12	0.29	0.72
**08:01*	2	8	0.21	0.54	**15:03*	8	10	0.09	1.9
**08:03*	0	5	0.12	0.21	**16:01*	2	6	0.35	0.73
**08:04*	0	1	0.47	1.1	**16:02*	7	13	0.33	1.2
**08:07*	0	3	0.24	0.32	**16:03*	5	10	0.41	1.1
**09:01*	0	2	0.59	0.43					

P: Allele counts in the patient group; C: Allele counts in the control group.

Table 2. Frequencies of the *HLA-DQB1* polymorphic alleles.

Allele	P	C	p-value	OR	Allele	P	C	p-value	OR
**02:01*	11	33	0.20	1.2	**05:04*	2	3	0.32	1.5
**02:03*	0	4	0.17	0.62	**06:01*	4	6	0.26	1.5
**03:01*	7	16	0.47	0.97	**06:02*	18	19	0.02	1.8
**03:02*	4	17	0.10	0.48	**06:03*	8	13	0.22	1.4
**03:03*	3	8	0.39	0.82	**06:04*	1	4	0.29	0.54
**03:04*	2	6	0.35	0.73	**06:05*	2	3	0.32	1.5
**03:05*	0	1	0.47	1.1	**06:06*	0	4	0.17	0.26
**03:07*	1	2	0.46	1.1	**06:07*	3	5	0.34	1.3
**04:01*	6	14	0.46	0.95	**06:08*	3	9	0.32	0.72
**04:02*	2	5	0.44	0.88	**06:09*	0	0	NA	NA
**05:01*	13	33	0.23	0.75	**06:10*	0	0	NA	NA
**05:02*	5	9	0.34	1.2	**06:11*	0	2	0.35	0.54
**05:03*	9	16	0.27	1.3					

P: Allele counts in the patient group; C: Allele counts in the control group.

Table 3. Frequencies of the *HLA-DQA1* polymorphic alleles.

Allele	P	C	p-value	OR
**01:01*	11	27	0.38	0.88
**01:02*	19	39	0.35	1.1
**01:03*	8	19	0.43	0.92
**01:04*	5	11	0.48	1.0
**02:01*	14	38	0.22	0.75
**03:01*	13	36	0.21	0.74
**04:01*	8	14	0.27	1.3
**05:01*	20	33	0.09	1.5
**05:02*	6	14	0.46	0.95
**06:01*	0	1	0.47	1.1

C+: Allele counts in the control group; F%: Relative frequency percentage for P (patients) and C (controls); P+: Allele counts in the patients group.

Table 4. The *HLA-DRB1*15:01* allele in males vs. females.

	Patients (n = 52)		Controls (n = 126)			
	*DRB1*15:01-*	*DRB1*15:01+*	*DRB1*15:01-*	*DRB1*15:01+*	OR	p-value
Male	13	4	40	6	2.05	0.16
Female	24	11	73	7	4.78	0.001

Table 5. Frequencies of the *CIITA* genetic polymorphisms rs4774*C and rs4774*C as well as the *DRB1*15:01+* allele in the MS patients and healthy controls.

Polymorphism	C+	C-	C (F%)	P+	P-	P (F%)	OR	p-value
rs4774*C (FM)	24	102	19.05	17	35	32.69	2.06	0.02
rs4774*C + *DRB1*15:01+* (FM)	4	122	3.17	6	46	11.54	2.65	0.005
rs4774*C + *DRB1*15:01+* (F)	3	82	3.53	5	30	14.28	4.55	0.02
rs4774*C + *DRB1*15:01+* (M)	2	39	4.87	1	16	5.88	1.21	0.86

F: Female; M: Male; FM: Female + Male; C+: Controls bearing the allele; C-: Controls without the allele; F%: Relative frequency percentage for P (patients) and C (controls); P+: Patients bearing the allele; P-: Patients without the allele.

DISCUSSION

Systematic molecular genetic studies have provided important insights into MS susceptibility. In particular, the association between *HLA-class II* genes and the relative risk for MS has been investigated in several populations[1,6,9], and a link between *HLA-DRB1** and MS susceptibility in Brazilian patients has already been reported[19].

In our sample, which was taken from Rio de Janeiro State in Southeast Brazil, *HLA-DRB1*15:01* was observed to be a genetic susceptibility factor for MS. However, the significant association between *DRB1*15:01* and MS was female-specific (Table 4), consistent with previous reports based on different populations[20,21]. Indeed, women are twice as likely as men to develop MS, and this disparity has been increasing for at least 50 years in certain populations[2]. This phenomenon can be partly explained by genetic interactions between polymorphisms in the *estrogen receptor* (*ER*)[21] and *Vitamin D receptor* (*VDR*) genes[22] and the *HLA-DRB1*15:01* allele, which increase the risk for MS[21]. Furthermore, the *DRB1*15:01* allele was previously shown to be over-represented within Brazilian patients[9], and it was associated with both younger age at diagnosis and with being female; however, no association was observed between *DRB1*15:01* and disease course[23].

It has been reported that, in general, African-Brazilian patients (e.g., from Rio de Janeiro) possess certain European-derived alleles, such as *HLA-DQB1*06:02*, but do not possess the *DRB1*15:01* allele, which is more common in Brazilian Caucasians, African Americans and Europeans. The *HLA-DRB1*15:01-DQB1*06:02* association was already identified as a susceptibility factor for MS in Caucasian Brazilian samples[8]. Unlike previous studies conducted on Brazilian populations[8,24], we did not observe an association between the *HLA-DQA1*02:01-03:01* alleles and MS (Table 3). In addition, an association between *HLA-DQB1*06:02* and MS in the absence of *DRB1*15:01* was not observed in patients of African descent, which also does not agree with previous studies[10]. These inconsistent results may be due to differences in the ethnic admixtures of the analyzed population samples.

Although MS is considered to be rare in Brazil, the significant number of affected Brazilians of African descent has drawn the attention of researchers because this ethnic group is rarely affected by MS in other countries[25]. The fact that such

a phenomenon is observed in Brazil could be attributed to the degree of ethnic admixing among the local population[10].

In a recent genome-screening survey, several novel *loci* were identified that showed significant associations with MS outcome, including *IL2RA, IL7RA, CLEC16A, CD58, TNFRSFA1* and *IRF8*[27], the majority of which are located near genes with immune functions or that have been associated with other autoimmune diseases. The *CIITA* gene is a known regulator of *HLA-D* expression and is found within the *CLEC16A-SOCS1-CIITA* gene complex[28], a chromosomal region that has been associated with susceptibility to MS[28,29]. An association between the rs4774*C missense variant and susceptibility to MS – as well as to other autoimmune diseases, such as lupus erythematous – has been previously described[13]. Bronson et al.[13], using a European data set of 1,320 MS cases, identified an association between the missense mutation +1614G/C (rs4774) and the HLA-*DRB1*15:01* allele as a risk factor for MS in Caucasian European groups[13]. In contrast, earlier studies investigating the association between the +1614G/C mutation and MS did not find a significant association[30]. We also note that previous studies involving the rs3087456 variant of *CIITA* presented conflicting results[13]. In a study of a Nordic population, the authors observed significant differences in rs3087456 frequencies between MS patients and the healthy control group[30], although another case-control study found no significant differences with respect to this mutation between patients and control groups in Northern Ireland. In addition, Ramagoplan et al.[22] failed to identify a relationship between *CIITA* variants and MS types in a Canadian population. However, in a sample group taken from Rio de Janeiro, Brazil, we found that a combination of the +1614G/C (rs4774) mutation and the *HLA-DRB1*15:01* allele increased susceptibility to MS and that the *HLA-DRB1*15:01*-MS association was stronger in female patients (Table 4). These findings reinforce the multifactorial and polygenic nature of MS.

In conclusion, our results indicated that the *HLA-DRB1*15:01* allele was associated with susceptibility to MS in a sample population from Rio de Janeiro, Brazil. Furthermore, this association was more significant in female patients. Therefore, we conclude that the rs4774*C mutation in combination with the *HLA-DRB1*15:01* allele increases susceptibility to MS in this population.

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