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Genetic association study of the HLA class II alleles DRB1, DQA1, and DQB1 in patients with pharmacoresistant temporal lobe epilepsy associated with mesial hippocampal sclerosis

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ABSTRACT

Purpose: Temporal lobe epilepsy (TLE) is the most common variety of focal epilepsy among adults. The neuroinflammatory mechanisms of epilepsies may be involved in the genesis of seizures and refractory epilepsies, particularly in the case of progressive syndromes such as TLE associated with mesial hippocampal sclerosis (TLE-HS). The goal of the present study is investigate the genetic profile of susceptibility of individuals with TLE-HS by analyzing the possible association of TLE-HS with human leukocyte antigen (HLA) DRB1, DQA1 and DQB1 alleles.
Methods: Peripheral blood samples were collected from 42 individuals with pharmacoresistant TLE-HS and 89 healthy controls. The typing of the HLA class II alleles from DRB1, DQB1, and DQA1 *loci* were analyzed using sequence-specific primer-polymerase chain reaction (SSP-PCR) and identified through sequencing. Statistical analysis of relative allele frequencies was performed using an Excel spreadsheet; *p*-value, relative risk (RR), and odds ratio (OR) were calculated using the software Epi Info 6.0. *p*-values <0.05 following Bonferroni's method correction were considered statistically significant.
Results: *HLA-DRB1*13:02* was the only allele with a statistically significant difference ($p = 0.01$) in frequency between patients and controls. However, the significance was lost following Bonferroni's method correction ($p = 0.44$). The remainder of the alleles in the *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1* regions did not exhibit any significant association.
Conclusion: The allele *HLA DRB1*13:02* has exhibited a tendency to behave as a susceptibility factor for TLE-HS.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common epileptic syndrome among adults and accounts for approximately 40% of epilepsy cases and 60% of the ones with focal onset epilepsy [1,22]. Hippocampal sclerosis is associated with TLE and is present in 70–80% of the individuals with this type of epilepsy [1–4].

Epileptic episodes begin in childhood, adolescence or adulthood, but onset most frequently occurs between the ages of 10 and 20 years old. Patients typically undergo one or more episodes of febrile seizures in childhood before development of mesial temporal lobe epilepsy [5]. Several etiologies have been attributed to the cause of brain injury leading to progressive gliosis of the temporal lobe, known as initial precipitating incidents (IPIs) [6,7]. TLE-HS is clinically relevant due to its high prevalence as well as to the high proportion of patients with seizures that are refractory to pharmacological treatment.

Hippocampal sclerosis (HS) is one of the causes of this condition and is present in 50–70% of patients with pharmacoresistant TLE [8,9]. Neuroinflammatory findings have been described as a associated to the onset of seizures and refractory epilepsies, particularly in the case of progressive syndromes such as TLE-HS [10]. Vezzani and Granata [16], demonstrated the participation of

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proinflammatory cytokines such as interleukin-1 beta (IL-1β) in the activation of astrocytes through lesions of the blood-brain barrier (BBB). Recently, we have shown that the levels of tumor necrosis factor alpha (TNF-α), a highly relevant proinflammatory cytokine, were reduced in patients with TLE-HS subjected to surgical treatment [11–13], found that the number of macrophages in microglial cells was higher in human leukocyte antigen-D related (HLA-DR)-labeled human hippocampi surgically removed from patients with TLE-HS compared with controls. Ozkara et al. [14], found an association of HLA-DR4, HLA-DQ2 and HLA-DR7 with TLE-HS. Together, these findings indicate the possible participation of genes involved in immune response in the susceptibility to neuroinflammatory diseases, including TLE-HS.

The aim of the present study was to investigate the possible genetic susceptibility of patients with TLE-HS associated with the HLA class II *DRB1, DQA1* and *DQB1* alleles.

2. Materials and methods

Samples of peripheral blood were collected from 42 individuals (22 females (52.36%) and 20 males (47.64%)) aged 15–65 years old (mean = 42.8 years old) who met the diagnostic criteria for pharmacoresistant TLE-HS at the Epilepsy Center of the Clementino Fraga Filho University Federal Hospital (Federal University of Rio de Janeiro/Universidade Federal do Rio de Janeiro – UFRJ) and 89 age- and gender-matched healthy controls (47 females (52.8%) and 42 males (47.2%)).

DNA was extracted by organic method using phenol:clorophorm:isoamyl alcohol (25:24:1) and quantified in the NanoDrop Lite Spectrophotometer (Thermo Fisher Scientific). The expression and typing of the HLA class II alleles from DRB1, DQB1, and DQA1 *loci* in patients and controls were analyzed by sequence-specific primer-polymerase chain reaction (SSP-PCR) and identified by high- and low-resolution specific sequencing using a One Lambda kit (Canoga Park, CA, USA) following the manufacturer's recommendations.

Statistical analysis of the relative allele frequencies was performed using an Excel spreadsheet; *p*-value, relative risk (RR) and odds ratio (OR) were calculated using the software Epi Info 6.0. *p*-values <0.05 following Bonferroni correction were considered to be statistically significant.

According to the study protocol that was approved by the institutional ethics committee, all of the participants were provided due information as to the use of their clinical and genetic information, and information, and have signed the informed.

3. Results

A significant genetic association was not found when the frequencies of the allelic regions were compared between patients and controls relative to the *HLA-DRB1*, *HLA-DQB1* and *HLA-DQA1* regions identified using the low-resolution system (Tables 1–3).

Only the difference in the frequency of allele *HLA-DRB1*13:02* was significant between patients and controls ($p = 0.01$). However, this frequency lost significance following Bonferroni correction ($p = 0.44$). The RR of the allele was 0.29. The frequency of the remainder of the *HLA-DRB1* alleles did not differ between patients and controls, even in the case of the *DRB1*15:03* allele, which was the most frequent and was detected in seven patients (Table 4).

The *HLA-DQB1*04:01* allele was the most frequent and was detected in 10 patients. However, neither its frequency nor that of the other *HLA-DQB1* alleles exhibited a significant difference between patients and controls (Table 5).

The *HLA-DQA1*05:01* allele was the most frequent in both groups, but neither its frequency nor that of the other DQA1 alleles exhibited a significant difference between patients and controls (Table 6).

Table 1
Distribution of alleles in the HLA CLASS II DRB1 region identified by the low-resolution system.

Allele	Patients ($N = 42$)	F_R%	Controls ($N = 89$)	F_R%	*p*-value	RR	OR
*DRB1*01*	07	8.33	12	6.74	0.62	1.18	1.28
*DRB1*03*	07	8.33	15	8.42	0.97	0.99	0.99
*DRB1*04*	12	14.28	23	12.92	0.74	1.10	1.15
*DRB1*07*	02	2.38	02	1.12	0.43	1.59	2.17
*DRB1*08*	05	5.95	13	7.30	0.67	0.85	0.79
*DRB1*09*	0	0	02	1.12	0.32	IND	IND
*DRB1*10*	0	0	01	0.56	0.49	IND	IND
*DRB1*11*	05	5.95	18	10.11	0.73	0.89	0.85
*DRB1*12*	09	10.71	10	5.61	0.12	1.61	2.15
*DRB1*13*	11	13.09	16	8.98	0.16	1.47	1.83
*DRB1*14*	05	5.95	22	12.35	0.09	0.52	0.41
*DRB1*15*	12	14.28	23	12.92	0.74	1.10	1.15
*DRB1*16*	09	10.71	21	11.79	0.78	0.92	0.88
Total	84		178				

Caption: RR = relative risk, OD = odds ratio, IND = indefinite.

Table 2
Distribution of alleles in the HLA CLASS II DQB1 region identified by the low-resolution system.

Allele	Patients ($N = 42$)	F_R%	Controls ($N = 89$)	F_R%	*p*-value	RR	OR
*DQB1*02*	10	11.94	25	14.04	0.60	0.86	0.80
*DQB1*03*	17	20.23	29	16.29	0.37	1.26	1.41
*DQB1*04*	16	19.04	26	14.60	0.30	1.30	1.49
*DQB1*05*	18	21.42	38	21.34	0.98	1.0	1.01
*DQB1*06*	23	27.38	60	33.70	0.16	0.70	0.59
Total	84		178				

Caption: RR = relative risk, OD = odds ratio.

Table 3
Distribution of alleles in the HLA CLASS II DQA1 region identified by the low-resolution system.

Allele	Patients ($N = 42$)	F_R%	Controls ($N = 89$)	F_R%	*p*-value	RR	OR
*DQA1*01*	34	40.47	53	29.77	0.06	1.73	2.17
*DQA1*02*	12	14.28	17	9.55	0.35	1.31	1.50
*DQA1*03*	08	9.52	24	13.48	0.32	0.73	0.64
*DQA1*04*	08	9.52	23	12.92	0.24 0.67	0.57	
*DQA1*05*	22	26.19	61	34.26	0.07	0.64	0.50
Total	84		178				

Caption: RR = relative risk, OD = odds ratio.

4. Discussion

Studies on inflammatory mechanisms and their relationship with diseases of the central nervous system have been consistently relevant in the epilepsy field in the last decade. Neuroinflammatory mechanisms appear to be a common and crucial component of the pathogenesis of epilepsy and its resistency to pharmacological treatment [10,15,16]. In the hippocampal samples surgically removed from patients with TLE, Ravizza et al. [12,13] found increased HLA-DR expression and macrophage infiltrates in the microglial cells and increased IL-1β expression in the astrocytic

Table 4
Distribution of *HLA-DRB1* alleles identified by the high-resolution system.

Allele	Patients ($N=42$)	F_R%	Controls ($N=89$)	F_R%	p-value	B	RR	OR
*01:01	2	2.32	3	1.68	0.69		0.88	0.7
*01:02	1	1.19	3	1.68	0.75		1.11	1.43
*01:03	4	4.76	6	3.37	0.57		0.87	0.69
*03:01	5	5.95	6	3.37	0.32		0.79	0.53
*03:05	2	2.32	6	3.37	0.65		1.11	1.45
*03:08	0	0.0	3	1.68	0.22		1.49	IND
*04:02	2	2.32	6	3.36	0.65		1.11	1.45
*04:03	1	1.19	2	1.12	0.96		0.98	0.94
*04:06	0	0.0	1	0.56	0.49		1.48	IND
*04:07	1	1.19	0	0.0	0.14		IND	0
*04:08	2	2.32	4	2.24	0.94		0.98	0.94
*04:09	1	1.19	1	0.56	0.58		0.73	0.47
*04:10	1	1.19	3	1.68	0.75		1.11	1.43
*04:11	4	4.76	6	3.37	0.57		0.87	0.69
*07:01	2	2.32	2	1.12	0.43		0.73	0.46
*08:01	2	2.32	3	1.68	0.69		0.88	0.7
*08:03	3	3.57	6	3.37	0.93		0.98	0.94
*08:04	0	0.0	2	1.12	0.32		1.48	IND
*08:07	0	0.0	2	1.12	0.32		1.48	IND
*09:01	0	0.0	2	1.12	0.32		1.48	IND
*10:01	0	0.0	1	0.56	0.49		1.48	IND
*11:01	4	4.76	5	2.80	0.73		0.92	0.77
*11:02	1	1.19	3	1.68	0.75		1.11	1.43
*11:03	1	1.19	3	1.68	0.75		1.11	1.43
*12:01	5	5.95	9	5.05	0.75		0.94	0.83
*12:02	4	4.76	1	0.56	0.96		0.98	0.94
*13:01	3	3.57	4	2.24	0.52		0.83	0.61
*13:02	4	4.76	1	0.56	0.01	0.44	0.29	0.11
*13:03	3	3.57	5	2.80	0.73		0.92	0.77
*13:04	0	0.0	1	0.56	0.49		1.48	IND
*13:06	1	1.19	3	1.65	0.75		1.11	1.43
*13:09	0	0.0	2	1.12	0.32		1.48	IND
*14:01	0	0.0	3	1.65	0.22		1.49	IND
*14:02	2	2.32	3	1.65	0.69		0.88	0.7
*14:05	1	1.19	9	5.05	0.11		1.36	4.61
*14:06	2	2.32	7	3.93	0.51		1.16	1.71
*15:01	2	2.32	9	5.05	0.3		1.23	2.25
*15:02	3	3.57	5	2.80	0.73		0.92	0.77
*15:03	7	8.33	9	5.05	0.28		0.81	0.56
*16:01	2	2.32	7	3.93	0.51		1.16	1.71
*16:02	3	3.57	8	4.49	0.72		1.08	1.28
*16:03	4	4.76	6	3.37	0.57		0.87	0.69
Total	84		178					

Caption: B = Bonferroni, RR = Relative Risk, OD = Odds Ratio, IND = indefinite.

cells. We have recently reported a substantial reduction of the inflammation cytokines TNF-alfa, IL-1beta in patients subjected to surgical removal of the hippocampus and that achieved seizure control. These findings suggested the role of those cytokines in the perpetuation of epileptic episodes in human patients with TLE-SH [11,17]. As some HLA class II alleles are associated with a susceptibility to inflammatory diseases characterized by the increased expression of cytokines such as TNF-α and IL-1β, as in TLE-SH [18], we have hypothesized that the HLA-DRB1, HLA-DQB1, and HLA-DQA1 alleles might participate in the inflammatory response to different antigens during the first years of life, eventually leading to TLE-SH in susceptible individuals. In the present study, the DRB1*1302 ($p = 0.01$) allele was significantly correlated with susceptibility to TLE-SH; however, this significance was lost following Bonferroni correction. No previous study has demonstrated an association of this allele with TLE-SH, either as a protective or a susceptibility factor. Regarding *HLA DR13* association studies in other types of epilepsy, there has been no evidence to indicate that susceptibility to juvenile myoclonic epilepsy (JME) phenotype; and none of the investigated alleles or haplotypes (*DRB1*13:01-DQB1*06:03 or DRB1*13:02-DQB1*06:04*) has exhibited significant differences between patients and controls as either protective or susceptibility factors [19]. It is worth noting that the natural history of JME is not characterized by IPI or progression, which are present in most cases of TLE-SH, suggesting that tissue reorganization and neuroplasticity may be orchestrated by local phenomena.

Our results contrast from those reported by Ozkara et al. [14], who were the only previous authors to analyze the role of HLA class II alleles in TLE-SH. They have found a higher frequency of HLA-DR4, HLA-DR7, and HLA-DQ2 in individuals with TLE-HS compared with controls and thus suggesting that these alleles might be involved in susceptibility to the disease. They concluded that these haplotypes appear to behave as risk factors but are not essential for the onset of disease. In our study, in addition to haplotypes, we also analyzed the alleles in the *HLA-DRB1*, *HLA-DQB1*, and *HLA-DQA1* regions separately but did not find that their expression was increased in individuals with TLE-SH compared with controls, except for the tendency of HLA DRB1*1302 to behave as a susceptibility factor. Some of the alleles investigated by Ozkara et al., such as DQB1*02:02, which is part of the DQ2 region; DRB1*04:11, *04:12, *04:04, *04:51, *04:52, *04:12, *04:13, *04:14, *04:15, *04:16, *04:17, *04:18, *04:19, *04:20, *04:21, *04:22, *04:23, *04:24, *04:25, *04:26, and *04:27, which form region DR4; and DRB1*07:02, which forms region DR7, were not found in either patients or controls in our study. We were unable to

Table 5
Distribution of *HLA-DQB1* alleles identified by the high-resolution system.

Alleles	Patients ($N=42$)	F_R%	Controls ($N=89$)	F_R%	*p*-value	RR	OR
*02:01	8	9.52	19	10.67	0.76	1.05	1.15
*02:03	2	2.38	6	3.37	0.65	1.11	1.45
*03:01	4	4.76	6	3.37	0.57	0.87	0.69
*03:02	3	3.57	5	2,80	0.73	0.92	0.77
*03:03	3	4.57	5	2.80	0.73	0.92	0.77
*03:04	5	5.95	8	4.49	0.6	0.9	0.73
*03:05	0	0.0	2	1.12	0.32	1.48	IND
*03:07	2	2.38	3	1.68	0.69	0.88	0.7
*04:01	10	11.90	15	8.42	0.34	0.86	0.65
*04:02	6	7.14	11	6.17	0.75	0.95	0.85
*05:01	8	9.52	14	7.86	0.63	0.92	0.79
*05:02	2	2.38	5	2.80	0.83	1.05	1.19
*05:03	6	7.14	9	5.05	0.48	0.87	0.68
*05:04	2	2.38	10	10.11	1.44	1.26	2.53
*06:01	2	2.38	3	1.68	0.69	0.88	0.7
*06:02	8	9.52	14	7.86	0.63	0.92	0.79
*06:03	5	5.95	9	5.05	0.75	0.94	0.83
*06:04	0	0.0	2	1.12	0.32	1.48	IND
*06:05	3	4.57	8	4.49	0.72	1.08	1.28
*06:06	0	0.0	3	1.68	0.22	1.49	IND
*06:07	0	0.0	3	1.68	0.22	1.49	IND
*06:08	2	2.38	9	5.05	0.3	1.23	2.25
*06:11	3	4.57	9	5.05	0.58	1.12	1.46
Total	84		178				

Caption: RR = relative risk, OD = odds ratio, IND = indefinite.

Table 6
Distribution of *HLA-DQA1* alleles identified by the high-resolution system.

Allele	Patients ($N=42$)	F_R%	Controls ($N=89$)	F_R%	*p*-value	RR	OR
01:01	10	11.90	18	10.11	0.87	1.02	1.08
01:02	8	9.52	13	7.30	0.51	0.9	0.73
01:03	9	10.71	14	7.86	0.42	0.88	0.68
01:04	7	8.33	8	4.49	0.19	0.76	0.49
02:01	12	14.28	17	9.55	0.35	0.87	0.67
03:01	8	9.58	24	13.48	0.32	1.14	1.57
04:01	8	9.58	23	12.92	0.24	1.17	1.74
05:01	16	19.04	42	23.59	0.32	1.12	1.45
05:02	6	7.14	19	10.67	0.33	1.15	1.63
Total	84		178				

Caption: RR = relative risk, OD = odds ratio, IND = indefinite.

detect any association even when our results were compared with the allelic regions obtained before high-resolution analysis.

We have attribute our findings and the loss of statistical significance of the *HLA-DRB1*13:02* allele to the small number of patients included in the study and to the fact that we have analyzed samples of peripheral blood. We believe that the *HLA-DRB1*13:02* allele is a probable candidate for susceptibility to TLE-SH due to its role in the recognition of autoantigens that might interfere with the progression and morbidity of patients. As the hippocampi of individuals with TLE-SH who were subjected to surgery exhibit increased expression of HLA-DR, in addition to increased numbers of macrophages in the microglial cells and increased expression of IL-1ß in the astrocytic cells, we believe that the aforementioned loss of statistical significance was due to transcriptional factors and the small sample size. Thus, a role for HLA-DR alleles in the inflammatory mechanisms of epilepsies appears to be supported by the results of histopathological studies [12,13].

Epilepsies are, as a whole, the result of multifactorial conditions and interactions among multiple genes. Otherwise, the mechanism of susceptibility mediated by HLA class I and the inflammatory reaction by means of innate immunity during disease progression might explain the greater presence of macrophage infiltrate in the resected tissue. This mechanism might also account for the fact that we did not find class II alleles associated with susceptibility to TLE-SH, which may instead be correlated with HLA class I alleles. This hypothesis is further supported by the results reported by Nakahara et al. [20], who found increased numbers of CD4+ and CD8+ T cells in hippocampi surgically removed from individuals with TLE-SH. The number of these cells varied from one patient to another, but overall, the number of CD8+ T cells was significantly higher than the number of CD4+ T cells. This higher number of CD8+ T cells appears to support and justify the results we obtained. Experimental induction of epileptic seizures in rodents was associated with increased expression of molecules of major histocompatibility complex (MHC) class I, the animal version of the human HLA class I, in some brain areas several hours after stimulation. Concurrently, regenerative processes are activated and also appear to involve the participation of MHC class I molecules [21].

Although the HLA class II system exhibits remarkable polymorphism and is involved in susceptibility to several diseases, our findings may suggest that multiple factors may influence its correlation, or lack thereof, with TLE-SH.

We conclude that genetic susceptibility to TLE-SH is not determined by HLA class II alleles in the DRB1, DQB1, and DQA1 regions but that the HLA DRB1*1302 allele exhibited a tendency to behave as a susceptibility factor for TLE-SH.

4.1. Perspectives and limitations of the present study

The small number of patients included may have been a limitation to this study. Nevertheless, the innovative character of high-resolution studies of genetic susceptibility involving genes that are strong mediators of the inflammatory response may contribute to genetic research aiming at elucidating the intricate mechanism underlying TLE-SH.

Conflict of interest

The authors have no conflict of interest.

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