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Class-I human leukocyte alleles in leprosy patients from Southern Brazil

Alelos leucocitários humanos em pacientes com hanseníase do sul do Brasil

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ABSTRACT

Introduction: The present study was designed to investigate a possible role of HLA (histocompatibility leucocyte antigen) class-I alleles (HLA-A, -B, and -C) in leprosy patients from Southern Brazil. **Methods:** Two hundred and twenty-five patients with leprosy and 450 individuals for the control group were involved in this research. *HLA* genotyping was performed through PCR-SSO protocols (One Lambda, USA); the frequency of these alleles was calculated in each group by direct counting, and the frequencies were then compared. **Results**: There was an association between HLA-A*11 (6.9% *vs* 4.1%, p=0.0345, OR=1.72, 95% CI=1.05-2.81), HLA-B*38 (2.7% vs. 1.1%, p=0.0402, OR=2.44, 95% CI=1.05-5.69), HLA-C*12 (9.4% vs. 5.4%, p=0.01, OR=1.82, 95% CI=1.17-2.82), and HLA-C*16 (3.1% vs. 6.5%, p=0.0124, OR=0.47, 95% CI=0.26-0.85) and leprosy per se. In addition, HLA-B*35, HLA-C*04, and HLA-C*07 frequencies were different between lepromatous (LL) and tuberculoid (TT) patients. However, after adjusting for the number of alleles compared, Pc values became nonsignificant. **Conclusions:** Although our results do not support the previous findings that HLA class-I alleles play a role in leprosy pathogenesis, we suggest new studies because of the importance of the association between the HLA and KIR in the innate immune response to leprosy.

Keywords: HLA class-I genes. Leprosy. *Mycobacterium leprae.* Genetic susceptibility.

RESUMO

Introdução: O presente estudo foi desenhado para investigar um possível papel para os alelos *HLA* (*histocompatibility leucocyte antigen*) de classe I (*HLA-A, -B*, and *-C*) em pacientes com hanseníase do sul do Brasil. **Métodos**: Duzentos e vinte e cinco pacientes com hanseníase e 450 indivíduos para o grupo-controle foram envolvidos nesse estudo. O genótipo *HLA* foi determinado por protocolos PCR-SSO (One Lambda, USA) e, a frequência desses alelos foi calculada em cada grupo por contagem direta e, após, comparadas. **Resultados:** Houve associação entre *HLA-A*11* (6,9% *vs* 4,1%; p = 0,0345; OR = 1,72; CI = 1,05 – 2,81), *HLA-B*38* (2,7% *vs* 1,1; p = 0,0402; OR = 2,44; CI 95% = 1,05-5,69), *HLA-C*12* (9,4% *vs* 5,4%; p = 0,01; OR = 1,82; CI 95% = 1,17-2,82) e *HLA-C*16* (3,1 *vs* 6,5%; p = 0,0124; OR = 0,47; CI 95% = 0,26-0,85) e hanseníase *per se*. Além disso, as frequências de *HLA-B*35*, *HLA-C*04* e *HLA-C*07* foram diferentes entre os pacientes com as formas lepromatosa (LL) e tuberculoide (TT). Contudo, após o ajuste para o número de alelos comparados, os valores de p se tornaram não significativos. **Conclusões:** Embora nossos resultados não sustentem as conclusões anteriores de que os alelos HLA de classe I desempenham um papel na associação com a patogênese da hanseníase, sugerimos novos estudos devido à importância da associação entre HLA e KIR na resposta imune inata à hanseníase.

Palavras-chaves: Genes HLA de classe I. Hanseníase. *Mycobacterium leprae.* Susceptibilidade genética.

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INTRODUCTION

Leprosy is a chronic mycobacterial infection caused by the intracellular macrophage pathogen *Mycobacterium leprae*[1], with about 260,000 new cases per year[2]. A major proportion of the leprosy cases remaining in the world are in India and a few other countries such as Brazil.

The more benign paucibacillary (PB) forms, borderline tuberculoid (BT) and tuberculoid tuberculoid (TT), are characterized by the predominance of a Th1-type immune response. In contrast, in the multibacillary (MB) forms, borderline borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL), Th2-type immune response is responsible for the high antibody levels[3].

The variability of the host response to infection seems to be genetically and environmentally influenced. The major histocompatibility complex (MHC), located on the short arm of human chromosome 6p21, is a candidate region for controlling disease susceptibility. The influence of the MHC on antigen presentation to T cells may be directly responsible for the genetic susceptibility to disease[4].

In humans, histocompatibility leucocyte antigen (HLA) molecules are cell surface glycoproteins divided into two classical groups: HLA class-I (A, B, and Cw) and class-II (DR, DQ, and DP) antigens. The class-I *loci* encode molecules that bind antigenic epitopes usually derived from intracellular pathogens and present them to CD8+ T cells, thereby initiating a cytotoxic T cell response. The class-II *loci* specify molecules that primarily bind peptides of extracellular origin and present them to CD4+T cells, resulting in cytokine production and T cell help in the antibody production.

The most consistent findings are for associations between HLA class-II alleles and leprosy. Many studies in India, Brazil, and China showed a positive association of HLA-DRB1*15 and DRB1*16 alleles and leprosy per se or subtypes[5-12] and a negative

association of HLA-*DRB1**04 and leprosy *per se* or LL form[9-10, 12-13]. Moreover, other studies have been summarized in several reviews[14-17].

Some results have been found for class-I HLA alleles. *HLA-B*46* allele was associated with multibacillary leprosy cases in South China[18]; while, in Turkey, HLA-A9, A10, A32, B5, B21, Bw4, Bw6, Cw1, and Cw2 were associated with leprosy susceptibility[19]. In India, while several HLA class-I antigens were associated with susceptibility to leprosy (HLA-A2, A11, B40, and Cw7), others were associated to protection (A28, B12, and Cw4)[20]. HLA class-I alleles were also determined in multibacillary leprosy patients, resulting in a positive association with *HLA-A*02:06, A*11:02, B*18:01, B*51:10, C*04:07*, and *C*07:03* alleles, and in a negative association with *C*04:11*[21].

Therefore, this study aims at evaluating the influence of HLA class-I alleles on the susceptibility or resistance to leprosy and their clinical forms in Southern Brazilians.

METHODS

Patients and controls

Two hundred and twenty-five patients with leprosy assisted at 15th Regional de Saúde do Estado do Paraná, Maringá, Brazil were involved in this study. All the patients were from Paraná, Brazil. The individuals were classified in four distinct groups according to clinical and laboratorial observations offered by the dermatologist responsible for leprosy diagnosis: TT (46; 20.4%), LL (88; 39.1%), B (66; 29.3%), and indeterminate (23; 10.2%); two patients had no defined observation. Patient's age varied between 22 and 82 years (53.7±13.0); 97 were female, and 128 were male. Volunteers who were identified through a questionnaire as positive for other infectious or auto-immune diseases were excluded from the study.

The control group was constituted of 450 healthy subjects matched according to age, sex, ethnic group, and occupation, with no history of HLA-associated diseases and other demographic parameters. They were typified by Laboratório de Imunogenética at Universidade Estadual de Maringá. Control's age varied between 13 and 89 years (37.1±12.3); 240 were female, and 210 were male.

Paraná's population is predominantly of European origin (80.6%), with a small but significant contribution of African (12.5%) and Amerindian (7%) genes[22]. In this study, both patients (60.4% of European and 39.6% African origin) and controls (63.6% of European and 36.4% African origin) were classified as mixed ethnic groups, according to phenotypic characteristics, as according to Parra et al.[23], in Brazil, at an individual level, skin color determined by physical evaluation is a poor predictor of genomic African ancestry.

The risk of population stratification bias due to differences in the ethnic background between patients and controls and variations of allele frequencies according to ethnic background was minimized by including patients and controls matched for the same ethnic background, residing in the same geographical area of leprosy prevalence.

DNA extraction

Venous blood samples (10 mL) were collected from the subjects, centrifuged for obtaining the buffy-coat and conserved at -20ºC until the use. The genomic DNA was extracted by EZ-DNA (Biological Industries®, Kibbutz Beit Haemek, Israel) or Neoscience (One Lambda®, CA, USA) kits from 150 µL of frozen blood, and then stored in a freezer at -20ºC.

Determination of alleles of the HLA system

After the evaluation of DNA purity and adjusting the concentration by optical density, HLA class-I alleles were genotyped by polymerase chain reaction-sequence specific of oligonucleotides (PCR-SSO) protocols with the Luminex 100xMAP flow cytometry dual-laser system to quantify fluorescently labelled oligonucleotides attached to color-coded microbeads (One Lambda®, CA, USA), according to the manufacturer's instructions.

Statistical analysis

The frequency of alleles was obtained through direct counting of the alleles and expressed as percentage frequency. The data were tested for their fit to Hardy-Weinberg equilibrium by calculating the expected frequencies of the genotypes and comparing them with the observed values using the Arlequin software, version 3.1, available at http://cmpg.unibe.ch/software/arlequin3.

The analysis of the association between the HLA variables and the occurrence of leprosy types was performed using Fisher's exact test, with the Graph Pad Software program (San Diego, CA, USA), available at http://www.graphpad.com/quickcalcs/contingency1.cfm.

The odds ratio (OR) with 95% confidence intervals (95% CI) was calculated using SISA statistics online, available at http://www.quantitativeskills.com/sisa/index.htm, to evaluate the risk of the individual to develop the disease having an HLA type. Data were considered statistically significant when $p<0.05$.

As each individual is tested for several HLA alleles and the same data were used for comparing the frequencies, it is possible that one of the alleles will by chance deviate significantly. To overcome this error, the p value is corrected by the use of Bonferroni inequality method, that is, by multiplying it with the number of alleles compared in each *locus*.

Ethical considerations

All the participants signed written informed consent forms, authorizing the use of their samples in this study, which was approved by the Ethics Committee for Human Research of the Universidade Estadual de Maringá.

RESULTS

Table 1 summarizes the allele frequencies of class-I *HLA* alleles in leprosy *per se* and control populations and the results of the association analyses. Conformation to Hardy-Weinberg proportions was examined at all *loci* in the control group, and the examination did not show any deviation ($p>0.05$).

There was a positive association between leprosy per se and *HLA-A*11* (6.9% vs 4.1%, p=0.0345, OR=1.72, 95% CI=1.05-2.81), *HLA-B*38* (2.7% vs 1.1%, p=0.0402, OR=2.44, 95% CI=1.05-5.69), and *HLA-C*12* (9.4% vs 5.4%, p=0.01, OR=1.82, 95% CI=1.17-2.82), and negative association with *HLA-C*16* (3.1% vs 6.5%, p=0.0124, OR=0.47, 95% CI=0.26-0.85).

Percent allele frequencies of class-I *HLA* alleles in opposite poles of leprosy are represented in **Table 2**. The frequencies of *HLA-B*35* and *HLA-C*04* were lower in LL as compared with TT patients, while the frequency of *HLA-C*07* was higher. Therefore, our association analysis of stratified patient groups indicates that *HLA-B*35* and *HLA-C*04* could be protective alleles against LL leprosy, while *HLA-C*07* could predispose to this form of disease.

TABLE 1 - Human leukocyte antigens class-I allelic frequencies in patients with leprosy *per se* compared with those in control subjects.

	Leprosy (N=224)		Controls (N=446)			Leprosy (N=223)		Controls (N=446)			Leprosy (N=224)		Controls (N=418)	
HLA	n	%	n	%	HLA	n	%	n	%	HLA	n	%	n	%
*A*01*	41	9.2	79	8.9	*B*07*	43	9.6	60	6.7	*C*01*	16	3.6	22	2.6
*A*02*	119	26.6	228	25.6	*B*08*	15	3.4	52	5.8	*C*02*	18	4.0	52	6.2
*A*03*	48	10.7	85	9.5	*B*13*	12	2.7	16	1.8	*C*03*	37	8.3	82	9.8
*A*11*[a]	31	6.9	37	4.1	*B*14*	21	4.7	46	5.2	*C*04*	79	17.6	120	14.4
*A*23*	21	4.7	48	5.4	*B*15*	36	8.1	78	8.7	*C*05*	26	5.8	64	7.7
*A*24*	37	8.3	83	9.3	*B*18*	26	5.8	64	7.2	*C*06*	35	7.8	69	8.3
*A*25*	6	1.3	13	1.5	*B*27*	3	0.7	16	1.8	*C*07*	113	25.2	209	25.0
*A*26*	17	3.8	31	3.5	*B*35*	60	13.5	90	10.1	*C*08*	18	4.0	40	4.8
*A*29*	19	4.2	44	4.9	*B*37*	6	1.3	13	1.5	*C*12*[c]	42	9.4	45	5.4
*A*30*	18	4.0	60	6.7	*B*38*[b]	12	2.7	10	1.1	*C*14*	17	3.8	15	1.8
*A*31*	29	6.5	45	5.0	*B*39*	20	4.5	33	3.7	*C*15*	17	3.8	42	5.0
*A*32*	9	2.0	21	2.4	*B*40*	19	4.3	44	4.9	*C*16*[d]	14	3.1	54	6.5
*A*33*	12	2.7	23	2.6	*B*41*	4	0.9	12	1.3	*C*17*	14	3.1	18	2.2
*A*34*	4	0.9	5	0.6	*B*42*	8	1.8	11	1.2	*C*18*	2	0.4	4	0.5
*A*36*	0	0.0	4	0.4	*B*44*	43	9.6	107	12.0					
*A*43*	0	0.0	0	0.0	*B*45*	4	0.9	14	1.6					
*A*66*	5	1.1	9	1.0	*B*46*	0	0.0	0	0.0					
*A*68*	25	5.6	58	6.5	*B*47*	1	0.2	2	0.2					
*A*69*	0	0.0	4	0.4	*B*48*	6	1.3	5	0.6					
*A*74*	3	0.7	16	1.8	*B*49*	11	2.5	29	3.3					
*A*80*	4	0.9	1	0.1	*B*50*	5	1.1	18	2.0					
					*B*51*	43	9.6	68	7.6					
					*B*52*	9	2.0	18	2.2					
					*B*53*	7	1.6	23	2.6					
					*B*54*	0	0.0	0	0.0					
					*B*55*	3	0.7	10	1.1					
					*B*56*	2	0.4	4	0.4					
					*B*57*	16	3.6	20	2.2					
					*B*58*	10	2.2	27	3.0					
					*B*59*	0	0.0	0	0.0					
					*B*67*	1	0.2	0	0.0					
					*B*73*	0	0.0	0	0.0					
					*B*78*	0	0.0	1	0.1					
					*B*81*	0	0.0	1	0.1					
					*B*82*	0	0.0	0	0.0					
					*B*83*	0	0.0	0	0.0					

HLA: human leukocyte antigens, **N:** number of patients, **n:** allelic number, **[a]**p=0.0345, Pc=0.7245, OR=1.72, 95% CI=1.05-2.81, **[b]**p=0.0402, Pc=1.447, OR=2.44, 95% CI=1.05-5.69, **[c]**p=0.01, Pc=0.14, OR=1.82, 95% CI=1.17-2.82, **[d]**p=0.0124, Pc=0.1736, OR=0.47, 95% CI=0.26-0.85.

TABLE 2 - Comparison of human leukocyte antigens class-I allelic frequencies between patients with lepromatous and those with tuberculoid clinical forms of leprosy.

	LL (N=88)		TT (N=46)			LL (N=88)		TT (N=46)			LL (N=88)		TT (N=46)	
HLA	n	%	n	%	HLA	n	%	n	%	HLA	n	%	n	%
A*01	21	11.9	8	8.7	*B*07*	18	10.2	8	8.7	*C*01*	5	2.8	2	2.2
A*02	42	23.9	24	26.1	*B*08*	8	4.5	1	1.1	*C*02*	10	5.7	4	4.3
A*03	13	7.4	10	10.9	*B*13*	5	2.8	4	4.3	*C*03*	14	9.7	4	3.3
A*11	9	5.1	8	8.7	*B*14*	8	4.5	3	3.3	*C*04*[b]	20	14.8	22	25.0
A*23	11	6.3	4	4.3	*B*15*	12	6.8	7	7.6	*C*05*	8	5.1	5	6.5
A*24	15	8.5	5	5.4	*B*18*	11	6.3	6	6.5	*C*06*	12	8.5	8	8.7
A*25	3	1.7	1	1.1	*B*27*	1	0.6	0	0.0	*C*07*[c]	42	31.8	16	18.5
A*26	4	2.3	5	5.4	*B*35*[a]	18	10.2	20	21.7	*C*08*	5	2.8	2	2.2
A*29	6	3.4	3	3.3	*B*37*	3	1.7	0	0.0	*C*12*	10	6.3	6	6.5
A*30	7	4.0	5	5.4	*B*38*	3	1.7	3	3.3	*C*14*	6	4.0	4	4.3
A*31	14	8.0	5	5.4	*B*39*	10	5.7	1	1.1	*C*15*	3	2.3	4	5.4
A*32	3	1.7	3	3.3	*B*40*	10	5.7	3	3.3	*C*16*	3	2.3	3	3.3
A*33	2	1.1	5	5.4	*B*41*	2	1.1	2	2.2	*C*17*	17	3.4	7	7.6
A*34	3	1.7	0	0.0	*B*42*	3	1.7	4	4.3	*C*18*	1	0.6	1	1.1
A*36	0	0.0	0	0.0	*B*44*	17	9.7	9	9.8					
A*43	0	0.0	0	0.0	*B*45*	2	1.1	1	1.1					
A*66	2	1.1	1	1.1	*B*46*	1	0.6	0	0.0					
A*68	17	9.7	3	3.3	*B*47*	1	0.6	0	0.0					
A*69	0	0.0	0	0.0	*B*48*	1	0.6	1	1.1					
A*74	2	1.1	1	1.1	*B*49*	6	3.4	0	0.0					
A*80	2	1.1	1	1.1	*B*50*	3	1.7	0	0.0					
					*B*51*	14	8.0	8	8.7					
					*B*52*	3	1.7	2	2.2					
					*B*53*	2	1.1	3	3.3					
					*B*54*	0	0.0	0	0.0					
					*B*55*	1	0.6	0	0.0					
					*B*56*	0	0.0	0	0.0					
					*B*57*	9	5.1	3	3.3					
					*B*58*	2	1.1	3	3.3					
					*B*59*	0	0.0	0	0.0					
					*B*67*	0	0.0	0	0.0					
					*B*73*	0	0.0	0	0.0					
					*B*78*	0	0.0	0	0.0					
					*B*81*	0	0.0	0	0.0					
					*B*82*	0	0.0	0	0.0					
					*B*83*	0	0.0	0	0.0					

HLA: human leukocyte antigens, **N:** number of patients, **n:** allelic number, **LL:** lepromatous leprosy, **TT:** tuberculoid leprosy, [a]p=0.0156, Pc=0.5616, OR=0.41, 95% CI=0.20-0.82, [b]p=0.0464, Pc=0.6496, OR=0.52, 95% CI=0.28-0.98, [c]p=0.0211, Pc=0.2954, OR=2.06, 95% CI=1.11-3.81.

DISCUSSION

Several studies have shown association of specific HLA class-II antigens/alleles with decreased or increased risk of leprosy in populations around the world (reviewed recently by Francheschi et al.[17]). However, consistent association of HLA class-I antigens/alleles with leprosy or its progression toward clinical forms has not been well documented.

This control-case study investigated the genetic variation present in HLA-A, -B, and -C genes and its relation with leprosy and subtypes.

Although after the correction of probabilities by multiplying p values by the numbers of variants tested in each *locus*, the results have been clearly statistically insignificant, we can note that the same association with *HLA-A*11* and leprosy was also observed in other studies in Korea[24] and South India[20-21]. HLA-A11 was also significantly increased in erythema nodosum leprosum (ENL) leprosy patients from North India[25].

In the Turkish population, different results were observed. HLA class-I antigens A9, A10, A32, B5, B21, Bw4, Bw6, Cw1, and Cw2 were found to be significantly more frequent in patients with leprosy, while HLA class-I antigens A3, B44, B49 were significantly more frequent in controls[19].

When the groups were stratified, *HLA-B*35* and *HLA-C*04* showed to be protective against LL leprosy, perhaps due to the best presentation of bacillus to T cell, while *HLA-C*07* showed to be a

susceptive variant. Likewise, the corrected probabilities were not more significant.

Nevertheless, some similar findings for HLA-C were observed by Shankarkumar et al.[21] who found a significant increase in the frequency of *HLA-A*24*:13, *B*07:06*, *B*40:16*, *C*07:08*, and *C*15:05* and a decrease in the frequency of *HLA-A*01:01*, *C*04:11*, and *C*06:02* in LL patients as compared with the controls.

Nowadays, it is important to study the class-I HLA association with infectious diseases, as recent studies have shown important interactions among immune response cells and infected cells through membrane receptors. KIR3DL2 is an inhibitory receptor present principally, on the surfaces of natural killer (NK) cells[26], which have an important role in innate response to intracellular pathogens, such as *M. leprae*. Although direct evidence is lacking, KIR3DL2 seems to interact with *HLA-A3/11*[27]. The gene that codifies this protein is KIR3DL2, which, in association with *HLA-A*3/*11*, was associated to leprosy in a recent study performed by our group[28]. In this present study, we suppose that *HLA-A*11* could act with KIR3DL2 for decreasing the immune response and, consequently, induce leprosy development infection.

Franceschi et al.[28] also showed that *KIR3DL1* associated with Bw4 and *KIR2DL3* associated with C1 were increased in LL in comparison to TT patients. *HLA-B*38* is associated with the supertype Bw4[29] (Schreuder et al., 1975), which, in this present study, was increased in leprosy patients.

*HLA-C*07*, *HLA-C*12*, and *HLA-C*16* are considered part of group C1, which is a specific ligant for KIR2DL2/2DL3/2DS2[30], while *HLA-C*04* is part of group C2, which is ligant for KIR2DL1/2DS1. The underlying mechanism regarding the association between these genes and leprosy could be correlated to major or minor inhibitor effect of these associations.

In summary, although our results do not support previous findings that *HLA* class-I alleles play a role in leprosy pathogenesis, we suggest new studies because of the importance of the association between the HLA and KIR in the innate immune response to leprosy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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