






# Association of HLA Alleles and HLA Haplotypes with Psoriasis, Psoriatic Arthritis and Disease Severity in a Miscegenated Population

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**Background:** The study of HLA classes I and II in Brazilian psoriasis patients may contribute to a better understanding of their association with the disease.

**Objective:** To describe HLA classes I and II of Brazilian patients with psoriasis, with or without arthritis, compare them to controls and correlate HLA markers with epidemiological and evolutionary aspects of psoriasis.

**Methods:** A total of 55 patients with more than 5 years of psoriasis, with or without arthritis, answered a questionnaire on ethnic background and disease severity. A total of 134 bone marrow donors were controls. HLA class I and II genotyping was determined by PCR-SSP.

**Results:** Mean age was 42.4 years; 23 women and 32 men. HLA-B\*57 was present in 23.6% patients and in 7.5% controls ( $p=0.00200$ ,  $OR=3.8381$ ), and HLA-C\*06 in 29.1% patients and in 16.4% controls ( $p=0.04832$ ,  $OR=2.0886$ ). HLA-B\*57 and HLA-C\*18 were significantly present in patients with arthritis ( $p=0.00104$ ,  $OR=6.6769$  and  $p=0.00269$ ,  $OR=16.50$ , respectively). HLA-B\*57 was significantly present in patients with history of erythroderma ( $p=0.00548$ ,  $OR=5.1059$ ), as was HLA-C\*06 ( $p=0.02158$ ,  $OR=3.0545$ ). HLA-B\*57 was also frequent in patients with history of hospital internment due to psoriasis ( $p=0.00094$ ,  $OR=7.8909$ ) and in the ones with history of systemic treatment for psoriasis ( $p=0.00011$ ,  $OR=5.3733$ ). Haplotype HLA-A\*02 B\*57 C\*06 DRB1\*07DQB1\*03 was the most common among the patients ( $p=0.00069$ ,  $OR=3.528$ ).

**Conclusion:** HLA-B\*57 and HLA-C\*06 were significantly increased in the patients indicating risk for psoriasis. HLA-B\*57 remained high in patients with history of erythroderma, hospital internment, systemic treatment, and psoriatic arthritis, showing association with disease severity. HLA-C\*18 was significantly high only in patients with psoriatic arthritis. HLA-B\*57 and HLA-C\*06 and haplotype HLA-A\*02B\*57Cw\*06DRB1\*07 DQB1\*03 seen in this study were already described before, associated with psoriasis. HLA-Cw\*18 was not described in other populations in association with psoriasis.

**Keywords:** psoriasis, psoriatic arthritis, HLA, population study

## Introduction

Psoriasis is a chronic inflammatory disease mediated by T lymphocytes, with participation of dendritic cells. Genetic and environmental factors contribute or are required for the development of overt disease. The lesions are characterized by erythema and desquamation, configuring different clinical forms, from sharply delimited plaques to diffuse erythroderma. Up to 30% of patients may also have joint involvement, which may result, if untreated, in erosive disease and incapacity.

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It is considered a prevalent disease, affecting 2% of the population in Western countries.

Many of the psoriasis-associated genes seem to support the hypothesis that a particular immunologic disposition increases the risk of developing psoriasis. PSORS1 is the most associated gene. This locus maps to chromosome 6p21.3, comprising many different class I antigens associated with disease expression. HLA-C has been repeatedly described as the PSORS1 gene, and HLA-Cw\*06:02 as the susceptibility allele. Tumor necrosis factor promoter polymorphism TNF\*-857 is a risk allele for psoriatic arthritis independent of the PSORS1 locus.<sup>1</sup>

The activation of T cells in conjunction with mature antigen presenting cells is a multi-step process, which requires the stimulation of T cell receptors and many accessory signals. The initial interaction that triggers T cell activation is the recognition of the peptide antigen that is bound to the HLA class I molecule (for intracellular antigens) or HLA class II (for extracellular antigens) in the antigen presenting cells. The study of the HLA molecules associated with psoriasis may not only point to disease susceptibility genes, but also to clarify some aspects of its pathogenesis and therefore potential targets to therapy. HLA molecules may bind to psoriasis related antigens through the clefts they form, determining the size and charge of the peptide antigen.<sup>2-4</sup>

The association of HLA molecules with the occurrence of psoriasis vulgaris and psoriatic arthritis is widely described in the literature.<sup>5-15</sup> Studies in populations of different ethnic origins show the increased frequency of different HLA specificities and haplotypes in patients with psoriasis when compared to control groups.<sup>8,16-18</sup> Often, this frequency is even higher in patients with early-onset psoriasis and familial history of the disease.<sup>19-22</sup>

The miscegenation of Caucasians, Africans and native Indians is the main feature of the Brazilian population, which has in the “mestizos” its greatest representation. The study of class I and II HLA in Brazilian psoriasis patients contributes to a better understanding their association with the disease, especially when compared to other populations of different ethnic origins. The study of class I and II HLA genes of Brazilian psoriasis vulgaris patients, with or without arthritis, may contribute with new information regarding immunopathogenesis and susceptibility to disease in this group of patients.

The aim of this study is to determine allelic groups and haplotypes of human leukocyte antigens (HLA) in a psoriasis group of patients characterized by miscegenation and

correlate them with disease severity, through evolutionary aspects seen in our patients.

## Methods

Fifty-five patients with clinical and/or histopathological diagnosis of psoriasis vulgaris, with at least 5 years of disease duration, and with or without arthritis, were included in the study. They answered a questionnaire on ethnic background, family history and duration of disease. They were clinically evaluated in respect to distribution and morphology of skin lesions, joint involvement and disease activity and were submitted to laboratorial tests. The criteria used to assess the severity of the disease (unfavorable evolution) were episodes of hospitalization, the use of systemic treatment, episodes of erythroderma and/or presence of arthritis, as many patients were under treatment when were enrolled. PASI (Psoriasis Activity and Severity Index) was not used as a severity parameter for the same reason. Patients enrolled have had psoriasis for at least five years (as an inclusion criteria) and PASI of 10 or more sometime during follow up, configuring moderate to severe psoriasis. Psoriasis was classified as type I when the onset of the disease occurred until 30 years-old and type II after 30 years-old.

Cases and controls were matched for age, sex and ethnic origin. One hundred and thirty-four healthy bone marrow donors served as controls after informed consent. They answered the same questionnaire on ethnic background. Controls had no family history of psoriasis or diseases related to HLA-C. Allelic typing of class I and II genes were determined by PCR-SSP. Differences between the two groups were evaluated through Chi-square or Fisher exact tests.

## HLA Typing

Peripheral blood (15 mL) was collected in sterile tubes containing anticoagulant. Genomic DNA from both psoriasis patients and controls was isolated from leukocytes using a GFX Genomic Blood DNA Purification (Amersham Biosciences, LTD, UK) kit. HLA -A -B -C -DR -DQ alleles were determined using microplates containing the sequence specific primers (PCR/SSP). PCR amplification was carried out in 30 cycles that included denaturation at 96°C for 10 sec, annealing at 63°C for 60 sec and extension at 72°C for 30 sec, as fabricant protocol (One Lambda, INC, CA, USA). PCR products were analyzed by electrophoresis in ethidium bromide-stained 2% agarose gel. Presence of the specific PCR products were

interpreted by analysis of positive bands using worksheets and an interpretation software (DNA LMT – One Lambda, INC, CA, USA).

## Results

### Patients

Fifty-five patients with psoriasis vulgaris and 134 controls were included in the study. The mean age of patients was 42.4 years (SD 10.5262), while the median was 43.0 years (from 19.0 to 63.0 years). The mean age of the controls was 40.5 years (SD 8.5423) and median 41.5 years (22.0 to 59.0 years). There were 23 (41.8%) female and 32 (58.2%) male patients and in the control group, 65 (48.5%) were female and 69 (51.5%) were male (Table 1).

Seventeen (30.9%) patients had a positive family history for psoriasis. Eighteen (32.7%) had been hospitalized because of psoriasis, 24 (43.6%) have had one or more episodes of erythroderma (erythrodermic psoriasis) and 43 (78.2%) have used a systemic treatment for the disease. Of the 43 with systemic treatment history, 19 have arthritis and 23 had a history of erythroderma. Ten patients had a history of both erythroderma and arthritis (Table 2).

The average age of onset of the disease was 26.56 years and the mean duration of disease was 16.90 years. In 33 (60.0%) patients psoriasis began before age 30 (type I psoriasis), and the mean age of onset of the disease 19.09 years. In the other 22 (40.0%), it emerged from 30 years (psoriasis type II) with a mean age of onset of the disease 37.77 years. The family history of psoriasis was positive in 10 (30.3%) patients with psoriasis type I and in 7 (31.8%)

patients with psoriasis type II ( $p = 0.90517$ ), as seen in Table 3.

Psoriatic arthritis was found in 20 (36.4%) of the patients included in the study, 11 males and 9 females. The mean duration of arthritis was 11.05 years. Of the 20 patients, 15 (75%) showed involvement of peripheral (polyarthritis: 13 and oligoarthritis: 2) and 5 (25%), axial involvement. Of these, 2 patients were diagnosed with sacroileitis and 2 with ankylosing spondylitis, only 1 had spondylitis and erosive arthritis. No patient had only distal interphalangeal arthritis.

### Frequency of HLA Allelic Groups

Two allelic groups showed to be increased in the patients with psoriasis compared to controls. HLA-B\*57 was present in 13 (23.6%) patients and in 10 (7.5%) controls ( $p = 0.00200$ ,  $RC = -9.3988$  1.5673 3.8381 CI) and HLA-C\*06 was present in 16 (29.1%) patients and in 22 (16.4%) controls ( $p = 0.04832$ ,  $RC = 2.0886$ ,  $CI = 0.9965$  -4.3773).

HLA-B\*07 was present more often in the control group, with statistical significance: it was positive in 19 (14.2%) controls and 2 (3.6%) patients ( $p = 0.02599$ ,  $RC = 0.2284$ ,  $CI = 0.0513$  to 1.0164).

HLA-B\*57 was significantly present in the psoriatic arthritis patient group ( $p = 0.0010493305$ ,  $RC = 6.6769$  CI = 2.1736 to 20.5099). The HLA-C\*18 was also increased significantly in the group of patients with arthritis ( $p = 0.0026978977$ ,  $RC = 16.5000$ ,  $CI = 2.7967$  to 97.3486). The HLA-B\*51 was considered a protective allele, as it was present in 23 (17.2%) controls and no

**Table 1** Distribution of Cases and Controls (Age, Gender and Ethnicity)

	Psoriasis (n=55)	Controls (n=134)	p
<b>Median age (sd)</b>	42.4 years ( $\pm$ 10.5262)	40.5 years ( $\pm$ 8.5423)	0.2075
<b>Mean</b>	43.0 years (19.0–63.0)	41.5 years (22.0–59.0)	
<b>Gender</b>			0.4036
Male	32 (58.2%)	69 (51.5%)	
Female	23 (41.8%)	65 (48.5%)	
<b>Ethnicity</b>			0.5028
White	10 (18.2%)	36 (26.9%)	
Mestizo/White	18 (32.7%)	35 (26.1%)	
Mestizo/Indian	11 (20%)	19 (14.2%)	
Mestizo/Black	7 (12.7%)	24 (17.9%)	
Black	9 (16.4%)	20 (14.9%)	

**Note:** Groups are comparable in relation to age, Gender and ethnicity ( $p > 0.05$ ).

**Abbreviation:** sd, standard deviation.

**Table 2** Major Clinical and Epidemiological Characteristics of Psoriatic Patients

Patients	Gender	Age	Ethnics	Psoriasis Type	Age of Onset (Years)	Duration of Disease (Years)	FH	Arthritis	Erythroderma	Hospital Internment	Systemic Treatment	PASI*
1	F	46	Mest/cau	I	18	28	Y	Y	N	N	Y	8.9
2	M	36	Caucasian	I	17	19	Y	N	N	N	Y	2.2
3	M	47	Caucasian	II	30	17	Y	N	N	N	Y	31.8
4	M	38	Caucasian	II	32	6	N	Y	Y	Y	Y	22.0
5	F	19	Mest/blac	I	14	5	N	N	N	N	Y	19.2
6	F	34	Mest/blac	I	19	25	N	N	N	N	Y	2.1
7	M	53	Black	II	43	10	N	N	N	N	Y	12.3
8	M	46	Mest/ind	I	19	26	N	Y	Y	Y	Y	10.8
9	M	43	Mest/ind	II	36	7	Y	N	N	N	N	6.8
10	M	31	Mest/cau	I	10	21	Y	N	N	N	N	16.6
11	M	37	Mest/cau	II	30	7	N	N	N	N	N	0.9
12	F	28	Black	I	6	22	N	N	N	Y	Y	1.0
13	M	49	Mest/blac	II	34	15	Y	Y	Y	N	Y	2.8
14	M	51	Mest/cau	I	25	26	N	N	Y	N	Y	18.4
15	F	50	Caucasian	II	33	17	N	N	N	N	N	0.6
16	F	53	Mest/cau	I	29	27	N	N	N	N	Y	8.7
17	F	32	Black	I	22	10	N	N	N	N	N	9.9
18	F	54	Mest/cau	II	34	20	Y	Y	Y	N	Y	16.4
19	F	42	Mest/cau	I	9	33	Y	Y	N	Y	Y	2.1
20	F	24	Mest/ind	I	14	10	Y	Y	N	N	Y	22.6
21	M	44	Caucasian	I	9	35	Y	N	N	N	Y	6.0
22	M	29	Mest/cau	I	20	9	N	N	Y	Y	Y	4.6
23	M	60	Mest/cau	II	50	10	Y	N	Y	Y	Y	34.8
24	F	61	Mest/cau	II	53	8	N	N	N	N	N	2.3
25	M	52	Caucasian	II	47	5	N	N	N	N	Y	5.1
26	M	45	Mest/blac	I	22	45	N	N	Y	Y	Y	13.6
27	M	56	Mest/cau	II	32	24	Y	N	Y	Y	Y	12.8
28	M	41	Mest/cau	II	36	5	N	Y	N	N	Y	10.3
29	M	59	Mest/ind	II	35	24	N	S	N	Y	Y	0.0
30	M	40	Caucasian	II	30	10	N	N	N	N	Y	5.0
31	M	44	Caucasian	II	34	10	N	Y	N	N	Y	27.2
32	M	34	Mest/cau	I	21	13	N	N	N	N	Y	20.0
33	F	38	Black	I	20	18	N	N	N	N	Y	1.5
34	M	43	Mest/ind	II	30	13	Y	Y	N	N	Y	3.0
35	M	30	Black	I	25	5	N	N	Y	Y	Y	15.2
36	F	48	Caucasian	II	40	8	N	N	N	N	N	1.8
37	M	35	Mest/ind	I	25	35	N	Y	N	Y	Y	9.6
38	F	56	Mest/cau	II	50	6	N	N	N	N	N	3.6

39	M	39	Caucasian	I	19	20				Z	Y	Y	2.7
40	M	34	Mest/ind	I	24	10				Z	Y	Y	25.5
41	M	29	Mest/cau	I	19	10				Z	Y	Y	15.0
42	F	46	Mest/cau	II	31	15				Z	Z	Y	3.0
43	F	63	Black	II	56	7				Z	Y	Z	7.8
44	F	58	Mest/cau	I	24	35				Z	Z	N	3.3
45	F	33	Mest/ind	I	27	6				Z	Z	Y	4.8
46	F	40	Mest/ind	I	20	20				Z	Z	Y	12
47	M	63	Mest/cau	I	28	35				Z	Z	Y	0.6
48	M	31	Black	I	23	8				Z	Z	N	3.0
49	M	44	Mest/cau	I	6	37				Z	Z	Y	17.4
50	M	43	Mest/blac	I	25	18				Z	Z	Y	12.8
51	F	30	Mest/blac	I	24	6				Z	Z	Y	21
52	F	40	Mest/ind	II	35	5				Z	Z	Y	3.0
53	M	28	Mest/blac	I	14	14				Z	Z	Y	10.8
54	F	38	Black	I	18	20				Z	Z	N	2.8
55	F	45	Black	I	15	30				Z	Z	Y	0.0

Note: \*PASI was evaluated when patient was enrolled. Abbreviations: FH, family history of psoriasis; M, male; F, female; cau, Caucasian; mest, Mestizo; ind, Indian; blac, Black; Y, yes; N, no.

patients ( $p = 0.0309950651$ ,  $RC = 0.0000$ ,  $CI = Undefined$ ). Only 1 patient was positive for HLA-B\*27; it is one of the five patients with axial involvement (spondylitis).

When patients were divided in relation to age of disease onset (before and after age 30), HLA-B\*57 and HLA-C\*06 remained significantly present in patients with type I compared to controls ( $p = 0.0002958858$ ,  $RC = 5.3913$ ,  $CI = 2.0173$  to  $14.4083$   $p = 0.0108075985$ ,  $RC = 2.9091$ ,  $CI = 1.2511$  to  $6.7641$ , respectively), both with significance greater than that seen in the group of patients when compared to controls. The allelic group HLA-DRB1\*13 was present in a statistically significant way in type I psoriasis patients only ( $p = 0.0108075985$ ,  $RC = 2.9091$ ,  $CI = 1.2511$  to  $6.7641$ ). In type II patients, allelic groups HLA-B\*14 and HLA-C\*08 were significantly increased when compared to controls ( $p = 0.0039573385$ ,  $RC = 4.8980$ ,  $CI = 1.7485$  to  $13.7203$  and  $p = 0.0134889571$ ,  $RC = 4.0000$ ,  $CI = 1.3939$  to  $11.4786$ , respectively). The presence of allelic groups HLA-B \* 57 and HLA-C \* 06 were not statistically significant in type II patients only. In patients with positive family history, there was no statistically significant allelic group.

HLA-B\*57 and HLA-C\*06 were seen in patients with erythrodermic psoriasis history ( $p = 0.0054885048$ ,  $RC = 5.1059$ ,  $CI = 1.7153$ – $15.1990$  and  $p = 0.0215894577$ ,  $RC = 3.0545$ ,  $CI = 1.1880$ – $7.8540$ , respectively). The HLA-B \* 57 was also increased in patients with hospital admissions for psoriasis ( $p = 0.0009478272$ ,  $RC = 7.8909$ ,  $CI = 2.5087$ – $24.8200$ ) and in those with history of using systemic treatment for the disease ( $p = 0.0001128264$ ,  $RC = 5.3733$ ,  $CI = 2.1504$ – $13.4268$ ). The frequency of HLA-A, B, C, DRB1 and DQB1 allelic groups are seen on Tables 4–8.

## HLA Haplotypes

The haplotype HLA-A\*02 B\*57 Cw\*06 DRB1\*07 DQB1\*03 was the most common, but was present in only 4 (3.6%) patients and no controls ( $p = 0.0069$ ,  $OR = 3.528$ ,  $CI = 3.003$  to  $4.145$ ). Two other haplotypes were present in 3 (2.7%) patients and no controls ( $p = 0.0242$ ,  $HR = 3.505$ ,  $CI = 2.986$  to  $4.114$ ): HLA-A\*02 B\*13 Cw\*06 DRB1\*07 DQB1\*02 and HLA-A\*02 B\*14 Cw\*08 DRB1\*01 DQB1\* 5. Nine haplotypes were found in 2 (1.8%) patients and in no control ( $p = 0.0841$ ,  $HR = 3.481$ ,  $CI = 2.969$  to  $4.083$ ): HLA-A\*01 B\*08 Cw\*07 DRB1\*03 DQB1\*02, HLA-A\*02 B\*49 Cw \* 07 DRB1\*04 DQB1\*03, HLA-A\*02 B\*58 Cw\*07

**Table 3** Clinical and Epidemiological Characteristics of Patients with Type I and II Psoriasis

	Type I (n=33)	Type II (n=22)	p	OD (CI)
Mean age at disease onset –years (sd)	19.09 (6.1764)	37.77 (8.2285)	–	–
Mean time of duration of disease – years (sd)	20.6363 (11.019)	11.318 (5.987)	0.0007	–
Family history	10 (30.3%)	7 (31.8%)	0.90604	1.0733 (0.3350–3.4394)
Arthritis	12 (36.3%)	8 (36.3%)	1.0000	1.0000 (0.3258–3.0693)
Hospital internment	13 (39.3%)	5 (22.7%)	0.20009	0.4525 (0.1339–1.5286)
Erythroderma	17 (51.5%)	7 (31.8%)	0.15277	0.4392 (0.1423–1.3561)
Systemic treatment	28 (84.8%)	15 (68.1%)	0.14629	0.3827 (0.1035–1.4151)

**Note:** Both groups were similar ( $p > 0.05$ ) in relation to family history and criteria used to evaluate disease severity.

**Abbreviations:** OD, odds ratio; CI, confidence interval.

DRB1\*03 DQB1\*02, HLA-A\*03 B\*14 Cw\*08 DRB1\*03 DQB1\*02. HLA-A\*11 B\*55 Cw\*03 DRB1\*14 DQB1\*02, HLA-A\*24 B\*35 Cw\*04 DRB1\*11 DQB1\*03, HLA-A\*34 B\*14 Cw\*08 DRB1\*11 DQB1\*06, HLA-A\*68 B\*14 Cw\*08 DRB1\*01 DQB1\*05 and HLA-A\*74 B\*35 Cw\*04 DRB1\*03 DQB1\*04.

## Discussion

In this study, two allelic groups were more frequent in the group of patients with psoriasis compared to controls: the HLA-B\*57 and HLA-C\*06. Both were present even more in patients with psoriasis type I. In all studies in which the

HLA class I was typified, HLA-Cw6 or C\*06 was present with a statistically significant frequency in psoriasis patients.<sup>10,17,21–27</sup> In Germany, Thailand, China, Sweden and Croatia HLA-Cw6 was a marker only in psoriasis type I.<sup>8,20,22,25–28</sup> Oostveen et al found an association of HLA-Cw 06 with paediatric onset of psoriasis, but not with family history of psoriasis in a cohort of patients.<sup>29</sup>

The HLA-B \* 57 also was increased in Chinese patients with psoriasis vulgaris<sup>27</sup> and was seen in type I psoriasis patients in Germany<sup>20</sup> and Thailand.<sup>30,31</sup> Gonzaga et al<sup>23</sup> used serological methods to study 22 Brazilian patients with psoriasis vulgaris and showed an increased frequency

**Table 4** Frequency of HLA-A Allelic Groups in Patients and Controls

HLA-A*	Psoriasis n = 110	Controls n = 268	p	OD (CI)
01	10 (18.2%)	22 (16.4%)	0.76898	1.1313 (0.4964–2.5781)
02	27 (49.1%)	56 (41.8%)	0.35834	1.3431 (0.7151–2.5227)
03	9 (16.4%)	23 (17.2%)	0.89395	0.9442 (0.4061–2.1955)
11	5 (9.1%)	16 (11.9%)	0.57127	0.737 (0.2562–2.1229)
23	7 (12.7%)	20 (14.9%)	0.69486	0.8313 (0.3298–2.0952)
24	8 (14.5%)	22 (16.4%)	0.74898	0.8665 (0.3602–2.0849)
25	3 (5.5%)	6 (4.5%)	0.51538	1.2308 (0.2966–5.1067)
26	2 (3.6%)	10 (7.5%)	0.26665	0.4679 (0.0991–2.2088)
29	1 (1.8%)	10 (7.5%)	0.11805	0.2296 (0.0287–1.8387)
30	5 (9.1%)	15 (11.2%)	0.66942	0.7933 (0.2736–2.3006)
31	4 (7.3%)	7 (5.2%)	0.40329	1.4230 (0.3993–5.0707)
32	3 (5.5%)	10 (7.5%)	0.44464	0.7154 (0.1892–2.7056)
33	5 (9.1%)	9 (6.7%)	0.38443	13.889 (0.4436–4.3487)
34	4 (7.3%)	3 (2.2%)	0.11051	3.4248 (0.7405–15.8407)
36	1 (1.8%)	0	0.29100	(Undefined)
43	0	0	–	–
66	1 (1.8%)	5 (3.7%)	0.43711	0.4778 (0.0545–4.1864)
68	9 (16.4%)	14 (10.4%)	0.25849	1.6770 (0.6793–4.1403)
69	0	1 (0.7%)	0.35449	(Undefined)
74	1 (1.8%)	7 (5.2%)	0.26769	0.3360 (0.0404–2.7974)
80	1 (1.8%)	0	0.29100	(Undefined)

**Abbreviations:** OD, odds ratio; CI, confidence interval.



**Table 5** Frequency of HLA-B Allelic Groups in Patients and Controls

HLA-B*	Psoriasis n = 110	Controls n = 268	p	OR (CI)
<b>07</b>	<b>2 (3.6%)</b>	<b>19 (14.2%)</b>	<b>0.02599</b>	<b>0.2284 (0.0513–1.0164)</b>
08	3 (5.5%)	8 (6.0%)	0.59670	0.9087 (0.2319–3.5605)
13	3 (5.5%)	2 (1.5%)	0.148511	3.8077 (0.6183–23.448)
14	10 (18.2%)	14 (10.4%)	0.14691	1.9048 (0.7894–4.5962)
15	11 (20.0%)	22 (16.4%)	0.55571	1.2727 (0.5699–2.8422)
18	3 (5.5%)	14 (10.4%)	0.21286	0.4945 (0.1363–1.7942)
27	1 (1.8%)	10 (7.5%)	0.06906	0.2296 (0.0287–1.8387)
35	11 (20.0%)	38 (28.4%)	0.23365	0.6316 (0.2954–1.3505)
37	3 (5.5%)	2 (1.5%)	0.14851	3.8077 (0.6183–23.4484)
38	5 (9.1%)	6 (4.5%)	0.18461	2.1333 (0.6229–7.3061)
39	1 (1.8%)	11 (8.2%)	0.08832	0.2071 (0.0261–1.6443)
40	3 (5.5%)	4 (3.0%)	0.33105	1.8750 (0.4055–8.6689)
41	0	3 (2.2%)	0.35405	0 (Undefined)
42	1 (1.8%)	8 (6.0%)	0.20571	0.2917 (0.0356–2.3894)
44	8 (14.5%)	23 (17.2%)	0.65876	0.8215 (0.3428–1.9683)
45	1(1.8%)	2 (1.5%)	0.64594	1.2222 (0.1085–13.7627)
47	0	0	–	–
48	0	1 (0.7%)	0.70899	0 (Undefined)
49	5 (9.1%)	12 (9.0%)	0.58617	1.0167 (0.3405–3.0359)
50	1 (1.8%)	6 (4.5%)	0.34437	0.3951 (0.0464–3.3605)
51	6 (10.9%)	23 (17.2%)	0.27846	0.5909 (0.2264–1.5423)
52	2 (3.6%)	4 (3.0%)	0.56288	1.2264(0.2180–6.8985)
53	4 (7.3%)	6 (4.5%)	0.32377	1.6732(0.4532–6.1773)
54	0	0	–	–
55	2 (3.6%)	2 (1.5%)	0.33186	2.4906 (0.3419–18.142)
56	0	1 (0.7%)	0.70899	0 (Undefined)
<b>57</b>	<b>13 (23.6%)</b>	<b>10 (7.5%)</b>	<b>0.00200</b>	<b>3.8381 (1.5673–9.3988)</b>
58	6 (10.9%)	7 (5.2%)	0.13937	2.2216 (0.7111–6.9406)
59	0	0	–	–
67	0	0	–	–
73	0	0	–	–
78	0	0	–	–
81	0	2 (1.5%)	0.50157	0 (Undefined)
82	0	0	–	–

**Note:** Bold lines highlight p value < 0.05.

**Abbreviations:** OD, odds ratio; CI, confidence.

of HLA-B17 and Cw6. HLA-B57 and B58 correspond to the serologic HLA-B17 splits and in terms of DNA analysis, to the alleles B \* 5701, B \* 5702 or B \* 5801.

Allelic groups HLA-B\*14 and HLA-Cw\*08 were significantly increased in psoriasis type II patients. Although in linkage disequilibrium, they have not been described in the literature as susceptibility alleles to psoriasis. HLA-Cw7 and HLA-Cw\*01 were significantly increased in type II patients in Turkey and Thailand, respectively.<sup>17,30</sup>

Regarding HLA class II, the allelic group HLA-DRB1\*13 was statistically significant only in type I psoriasis. Rather, Cardoso et al<sup>32</sup> published a study with Brazilian and detected the HLA-DRB1\*1302 as a protective allele, but there is no description of the ethnic origin of the group studied. Serological studies in Croatia and Turkey showed an increased frequency of HLA-DR7 in type I patients,<sup>8,17</sup> and in both groups of Finnish patients.<sup>6</sup> Molecular methods showed that HLA-DRB1 \* 0701 was present more frequently in type I patients in Germany,<sup>19</sup> Croatia,<sup>24</sup> and Taiwan<sup>33</sup> and in all

**Table 6** Frequency of HLA-Cw Allelic Groups in Patients and Controls

HLA-C*	Psoriasis n = 110	Controls n = 268	p	OR (CI)
01	3 (5.5%)	7 (5.2%)	0.59750	1.0467 (0.2606–4.2044)
02	3 (5.5%)	19 (14.2%)	0.08936	0.3492 (0.0990–1.2322)
03	9 (16.4%)	17 (12.7%)	0.50500	1.3465 (0.5602–3.2367)
04	13 (23.6%)	47 (35.1%)	0.12491	0.5729 (0.2800–1.1726)
05	5 (9.1%)	9 (6.7%)	0.38443	1.3889 (0.4436–4.3487)
<b>06</b>	<b>16 (29.1%)</b>	<b>22 (16.4%)</b>	<b>0.04832</b>	<b>2.0886 (0.9965–4.3773)</b>
07	18 (32.7%)	49 (36.6%)	0.61618	0.8439 (0.4344–1.6393)
08	10 (18.2%)	14 (10.4%)	0.14691	1.9048 (0.7894–4.5962)
10	10 (18.2%)	23 (17.2%)	0.86706	1.0725 (0.4727–2.4332)
14	4 (7.3%)	5 (3.7%)	0.24593	2.0235 (0.5224–7.8384)
15	3 (5.5%)	14 (10.4%)	0.21286	0.4945 (0.1363–1.7942)
16	3 (5.5%)	12 (9.0%)	0.31463	0.5865 (0.1589–2.1655)
17	1 (1.8%)	10 (7.5%)	0.11805	0.2296 (0.0287–1.8387)
18	4 (7.3%)	2 (1.5%)	0.06048	5.1765 (0.9196–29.137)

**Note:** Bold line highlights p value < 0.05.

**Abbreviations:** OD, odds ratio; CI, confidence interval.

**Table 7** Frequency of HLA-DRB1 Allelic Groups in Patients and Controls

HLA-DRB1*	Psoriasis n = 110	Controls n = 268	p	OR (CI)
01	12 (21.8%)	33 (24.6%)	0.68049	0.8541 (0.4031–1.8099)
03	10 (18.2%)	24 (17.9%)	0.96480	1.0185 (0.4508–2.3014)
04	12 (21.8%)	29 (21.6%)	0.97867	1.0104 (0.4723–2.1619)
07	21 (38.2%)	42 (31.3%)	0.36499	1.3529 (0.7027–2.6048)
08	5 (9.1%)	22 (16.4%)	0.19103	0.509 (0.1824–1.4213)
09	0	4 (3.0%)	0.24936	0 (Undefined)
10	4 (7.3%)	9 (6.7%)	0.55535	1.0893 (0.3210–3.6972)
11	11 (20.0%)	28 (20.9%)	0.89009	0.9464 (0.4334–2.0667)
12	2 (3.6%)	3 (2.2%)	0.45410	1.6478 (0.2677–10.144)
13	15 (27.3%)	22 (16.4%)	0.08758	1.9091 (0.9027–4.0377)
14	4 (7.3%)	5 (3.7%)	0.24593	2.0235 (0.5224–7.8384)
15	6 (10.9%)	22 (16.4%)	0.33287	0.6234 (0.2379–1.6331)
16	2 (3.6%)	12 (9.0%)	0.16879	0.3836 (0.0830–1.7741)

**Abbreviations:** OD, odds ratio; CI, confidence interval.

**Table 8** Frequency of HLA-DQB1 Allelic Groups in Patients and Controls

HLA-DQB1*	Psoriasis n = 110	Controls n = 268	p	OR (CI)
02	23 (41.8%)	54 (40.3%)	0.84685	1.0648 (0.5629–2.0141)
03	24 (43.6%)	62 (46.3%)	0.43361	0.8991 (0.4779–1.6913)
04	4 (7.3%)	20 (14.9%)	0.15121	0.4471 (0.1454–1.3745)
05	25 (45.5%)	55 (41.0%)	0.57729	1.1970 (0.6358–2.2533)
06	20 (36.4%)	41 (30.6%)	0.44116	1.2962 (0.6693–2.5102)

**Abbreviations:** OD, odds ratio; CI, confidence interval.



patients, unrelated to the subtype, in Korea.<sup>24</sup> HLA-DRB1 \* 0701 was also present when patients with type II psoriasis were analyzed separately in Taiwan.<sup>33</sup>

The allelic group HLA-B \* 07 was present more frequently in the control group compared to patients and could be a protective allele, and has not been described in the literature as such. HLA-A66, and -Cw2, -Cw4,<sup>17</sup> HLA-A\*24, -A\*33 and Cw\*04<sup>30</sup> and Cw\*07<sup>10</sup> were previously described as protection antigens.

HLA-B\*57 was significantly increased in patients with history of erythrodermic psoriasis, in patients with hospital admissions caused by psoriasis and those with history of psoriasis systemic treatment, compared to the control group. Comparing HLA-B\*57 positive patients with negative patients, a difference remains in the ones with history of systemic treatment. Another study<sup>34</sup> correlated HLA-Cw\*0602 with clinical parameters. One thousand and nineteen patients from Iceland were typed and, of these, 654 (64.2%) were positive for Cw \* 0602. Comparing with Cw \* 0602 negative patients, positive patients had an early disease onset, more extensive skin involvement, more frequent relapses due to oropharyngeal infections, or the development of lesions in the sites of trauma.<sup>34</sup>

In patients with psoriatic arthritis, HLA-C\*18 was significantly increased compared to the control group. The significant difference was maintained when comparing patients with and without arthritis. HLA-C\*18 has not yet been described in the literature as psoriatic arthritis susceptibility. On the other hand, HLA-B\*57 has been described as a susceptibility marker,<sup>35</sup> and, in this study, it remained significantly frequent in this subgroup of patients compared to the control group. Other studies have also highlighted HLA-B17 in association with arthritis.<sup>36,37</sup> HLA-B17 corresponds to the HLA-B\*57 by molecular methods. HLA-B\*27 is the most often found in association with psoriatic arthritis<sup>38-42</sup> and is mostly associated with axial arthritis.<sup>7,43-47</sup>

Schmitt-Egenolf et al<sup>20</sup> and Choonhakarn et al<sup>30</sup> reported similar haplotype in German and Thai patients with psoriasis: HLA-B57 Cw6 DRB1 \* 0701 DQA1 \* 0201 DQB1 \* 0303, the EH-57.1 haplotype, so named because of the B57 antigen. Kastelan et al<sup>16</sup> found a similar haplotype in Croatian patients with psoriasis type I, with a single difference in DQB1: HLA B 57 Cw6 DRB1 \* 0701 DQA1 \* 0201 DQB1 \* 0201. Choonhakarn et al<sup>30</sup> found two haplotypes, HLA -A\*0207 -B\*4601 -Cw\*01 -DRB1\*09 -DQB1\*0303 (EH-46.1) and HLA -A\*30 -B\*13 -Cw\*0602 -DRB1\*07 -DQB1\*02 (EH-

13.1), the latter similar to that found in Korean patients<sup>24</sup> (HLA -A\*30 -B\*13 -Cw\*0602 -DRB1\*07 -DQA1\*02 -DQB1\*02), with one difference in DQA1 allele, which has not been typified by Choonhakarn et al.<sup>30</sup>

In the present study, the most frequent haplotype among patients were HLA-A\*02 B\*57 C\*06 DRB1\*07 DQB1\*03, similar to that described by Schmitt-Egenolf et al<sup>20</sup> and Choonhakarn et al.<sup>30</sup> Another haplotype also found was HLA-A\*02 B\*13 C\*06 DRB1\*07 DQB1\*02 similar to that found by Tai-Gyu et al<sup>24</sup> with one difference, HLA-A\*30 allele.

Population and familial studies of antigens and HLA alleles and psoriasis vulgaris show different markers depending on the ethnic origin of the patients. However, it is unclear whether HLA would be a predisposing factor for psoriasis. It is known that the alleles located near a mutation tend to be in linkage disequilibrium with it.<sup>48</sup> In this case, alleles whose frequency are increased in cohorts of patients could be used to help locate susceptibility genes. In addition, some polymorphic residues in the most common HLA specificities may have the ability to bind and present antigens related to psoriasis, because of the clefts they form in the HLA molecule, determining the size and charge of the binding antigenic peptide.<sup>2,4,33</sup> The study of HLA antigens associated with psoriasis may not only indicate the disease susceptibility genes, but also clarify aspects of its pathogenesis. A study in Italy<sup>49</sup> identified a sequence of four amino acids (Ala 73, Asn 77, Lys 80 and Asp 90) in the binding groove of HLA-Cw \*0602 and Cw\*04 in 77, 5% of patients with psoriasis and 50, 8% of controls (p = 0.0031). This sequence was also characteristic in female patients (80%) in familial forms (89.5%), psoriasis type I (81.8%) and arthropathic psoriasis (88.8%). The nature of the peptide binding grooves varies from one molecule to another, affecting the affinity of binding with endogenous HLA peptides.<sup>50</sup> The study of the binding of HLA molecules clefts found in patients with psoriasis can contribute to defining the pathogenic peptides that participate in triggering the immune response altered in psoriasis.<sup>49</sup>

## Conclusions

HLA-B\*57 and HLA-C\*06 were significantly higher in the patients indicating risk for psoriasis. HLA-B\*57 was high in patients with history of erythroderma, hospital internment, systemic treatment, and psoriatic arthritis, showing a relation with disease severity. HLA-C\*18 was only significantly high in patients with psoriatic arthritis. HLA-B\*57, HLA-C\*06 and haplotype HLA-A\*02B\*57C\*06DRB1\*07 DQB1\*03 associated to psoriasis were already described before, and HLA-

C\*18 was not described in association with psoriasis in other populations.

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## Disclosure

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