**HLA-C and TNF gene polymorphisms are associated with psoriasis in Brazilian patients**

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**Conflicts of interest:** None.

**Abstract**

**Background** Polymorphisms at the human leukocyte antigens (HLA-C) and tumor necrosis factor (TNF) genes have been associated with susceptibility to psoriasis in several worldwide populations. In this study, HLA-C and TNF (–238/–308) polymorphisms were performed in 125 Brazilian patients and 202 healthy controls.

**Methods** HLA-C and TNF promoter region alleles were typed by polymerase chain reaction using sequence-specific primer-polymerase chain reaction.

**Results** The presence of HLA-C*06 was associated with psoriasis onset, particularly in younger patients, being more frequent for patients with disease onset before the age of 20 years (P = 0.03), 25 years (P = 0.01), or 30 years (P = 0.03). No association between HLA-C*06 and psoriasis was observed for patients older than 35 years. Susceptibility to psoriatic arthritis was associated with the TNF–238 G/A genotype (P = 0.02). The TNF–308A allele was overrepresented in patients (P = 0.0061), and the TNF–308 G/A genotype was increased in generalized forms (erythrokeratoderma and generalized pustular psoriasis) compared to plaque psoriasis (P < 0.001). The TNF–238A/HLA-C*06 haplotype was overrepresented in patients (P = 0.025), while the TNF–238G/HLA-C*15 haplotype was increased in controls (P = 0.037).

**Conclusions** The strong association of HLA-C*06 allele with disease susceptibility, particularly in early onset psoriasis, indicates that younger ages could be considered to stratify psoriasis into early and late types. TNF–308 polymorphisms can be associated with psoriasis susceptibility and severity. Potential genetic markers of psoriasis in populations with a complex mixture of ethnicities should be investigated.

**Introduction**

Psoriasis is a common inflammatory disorder involving mostly skin and joints and affecting 1–3% of Caucasians. However, the prevalence rates vary greatly between individuals of different ethnic backgrounds and geographic locations.2,3 It is most common in Scandinavia and northern Europe, but the prevalence rates in Native Americans and Latin Americans and in Africa and Asia varied from no cases detected to estimates below 0.5%. Reasons for these variations are likely to be both genetic and environmental.4,5 Furthermore, differences by race in incidence for diseases associated with inflammation suggest that there may be underlying racial differences in inflammatory pathway genes.4

Major skin features of psoriasis consist of inflammatory changes in both dermis and epidermis with abnormal keratinocyte differentiation and proliferation, as well as infiltration of T lymphocytes and mononuclear cells.1

The etiology is multifactorial and is not very well known, and the major histocompatibility complex has been strongly associated with psoriasis susceptibility, primarily the HLA-C*06 allele group with early onset of psoriasis and the presence of family history (FH) of the disease.5,6 Previously, Henseler and Christophers proposed the classification of psoriasis based on the age of onset and FH: type I with early onset (<40 years, positive FH) and type II with late onset (>40 years, negative FH).5,6 Furthermore, there is considerable evidence that disregulation of the innate immune response can be central to the development of the disease. Tumor necrosis factor (TNF) is one of the proinflammatory cytokines that plays an important pathogenic role in psoriasis7 and psoriatic arthritis (PsA),8 and the encoded gene is located at chromosome 6, between HLA class I and class II genes.
Single nucleotide polymorphisms (SNP) at the TNF gene promoter, particularly guanine (G) to adenine (A) substitution at –238 and –308 positions, have been associated with psoriasis and PsA risk.9,10 The possible associations of HLA class I gene polymorphisms with TNF locus in different populations have been examined, and strong linkage disequilibrium between these loci could be associated with a predisposition to inflammatory conditions.11 Therefore, defining the population genetic composition of inflammation-related genes can be useful for the determination of general risk, prognostic, and therapeutic strategies. In this study, we evaluated the distribution of HLA-C and TNF promoter region alleles, genotypes, and haplotypes in a group of Brazilian patients presenting with psoriasis.

Materials and methods

Patients and controls

The study was carried out in 125 patients aged 18–75 years (median age 48.0 years); 69 men (median age 47.2 years) and 56 women (median age 49.1 years) followed up in the Dermatology Outpatient Clinic of the University Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo (São Paulo, Brazil). All patients underwent a clinical evaluation, including a complete history (particularly age of disease onset and FH of psoriasis) as well as physical and appropriated dermatological examination to classify the psoriasis according to clinical criteria.1 The diagnosis of PsA was made by a consultant rheumatologist according to the clinical criteria12 and/or radiological signs. The control group consisted of 202 healthy blood donor individuals (146 men) aged 18 or 59 years from the same geographical region of patients. The study was approved by the institutional Ethics Review Committee on Human Research and was conducted according to the Declaration of Helsinki protocols. All subjects gave written informed consent to participate in the study.

DNA preparation

Ten milliliters of heparinized blood were obtained from both patients with psoriasis and healthy controls. Genomic DNA was isolated from leukocytes in anticoagulated blood using a salting out procedure,13 precipitated with isopropyl alcohol, and resuspended in sterile water. DNA concentration (optical density 260) and purity (optical density 260/280) were determined using a spectrophotometer, and only DNA samples exhibiting a ratio between 1.6 and 1.8 were used.

Genotyping

HLA-C alleles were typed using the sequence-specific primer-polymerase chain reaction (SSP-PCR) technique (One Lambda Inc., Canoga Park, CA, USA).14 DNA amplification was carried out according to the following conditions: 30 cycles at 94 °C for 10 s for DNA denaturation, annealing at 59 °C for 60 s, and extension at 72 °C for 30 s. PCR-DNA amplification was analyzed by electrophoresis in ethidium bromide-stained 2% agarose gel. A standard ultraviolet transilluminator gel imaging system was used to visualize and register the presence of the specific PCR product.

The alleles and genotypes of polymorphisms of the TNF promoter region were typed using the SSP-PCR. The TNF promoter polymorphism –238G/A and –308G/A PCR amplifications were performed in duplicate using allele-specific primers and the generic primers (Table 1), producing fragments of 175 and 259 bp, respectively. An internal positive amplification control was performed using the primers HGBA-S and HGBA-A, which are specific for the hemoglobin genes. The final volume of the reaction was 10 μL, including 200 ng of genomic DNA, 3 pmol of each primer (the generic one and a specific one), 2 pmol of each internal control primer, 0.25 mM deoxynucleotide triphosphate (GE Healthcare Bio-Sciences AB, Uppsala, Sweden), 0.75 U of Taq DNA polymerase (Invitrogen, Carlsbad, CA, USA), 1.5 mM of MgCl2, and 1 × PCR buffer (20 mM Tris–Cl, pH 8.5, 50 mM KCl). In the thermal cycler

Table 1 Primers for the detection of single nucleotide polymorphisms (SNPs) of TNF –238 G/A and –308 G/A genes

<table>
<thead>
<tr>
<th>SNP</th>
<th>Primer</th>
<th>Sequence (5’-3’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF  -238G/A</td>
<td>TNF 238 UP</td>
<td>AGGCAATAGGTTTGAGGCGCAT</td>
</tr>
<tr>
<td></td>
<td>TNFAS 238G</td>
<td>CCCATCTCCTCGCTCC</td>
</tr>
<tr>
<td></td>
<td>TNFAS 238A</td>
<td>TCCCATCTCCTGCTCTT</td>
</tr>
<tr>
<td></td>
<td>HGBA.S</td>
<td>CGGTATTTGGAGGTACAGCAC</td>
</tr>
<tr>
<td></td>
<td>HGBA.A</td>
<td>CCCACCAAGAGACTTACTT</td>
</tr>
<tr>
<td>TNF  -308G/A</td>
<td>TNFAS 308.2</td>
<td>CAGCGAGGAAATCTCTTGGT</td>
</tr>
<tr>
<td></td>
<td>TNFAS 308G</td>
<td>ATAGGTTTTGAGGGGATGG</td>
</tr>
<tr>
<td></td>
<td>TNFAS 308A</td>
<td>ATAGGTTTTGAGGGGATGA</td>
</tr>
<tr>
<td></td>
<td>HGBA.S</td>
<td>CGGTATTTGGAGGTACAGCAC</td>
</tr>
<tr>
<td></td>
<td>HGBA.A</td>
<td>CCCACACCAAGAGACTTACTT</td>
</tr>
</tbody>
</table>

SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.
(GeneAmp PCR System 9700, Applied Biosystems, CA, USA), after an initial denaturing time of 5 min at 94 °C, PCR reactions run for 32 cycles including 45 s at 94 °C, 45 s at 64 °C, and 1 min at 72 °C, with a final extension at 72 °C for 5 min. All amplification products were visualized using 10% non-denaturing polyacrylamide gel under specific electrophoretic conditions (250 mV/1 h 15 min), followed by silver staining.15

Statistical analysis
The comparisons between patients and healthy controls were performed using the Fisher’s exact test after constructing 2 × 2 contingency tables. Odds ratio (OR) was calculated within 95% confidence intervals (CI). Haplotype reconstruction was performed using the PHASE and an expectation-maximization-based algorithm.16 Associations between the presence of psoriasis and various covariates were tested using the chi-square test or Fisher’s exact test for categorical variables and t-test for continuous variables. The interaction of positive familial history and HLA-C*06 phenotype variables, influencing on the age at psoriasis onset, was assessed by two-way ANOVA. All statistical analyses were performed using the (SPSS, version 17.0. Chigo: SPSS Inc.). P ≤ 0.05 was accepted as statistically significant.

Results

Demographic data
Most patients were Caucasians (88%; 110 of 125) and exhibited plaque psoriasis (80%; 100 of 125), and 48% (60 of 125) of them initiated symptoms before the age of 30 years. The average age at psoriasis onset was 34 years for women and 33.3 years for men. Positive FH cases (60 of 125) of them initiated symptoms before the age of 30 years. The average age at psoriasis onset was 34 years (60 of 125) and healthy controls (n = 202) is shown in Table 2. HLA-C*09, *10, *11, and *13 allele groups were not observed in patients or controls. Compared to healthy individuals, the HLA-C*06 allele group frequency was significantly increased in patients with psoriasis (n = 44) (P = 0.0005; 95% CI 1.49-4.18; OR 2.5). The age of psoriasis onset was significantly reduced for HLA-C*06 carriers (30 years) compared to non-HLA-C*06 carriers (35.7 years) (t = 3.36; P = 0.001).

HLA-C* allele frequency

HLA-C allele distribution in patients with psoriasis (n = 125) and healthy controls (n = 202) is shown in Table 2. HLA-C*09, *10, *11, and *13 allele groups were not observed in patients or controls. Compared to healthy individuals, the HLA-C*06 allele group frequency was significantly increased in patients with psoriasis (n = 44) (P = 0.0005; 95% CI 1.49-4.18; OR 2.5). The age of psoriasis onset was significantly reduced for HLA-C*06 carriers (30 years) compared to non-HLA-C*06 carriers (35.7 years) (t = 3.36; P = 0.001). The stratification according to the age at psoriasis onset revealed that HLA-C*06 allele frequency was increased in: (i) younger than 20 years compared to older ones (54.2% vs. 30.7%; P = 0.03; OR 2.63; 95% CI 1.08-7.69); (ii) younger than 25 years compared to older ones (50.5% vs. 27.2; P = 0.01; OR 2.70; 95% CI 1.25-5.88); and (iii) younger

Table 2 Distribution of HLA-C* allele frequency in patients with psoriasis and healthy controls

<table>
<thead>
<tr>
<th>HLA-C*</th>
<th>Psoriasis patients n = 125 (%)</th>
<th>Controls n = 202 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>4 (1.6)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>02</td>
<td>13 (6.2)</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>03</td>
<td>15 (6.0)</td>
<td>27 (6.7)</td>
</tr>
<tr>
<td>04</td>
<td>30 (12)</td>
<td>56 (13.9)</td>
</tr>
<tr>
<td>05</td>
<td>15 (6.0)</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>06</td>
<td>44 (17.6)</td>
<td>36 (8.9)</td>
</tr>
<tr>
<td>07</td>
<td>64 (25.6)</td>
<td>95 (23.5)</td>
</tr>
<tr>
<td>08</td>
<td>4 (1.6)</td>
<td>23 (5.7)</td>
</tr>
<tr>
<td>12</td>
<td>21 (8.4)</td>
<td>26 (6.4)</td>
</tr>
<tr>
<td>14</td>
<td>6 (2.4)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>15</td>
<td>3 (1.2)</td>
<td>13 (3.2)</td>
</tr>
<tr>
<td>16</td>
<td>11 (4.4)</td>
<td>30 (7.4)</td>
</tr>
<tr>
<td>17</td>
<td>3 (1.2)</td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>18</td>
<td>4 (1.6)</td>
<td>3 (0.7)</td>
</tr>
</tbody>
</table>

P-value, Fisher’s exact test: *P = 0.0005; 95% CI 1.49-4.18; OR 2.5.

Tumor necrosis factor polymorphism frequency distribution analyses
The TNF –238 G/A genotype was increased in patients, and the G/G genotype was increased in controls; however, significance was not observed. The TNF –238 G/A genotype (n = 34) was overrepresented in PsA compared to those without PsA (47.6% vs. 23.1%; P = 0.02; OR 3.03; 95% CI 1.15-8.00).

In relation to the TNF –308 polymorphism, the G/A genotype frequency was significantly higher in the patients (P = 0.0061; OR 2.20; 95% CI 1.2641-3.8451), whereas the frequency of the G/G genotype was significantly higher in controls (P = 0.05; OR 2.21; 95% CI 0.02643–0.7756). The TNF –308 G/A genotype frequency was significantly higher in generalized forms (erythrodermic
and generalized pustular psoriasis) compared to plaque psoriasis (64.3% vs. 19.5%; \( P < 0.001; \ OR \ 7.2; \ 95\% \ CI \ 2.16–23.99 \)).

No significant differences regarding both TNF polymorphic sites were observed when patient groups were stratified according to age at psoriasis onset; i.e., \( \leq 30 \) years and \( > 30 \) years. Table 3 summarizes the results of all the TNF promoter region polymorphisms studied.

### HLA-C and tumor necrosis factor haplotypes

The reconstruction of HLA-C*06 and TNF haplotypes showed that the TNF–238A/–308G/HLA-C*06 haplotype was overrepresented (\( P = 0.025; \ OR 2.36; \ 95\% \ CI 1.16–4.79 \)) and the TNF–238G/–308G/HLA-C*15 haplotype underrepresented (\( P = 0.037; \ OR 8.53; \ 95\% \ CI 0.051–1.023 \)) in patients when compared to healthy controls.

### Discussion

Different studies have shown HLA associations in psoriasis, emphasizing the role of several genes within the major histocompatibility complex region, located at chromosome 6p.\(^{17-19}\) Besides major histocompatibility complex genes, candidate psoriasis-susceptibility loci have been identified in other chromosomes, including \( 17q25, 4q, 1q21, 3q21, 19p13, 2p, 8q, 16q, \) and \( 20p \), designated as psoriasis susceptibility regions (PSORS).\(^{17-19}\) Among these loci, the HLA class I \( C^*06 \) allele group (PSORS-1) has been considered the locus most consistently associated with psoriasis, particularly with early onset psoriasis.\(^{5,17-20}\) It has been suggested that the interaction of sensitized T lymphocytes with keratinocytes exhibiting the HLA-C*06 molecules in the presence of a yet unknown psoriasis triggering peptide

![Figure 1](https://example.com/figure1.png)

**Figure 1** HLA-C*06 genotype frequencies in patients according to the age at psoriasis onset. Patients with psoriasis were divided into younger (gray column) and older (white column) groups (\( P \)-value, chi-squared test)

### Table 3

<table>
<thead>
<tr>
<th>HLA</th>
<th>(-C^*06 (+))</th>
<th>(-C^*06 (-))</th>
<th>Genotypes</th>
<th>TNF -238 position</th>
<th>TNF -308 position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>G/A</td>
<td>G/G</td>
<td>A/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Controls (202)</td>
<td>17.8</td>
<td>82.2</td>
<td>19.8</td>
<td>80.2</td>
<td>0</td>
</tr>
<tr>
<td>Patients (125)</td>
<td>35.2(^a)</td>
<td>64.8</td>
<td>27.2</td>
<td>72.8</td>
<td>0</td>
</tr>
<tr>
<td>Age of onset, year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 30 ) (60)</td>
<td>45.0(^b)</td>
<td>55.0</td>
<td>35.0</td>
<td>65.0</td>
<td>0</td>
</tr>
<tr>
<td>( &gt; 30 ) (65)</td>
<td>26.1</td>
<td>73.9</td>
<td>20.0</td>
<td>80.0</td>
<td>0</td>
</tr>
<tr>
<td>Clinical feature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaques (98)</td>
<td>35.7</td>
<td>64.3</td>
<td>27.5</td>
<td>72.5</td>
<td>0</td>
</tr>
<tr>
<td>Generalized (14)</td>
<td>28.6</td>
<td>71.4</td>
<td>28.6</td>
<td>71.4</td>
<td>0</td>
</tr>
<tr>
<td>Guttate (8)</td>
<td>50.0</td>
<td>50.0</td>
<td>37.5</td>
<td>62.5</td>
<td>0</td>
</tr>
<tr>
<td>Palms and soles (8)(^g)</td>
<td>12.5</td>
<td>87.5</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis (21)</td>
<td>38.1</td>
<td>61.9</td>
<td>47.6(^d)</td>
<td>52.4</td>
<td>0</td>
</tr>
</tbody>
</table>

\( P \)-value, Fisher’s exact test: \(^a\)\( P < 0.005; \ OR \ 2.3; \ 95\% \ CI \ 1.49–4.18 \) (patients vs. controls).
\(^b\)\( P = 0.03; \ OR 2.33; \ 95\% \ CI 1.09–5.00 \) (younger vs. older than 30 years).
\(^c\)\( P = 0.006; \ OR 2.20; \ 95\% \ CI 1.26–3.85 \) (patients vs. controls).
\(^d\)\( P = 0.05; \ OR 2.21; \ 95\% \ CI 0.026–0.77 \) (patients vs. controls).
\(^e\)\( P < 0.001; \ OR 7.2; \ 95\% \ CI 2.16–23.99 \) (generalized vs. plaques type).
\( P \)-value, chi-squared test: \(^f\)\( P = 0.02; \ OR 3.03; \ 95\% \ CI 1.15–8.00 \) (positive vs. negative psoriatic arthritis).
\(^g\)Palms and soles type: exclusive in five patients.
could exacerbate the cellular immune response, resulting in an unbalanced T-regulatory and effector T-lymphocyte function.\textsuperscript{21–23}

Our findings are in agreement with the results reported for distinct worldwide populations, as the high frequency of the HLA-C*06 allele group corroborates the role of this marker in the susceptibility to psoriasis, particularly in early onset psoriasis in Brazilian patients. The Brazilian population is genetically highly admixture, resulting from five centuries of crossings between Native Americans, Caucasians from western Europe, and Africans, but it has still been considered under a miscegenation process, as some genotypes are not in the Hardy–Weinberg equilibrium. For instance, the Pardo ethnicity is derived from a complex mixture of ethnicities, including the Native Indian population, which showed greater genetic similarity with white than black groups.\textsuperscript{24} The patterns of population differentiation of 32 polymorphisms related to adaptive immune response in four Native American populations showed the lowest difference with Asians, specifically Han Chinese of Beijing, China, when compared to Yoruba of Ibadan, Nigeria, and Utah residents with northern and western Europe ancestry.\textsuperscript{25}

Regarding the age onset, the HLA-C*06:02 allele was also strongly associated with psoriasis in patients younger than 30 years in Korean\textsuperscript{16} and Croatian populations,\textsuperscript{27} and in patients younger than 35 years in Han Chinese populations.\textsuperscript{28} When the age of onset before 20 years was considered in Polish patients, the association with HLA-C*06 was even stronger, being four times higher than that observed for patients with psoriasis as a whole and almost 80 times higher than controls.\textsuperscript{29} Early onset, considered <25 years, was associated with a high frequency of HLA-C*06 antigens in Greek patients.\textsuperscript{30} In the Swedish population, the HLA-C*06 frequency was sharply reduced among patients older than 22 years.\textsuperscript{31}

Overall, our findings indicated that early and late types might be appropriately defined in the range of 20–30 years in Brazilian patients. In addition, the early onset of psoriasis was strongly associated with FH of psoriasis and with the presence of the HLA-C*06 allele group. Previous studies in Brazilian patients associated HLA-B*07, -B*57, -C*06, and -C*12 alleles with type I psoriasis.\textsuperscript{12}

Taken together, the HLA-C*06 allele group seems to be associated with the early onset of psoriasis in different populations, and further studies should be conducted to define the age cohort to classify patients with early-onset psoriasis.

The association of the HLA-C*06 allele group with guttate has been suggested in previous studies,\textsuperscript{33,34} which was not confirmed in our findings, probably due to reduced representation of these clinical features.

Besides the association with the HLA-C locus, evidence indicates a disturbance of the innate immunity in patients with psoriasis, exhibiting high TNF levels in affected skin\textsuperscript{28} and in synovial fluid when PsA is present.\textsuperscript{3} Local TNF concentrations might be of greater relevance and under more control by specific polymorphisms.\textsuperscript{11} TNF–238 and –308 polymorphisms have been associated with susceptibility to psoriasis and PsA,\textsuperscript{9,10} as well as their severity features,\textsuperscript{35,36} however, conflicting results have been reported.

A meta-analysis study showed increased frequency of the TNF–238A allele in patients with psoriasis suggesting risk to psoriasis, whereas the TNF–308A allele frequency was reduced.\textsuperscript{37} The TNF–238A allele was strongly associated with psoriasis and PsA in the German population,\textsuperscript{10} but no associations were observed between these polymorphic sites in the Japanese\textsuperscript{18} and Chinese populations.\textsuperscript{39} In concordance to the German group, the TNF–238 G/A genotype was associated with PsA in our patient series. In addition, the frequency of the TNF–238A allele in patients with psoriasis, particularly in those younger than 30 years at disease onset, was increased; however, significance was not observed. Also, cytokine and cytokine receptor SNP allelic, genotypic, and haplotype frequencies can vary significantly by race.\textsuperscript{3}

Our findings showed higher frequency of the TNF–308 G/A genotype in patients, which was also associated with the generalized forms (erythrodermic and generalized pustular psoriasis), suggesting the TNF–308 polymorphism is associated with susceptibility and severity. The inclusion of these severe forms of psoriasis (erythrodermic and generalized pustular psoriasis) could have differentiated our findings, but as the reference hospital, the assistance for patients with moderate to severe psoriasis is our focus.

Corroborating the idea of the association of TNF promoter region polymorphisms with disease morbidity, Magalhães \textit{et al.} suggested that the TNF–238 polymorphism is associated with psoriasis severity.\textsuperscript{40} The TNF–308 and TNFbeta +252 polymorphisms were significantly associated with the presence of joint erosions in PsA and progression of joint erosions in early PsA.\textsuperscript{35} In addition, the TNF–308A has been associated with a more severe juvenile idiopathic arthritis, while the more common TNF–308G allele may be protective.\textsuperscript{41} In addition, a TNF–308 G/G genotype seems to be a better responder to anti-TNF treatment than those with A/A or A/G genotypes independent of the treated rheumatic disease (PsA, rheumatoid arthritis, or ankylosing spondylitis).\textsuperscript{42} HLA-C*06 carriers with psoriasis have also had an increased, faster, and maintained response to ustekinumab compared to HLA-C*06 non-carriers.\textsuperscript{43} Instead, the HLA-C genotype was not predictive of the treatment response to etanercept and/or adalimumab.\textsuperscript{44}
The simultaneous analysis of HLA-C* alleles with TNF polymorphisms has been reported in association with predisposition to psoriasis, particularly in the early disease onset.\(^4^5\) Al-Heresh \textit{et al.} observed that patients with psoriasis with PsA exhibiting the HLA-C*06 allele also presented at least one TNF –238A allele, suggesting a strong association of these alleles with PsA.\(^4^5\) In our simultaneous analysis of the HLA-C* and TNF –238I/308 alleles suggested an association of the TNF –238A/308G/HLA-C*06 haplotype with susceptibility, and the TNF –238G/308G/HLA-C*15 haplotype with protection against psoriasis.

In summary, our study on Brazilian patients with psoriasis confirmed the strong association of HLA-C*06 allele with disease susceptibility, particularly the early onset psoriasis, indicating that younger ages could be considered to stratify psoriasis into early and late types. TNF polymorphism, particularly the –238 locus, was associated with PsA, and the –308 locus seems to be associated with more severe psoriasis. Finally, we reported the differential association of the TNF –238A/HLA-C*06 and TNF –238G/HLA-C*15 haplotypes, conferring susceptibility or protection to psoriasis, respectively. More studies are needed to clarify the role of these and other potential genetic markers in the susceptibility to psoriasis and PsA, its phenotypes, severity, and clinical response to novelty therapies in different populations, particularly those with a complex mixture of ethnicities.

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