Research Article

Influence of TNF and IL17 Gene Polymorphisms on the Spondyloarthritis Immunopathogenesis, Regardless of HLA-B27, in a Brazilian Population

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Background and Objectives. Spondyloarthritis (SpA) represents a heterogeneous group of immune-mediated inflammatory diseases that have overlapping clinical features, genetic predisposition, and pathogenic mechanisms. Hence, we investigated, through a case-control study, whether single-nucleotide polymorphisms of TNF and IL17 genes are associated with SpA, ankylosing spondylitis (AS), and psoriatic arthritis (PsA) in a mixed Brazilian population.

Methods. Genotyping of TNF-308 (rs1800629), TNF-238 (rs361525), IL17A (rs2275913), IL17F (rs763780), and HLA-B27 polymorphisms was performed in 243 patients with SpA and 210 controls from Southern Brazil using SSOP-Luminex (One Lambda) and PCR-SSP assays.

Results. Significant associations were confirmed between the HLA-B27 marker and SpA, AS, and PsA diseases. While TNF-308 (rs1800629) AA/GA, IL17A (rs2275913) AA/GA, and IL17F (rs763780) CC/TC genotype frequencies were associated, in the dominance inheritance model, with SpA and AS, regardless of gender, the presence of HLA-B27, TNF-238 (rs361525) GA/AA, IL17A (rs2275913) AA/GA, and IL17F (rs763780) genotypes was associated with PsA. Conclusion. In this Brazilian population, TNF and IL17 gene polymorphisms responsible for the expression of important inflammatory cytokines were associated with overall SpA, and, specifically, with AS and PsA, regardless of gender and HLA-B27. However, future larger studies with different ethnicities may be necessary to confirm these genetic associations.

1. Introduction

Spondyloarthritis (SpA) represents a heterogeneous group of immune-mediated inflammatory diseases that have overlapping clinical features, genetic predisposition, and pathogenic mechanisms. The disease may be undifferentiated or manifest as reactive arthritis, psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease, or ankylosing spondylitis (AS) [1, 2].

The pathogenesis of SpA is partly attributed to the interaction between genetic factors and the environment. Males are affected more frequently than females according to results from two meta-analysis studies [3, 4], and genetic factors associated with HLA in the pathogenesis of SpA are best represented by the strong association between the HLA-B27 and AS [4]. However, the fact that only 1–3% of HLA-B27-positive people develop the disease, and not all patients with the disease possess the HLA-B27 antigen, suggests that other genes may be involved in the development of the pathology [5, 6].

Polymorphisms in genes encoding cytokines that interfere on cytokine level production have been associated with rheumatologic chronic inflammatory diseases [7–10]. However,
the role of the tumor necrosis factor (TNF) and interleukin (IL) 17A and IL17F genes, encoded on the same chromosome 6 of the HLA genes, and their clinical importance in the pathogenesis of SpA have not been fully elucidated [11–13]. Proinflammatory cytokines such as TNF-α and IL17 may be elevated in patients with SpA and may contribute to the pathogenesis of the disease (reviewed by Zambrano-Zaragoza et al.) [11]. These cytokines have cytotoxic effects and induce the secretion of other cytokines, such as TNF-α, IL1β, and IL6, which can cause generalized tissue damage [14].

Thus, the aim of the present study was to investigate whether the single-nucleotide polymorphisms (SNPs) of the TNF, IL17A, and IL17F genes are associated with SpA and its clinical forms, AS, and PsA, in a mixed population from the South of Brazil.

2. Patients and Methods

2.1. Patients and Controls. In this case-control study, 243 unrelated patients were diagnosed by the ASAS Criteria 2009 [14] for axial SpA and the ASAS Criteria 2011 [15] for peripheral SpA. All patients had magnetic resonance imaging of the sacroiliac joints and were evaluated for the presence of HLA-B27. In patients with PsA, we also used the CASPAR criteria [16], to complement the ASAS criteria, to provide greater security in the data obtained. Patients were selected at the Maringa University Hospital-Maringa State University and the Maringa Rheumatism Clinic, from Paraná State, Southern Brazil.

In addition, 210 individuals were selected to form the control group, following the criteria for inclusion: no autoimmune and/or rheumatic diseases, unrelated to the patient group, and belonging to the same ethnic group as the patients.

The population of Paraná is predominantly of European origin (80.6%), with a small but significant contribution of African (12.5%) and Amerindian (7.0%) genes [17]. Both the patients and healthy controls were classified as mixed ethnic groups, according to phenotypic characteristics, because according to Parra et al. [18], in Brazil, at an individual level, skin color determined by physical evaluation is a poor predictor of genomic African ancestry.

The project was approved by the Ethics Committee of the Maringa State University (number 687.222/2014). After terms of consent were signed, blood samples were collected, centrifuged, and frozen at −20°C until use.

2.2. Analysis of Genetic Cytokine Polymorphisms. Genotyping of TNF-238 (rs361525), TNF-308 (rs1800629), IL17A (rs2275913), and IL17F (rs763780) SNPs was performed with DNA samples by PCR-restriction fragment length polymorphism (RFLP) [19, 20]. Primer sequences, conditions, restriction enzymes, and size fragments are shown in Table 1.

2.3. Identification of HLA-B27. Genotyping of HLA-B27 was performed using PCR-SSP according to the method published before by our research group [21].

2.4. Statistical Analysis. The software Quanto (http://biostats.usc.edu/Quanto.html) was used to calculate the sample size using the less frequent allele (0.095 for TNF-238), population risk (1.5%), and OR (2.0–4.0).

The allele and genotype frequencies in patients and controls were estimated and compared by chi-square distribution tables using the OpenEpi 3.01 software (http://www.openepi.com/Menu/OF_Menu.htm). The statistical comparisons between groups were realized, and the estimated risk in individuals who hold genetic polymorphisms was calculated by the determination of OR (odds ratio) with 95% of confidence interval, adjusted for gender and age. All statistical analyses were performed by the software SNPStats (http://bioinfo.iconologia.net/index.php), which was also used for detecting the Hardy-Weinberg (HW) and odds ratio balance, with a 95% confidence interval (CI). The P ≤ 0.05 values were considered statistically significant to the chi-square test with Yates’ correction and logistic regression. The association tests were realized to the codominant, dominant, recessive, over-dominant, and log-additive genetic inheritance models.

Finally, because TNF-238, TNF-308, IL17A, and IL17F genes are located near chromosome 6, we performed a haplotype analysis for those SNPs associated with SpA, AS, and PsA, with the aim of establishing the disease risks if the individual possesses determined haplotype using the software SNPStats.

3. Results

Baseline characteristics of patients (n = 243) and controls (n = 210) regarding age, gender, and genetic marker HLA-B27 are presented in Table 2. The majority of them were females (55.2% of patients and 56.2% of controls), with an average age of 47 (±15.7) and 40 (±2.7) years, respectively. The HLA-B27-positive marker was present, in a higher percentage, in patients with SpA than in controls (36.6% versus 15.2%) and in patients with AS and PsA than in controls (40.8% and 26.9%, resp., versus 15.2%).

Allele and genotype polymorphisms for TNF-308, TNF-238, IL17A, and IL17F in patients and healthy controls are presented in the Supplementary Table available here. The distribution of the genotypic frequencies of these polymorphisms in controls was in HW equilibrium.

Multivariate analysis after adjustment for gender and the presence of the HLA-B27 marker revealed an independent effect of SpA susceptibility in the possession of such genotypes: TNF-308 GA/AA, IL17A GA/AA, and IL17F TC/CC, with an OR (95% CI) = 1.7 (1.1–2.5), 1.7 (1.2–2.6), and 4.5 (2.6–7.6), respectively (Table 3).

In patients with AS, there was a significant difference between TNF-308 GA/AA, IL17A GA/AA, and IL17F TC/CC genotypes, in the dominant model, independent of gender and HLA-B27 (Table 4).

Our analysis also showed the association between the PsA and TNF-238 GA/AA, IL17A GA/AA, and IL17F TC/CC genotypes, in the dominant model, regardless of both gender and HLA-B27 marker (Table 5).

In addition, there were statistical differences in haplotype distribution between patients and controls, independent of HLA-B27, for developing SpA, AS, and PsA if the patient possesses the haplotypes TNF-308/IL17A/IL17F GGC, GAC, and AAT (Table 6).
Table 1: Primer sequences, conditions, restriction enzymes, and size fragments.

| TNF and IL17 SNPs | Primer sequences | Conditions | Restriction enzymes | Size fragments |
|------------------|------------------|------------|--------------------|---------------|
| TNF-238 (rs361525) | 5-ATCTGGAGGAAGCGGTAGTG-3 5-AGAAGACCCCCCTCGGAACC-3 | 94°C—5 min 94°C—1 min 67°C—1 min 5x 72°C—1 min | MspI | 107 pb |
| TNF-308 (rs1800629) | 5-AGGCAATAGGTTTGTAGGAGGCCAT-3 5-TCCCTCCTGTCCGATCGATTGG-3 | 94°C—1 min 133°C—1 min | 35x | 133 + 19 pb |
| IL17A-G197A (rs2275913) | 5-AACAAGGTTAAGTAAAAGAGGAC-3 5-CCCCCAATGAGGTCATAGAAGAATC-3 | 94°C—1 min 102°C—30 s 60°C—45 s 35x | EcoRI | 68 + 34 pb |
| IL17F-T7488C (rs763780) | 5-ACCAAGGCTGCTCTGTTTCT-3 5-GGTAAGGAGTGGCATATTCTCA-3 | 96°C—1 min 143°C—1 min | NlaIII | 143 pb |

Table 2: Baseline characteristics of patients and healthy volunteers (controls).

|                          | SpA (N = 243) | AS (N = 174) | PsA (N = 67) | Controls (N = 210) |
|--------------------------|---------------|--------------|--------------|---------------------|
| Mean age (SD) years      | 47 (±15.7)    | 45 (±15.3)   | 51 (±16.1)   | 40 (±2.7)           |
| Gender, males [n (%)]    | 109 (44.9)    | 81 (46.6)    | 28 (41.8)    | 92 (43.8)           |
| Gender, females [n (%)]  | 134 (55.2)    | 93 (53.6)    | 39 (58.2)    | 118 (56.2)          |
| HLA-B *27 positive [n (%)] | 89 (36.6)⁴    | 71 (40.8)⁵    | 18 (26.9)⁶    | 32 (15.2)³⁴⁵       |

SpA: spondyloarthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis. Statistical analysis was performed by chi-square distribution table using OpenEpi 3.01 software: ⁴P < 0.001, OR (95% CI) = 3.2 (2.0–5.0). ⁵P < 0.001, OR (95% CI) = 8.3 (5.1–13.4). ⁶P < 0.03, OR (95% CI) = 2.0 (1.1–4.0).
4. Discussion

In this study, we investigated the association of genetic polymorphisms relative to TNF-α, IL17A, and IL17F cytokines, of particular interest in the inflammation seen in SpA [5], with the development of the disease and its clinical forms (AS and PsA) in a mixed Brazilian population. The results point genotypes and alleles of TNF-238, TNF-308, IL17A, and IL17F as risk factors for these diseases.

Accumulating evidence has demonstrated that HLA-B27 is strongly related to SpA inducing immune inflammatory responses, especially in AS patients [4–6]. In our current study, we confirmed these findings for SpA (36.2%), AS (59.8%), and PsA (26.9%) versus controls (15.7%).

Recently, a meta-analysis suggested a positive association between HLA-B27 and sex (male) in AS patients [4]. Then, we evaluated the risk of the inflammatory cytokine gene polymorphisms on the development of SpA, AS, and PsA diseases, considering the gender and the presence of the HLA-B27 marker.

In our current study, we found TNF and IL17 genotypes associated with these diseases, independent of these factors, which could provide more powerful evidence of association between these polymorphisms and SpA, AS, and PsA susceptibility.

In numerous studies, TNF-308 and TNF-238 polymorphisms were considered to be factors involved in SpA pathogenesis, although other groups failed to confirm this theory.

**Table 3: Association of TNF-308, IL17A, and IL17F with the risk of spondyloarthritis, stratified by gender and HLA-B27 marker.**

| Gene (SNP) | Allele genotypes | SpA (N = 243) [n (%)] | Controls (N = 210) [n (%)] | P value | OR (95% CI) |
|------------|------------------|------------------------|-----------------------------|---------|--------------|
| TNF-308 (rs1800629) | G/G 144 (59.3) | 150 (71.4) | | | |
| | G/A 95 (39.1) | 58 (27.6) | | | |
| | A/A 4 (1.6) | 2 (1.0) | | | |
| | G/A + A/A 99 (40.7) | 60 (28.6) | 0.01 | 1.7 (1.1–2.5) | |
| IL17A (rs2275913) | G/G 114 (46.9) | 123 (58.6) | | | |
| | G/A 102 (42.0) | 71 (33.8) | | | |
| | A/A 27 (11.1) | 16 (7.6) | | | |
| | G/A + A/A 129 (53.1) | 87 (41.4) | 0.005 | 1.7 (1.2–2.6) | |
| IL17F (rs763780) | T/T 161 (66.5) | 188 (90.0) | | | |
| | T/C 76 (31.4) | 20 (9.6) | | | |
| | C/C 5 (2.1) | 1 (0.5) | | | |
| | T/C + C/C 81 (33.5) | 21 (10.1) | <0.001 | 4.5 (2.6–7.6) | |

SNP: single-nucleotide polymorphism; SpA: spondyloarthritis; OR: odds ratio; CI: confidence interval. 1Statistical analysis was performed by SNPStats software based on a statistical dominant model.

**Table 4: Association of TNF-308, IL17A, and IL17F with the risk of AS, stratified by gender and HLA-B27 marker.**

| Gene (SNP) | Allele genotypes | AS (N = 172) [n (%)] | Controls (N = 210) [n (%)] | P value | OR (95% CI) |
|------------|------------------|------------------------|-----------------------------|---------|--------------|
| TNF-308 (rs1800629) | G/G 95 (55.2) | 150 (71.4) | | | |
| | G/A 74 (43.0) | 58 (27.6) | | | |
| | A/A 3 (1.7) | 2 (1.0) | | | |
| | G/A + A/A 77 (44.8) | 60 (28.6) | 0.004 | 1.9 (1.2–3.0) | |
| IL17A (rs2275913) | G/G 81 (47.1) | 123 (58.6) | | | |
| | G/A 74 (43.0) | 71 (33.8) | | | |
| | A/A 17 (9.9) | 16 (7.6) | | | |
| | G/A + A/A 91 (52.9) | 87 (41.4) | 0.01 | 1.7 (1.1–2.6) | |
| IL17F (rs763780) | T/T 119 (66.6) | 188 (90.0) | | | |
| | T/C 48 (28.1) | 20 (9.6) | | | |
| | C/C 4 (2.3) | 1 (0.5) | | | |
| | T/C + C/C 52 (30.4) | 21 (10.1) | <0.001 | 3.7 (2.1–6.6) | |

SNP: single-nucleotide polymorphism; AS: ankylosing spondylitis; OR: odds ratio; CI: confidence interval. 1Statistical analysis was performed by SNPStats software based on a statistical dominant model.
Table 5: Association of TNF-238, IL17A, and IL17F with the risk of PsA, stratified by gender and HLA-B27 marker.

| Gene (SNP)       | Allele genotypes | PsA (N = 67) [n (%)] | Controls (N = 210) [n (%)] | P value | OR (95% CI) |
|------------------|------------------|----------------------|-----------------------------|---------|-------------|
| TNF-238 (rs361525) | G/G              | 50 (74.6)            | 181 (86.2)                  |         |             |
|                  | G/A              | 16 (23.9)            | 28 (13.3)                   |         |             |
|                  | A/A              | 1 (1.5)              | 1 (0.5)                     |         |             |
|                  | G/A + A/A        | 17 (25.4)            | 29 (13.8)                   | 0.02    | 2.3 (1.1–4.5) |
| IL17A (rs2275913) | G/G              | (N = 67)             | 123 (58.6)                  |         |             |
|                  | G/A              | 30 (44.8)            | 27 (14.0)                   |         |             |
|                  | A/A              | 27 (40.3)            | 71 (33.8)                   |         |             |
|                  | G/A + A/A        | 37 (55.2)            | 87 (41.4)                   | 0.02    | 1.9 (1.1–3.4) |
| IL17F (rs763780) | T/T              | (N = 67)             | 188 (90.0)                  |         |             |
|                  | T/C              | 40 (59.7)            | 20 (9.6)                    |         |             |
|                  | C/C              | 26 (38.8)            | 16 (7.6)                    |         |             |
|                  | T/C + C/C        | 1 (1.5)              | 1 (0.5)                     |         |             |

Table 6: Distribution of TNF-308/IL17A/IL17F haplotypes in individuals with SpA, AS, and PsA (interaction analysis with gender covariate).

| Haplotype      | SpA (OR CI 95%) | AS (OR CI 95%) | PsA (OR CI 95%) |
|----------------|-----------------|---------------|-----------------|
| TNF-308/IL17A/IL17F |               |               |                 |
| GGC            | 3.9 (1.7–9.0)   | 2.5 (1.1–5.7) | 7.0 (2.8–17.7)  |
| GAC            | 5.0 (2.1–12.0)  | 4.1 (1.6–10.3)| 5.5 (1.4–22.1)  |
| AAT            | 4.2 (1.6–11.3)  | 4.4 (1.5–13.1)| 5.2 (1.1–23.7)  |

Potential reasons for this disagreement are the different ethnicities of the populations studied, the low number of patients and controls, the lack of pairwise criteria in the control group, and the noncompliance with other risk factors. Hence, in this study, care was taken with the pairing of patients and controls, regarding age, sex, and ethnicity. The control group included individuals of the minimum age at which disease develops and with the same proportion of men and women, since some forms of the disease may be more common in a specific gender. To minimize stratification errors due to differences in allelic frequencies in different ethnic groups, only patients and controls belonging to the mixed ethnic groups (descendants of immigrant Europeans, native Amerindians, and Africans) were included.

In TNF, IL17A, and IL17F genes, mapped on the same chromosome at position 6p12, several polymorphic sites, including microsatellites and promoter polymorphisms, have been detected, which may influence the expression of TNF-α, IL17A, and IL17F. The substitution of G for A at the −308 position of the TNF gene promoter leads to increased production of TNF-α, whereas the substitution of G by A at position −238 results in decreased expression [24–26]. Previous studies also show that genetic polymorphisms of IL17A G197A and IL17F T7488C affect the production of IL17A and IL17F, respectively [27, 28].

Our analysis showed that the TNF-308 GA/AA genotype was associated with the development of overall SpA and AS, independent of gender and HLA-B27 allelic group. This finding is in agreement with that of Höhler et al. who demonstrated an association of the TNF-308 A/A genotype with AS in German patients [29] and that of Romero-Sánchez et al. who showed that the A allele frequency of TNF-308 was increased in Columbian patients with SpA, AS, and rheumatoid arthritis [30]. This suggests that TNF-308A could be a susceptibility factor for this disease.

We have also found an association between the TNF-238 GA/AA genotypes and PsA in concordance to Rahman et al. [31] who examined the association between the TNF promoter gene polymorphisms and psoriatic arthritis in two well-characterized Canadian populations with the disease and carried out a meta-analysis of all TNF association studies in white populations with psoriatic arthritis.

However, a meta-analysis of 2247 Korean patients with AS showed no association of TNF-308 AA and AA/AG or TNF-238 A/G polymorphisms with the disease [23]. One hypothesis for this disagreement would be the ethnic admixture found among populations, since our study did not include Asian descendants.

In addition, we observed a higher risk of SpA in patients carrying the IL17A A/G genotype and A allele and the IL17F T/C genotype and C allele. To the best of our knowledge, an association of these genetic polymorphisms with SpA has not yet been described. Our group already reported that the AA genotype and A allele for IL17A were associated with susceptibility to chronic periodontitis in South Brazil, highlighting their involvement in a chronic inflammatory condition [18]. A weak association between rheumatoid arthritis and the promoter IL17A rs2275913 was found in the Norwegian population and more recently in the Brazilian population [7, 32]. Specifically, with the risk of AS and its severity, a...
strong association was observed with the rs4819554 SNP in the promoter region of IL17RA in two Spanish cohorts of patients and controls, but not involving the IL17A and IL17F polymorphisms that we have studied here [33]. Therefore, in patients of Northern Italy, IL17A and IL17RA gene allelic variants were not associated with PsA susceptibility [34].

In a study of 371 patients, Baeten et al. showed that treatment with anti-IL17 medication in both subcutaneous and intravenous forms led to an improvement in the clinical picture [35]. This provided evidence for the role of increased IL17 production in disease development. In another study, Berg and McInnes also demonstrated a good therapeutic response in 606 PsA patients treated with anti-IL17 medication [36]. The recent use of this inhibitor led to a significant and sustained reduction in the signs and symptoms of PsA, avoiding radiological progression and thereby improving patients’ quality of life [37].

Relevant result of this study was establishing risks to the development of SpA, AS, and PsA, related to the haplotype that the individual possesses for these cytokine SNPs on chromosome 6, regardless of HLA-B27. The risks were higher in patients with the haplotypes TNF-308/IL17A/IL17F GGC/GAC/AAT for SpA and AS and TNF-238/IL17A/IL17F GGC/GAC/AAT for PsA than in those who did not have. We may suggest that in the presence of the C allele for IL17F, the A allele for TNF-308 and IL17A is not required for a positive association with the diseases. However, if the A allele is present for both, the C allele for IL17F is not needed.

Previous findings have suggested IL17 and TNF haplotypes involved in the risk of developing obstructive coronary artery disease [38, 39], which has been reported in patients with SpA [40]. This could explain our findings involving cytokine gene polymorphisms associated with inflammatory responses observed in these patients suffering from rheumatic diseases.

Finally, these observations should be interpreted with caution due to limitations found in this study, such as the relatively small sample size and the fact that only the TNF and IL17 genes were considered in this study. Moreover, we did not evaluate the possibility of interactions between these genes and other genetic risk factors, beyond the gender and HLA-B27, known to interfere in the development of SpA.

5. Conclusion

In conclusion, in this mixed Brazilian population, TNF-308, IL17A, and IL17F gene polymorphisms were associated with SpA and AS, while TNF-238, IL17A, and IL17F gene polymorphisms were associated with PsA, regardless of gender and HLA-B27. The elucidation of the role of these biological markers together with the HLA-B27 marker, in the development of inflammatory diseases, in larger series of subjects, could provide the early diagnosis and treatment of the different clinical forms of this disease.

Conflicts of Interest

The authors state no conflict of interest.

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Supplementary Materials

Supplementary Table: genotype and allele frequencies of TNF-238, TNF-308, IL17A, and IL17F in patients with SpA, AS, and PsA and in controls are shown in this material. (Supplementary Materials)

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Mediators of Inflammation

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