Haplotypes of the IL10 Gene as Potential Protection Factors in Leprosy Patients

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Leprosy is an infectious disease caused by Mycobacterium leprae characterized by dermatoneurological signs and symptoms that has a large number of new cases worldwide. Several studies have associated interleukin 10 with susceptibility/resistance to several diseases. We investigated haplotypes formed by three single nucleotide polymorphisms (SNPs) located in the IL10 gene (A-1082G, C-819T, and C-592A) in order to better understand the susceptibility to and severity of leprosy in an admixed northern Brazil population, taking into account estimates of interethnic admixture. We observed the genotypes ACC/ACC (P = 0.021, odds ratio [OR] [95% confidence interval (CI)] = 0.290 [0.085 to 0.823]) and ACC/GCC (P = 0.003, OR [95% CI] = 0.220 [0.504 to 0.040]) presenting significant results for protection against leprosy development, framed in the profiles of low and medium interleukin production, respectively. Therefore, we suggest that genotypes A-1082G, C-819T, and C-592A formed by interleukin-10 polymorphisms are closely related to protection of the leprosy development in an admixed northern Brazil population, in particular ACC/ACC and ACC/GCC genotypes.

Leprosy is a contagious infectious disease caused by Mycobacterium leprae that affects mostly macrophages and Schwann cells in peripheral nerves, comprising two forms, tuberculoid (TT) and lepromatous (LL), with three intermediate forms (borderline-tuberculoid [BT], borderline-borderline [BB], and borderline-lepromatous [BL]). Multibacillary (MB) leprosy includes the BB, BL, and LL forms, while paucibacillary (PB) leprosy encompasses the TT and BT forms (1).

The degree to which the disease manifests greatly depends on the balance between Th1 (inflammatory) and Th2 (anti-inflammatory) during the immune response. This balance consists of a network of stimuli that includes macrophages, dendritic cells, leukocytes, natural killer (NK) cells, and inflammatory cytokines such as interleukin 1 (IL-1), IL-5, gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-α), and IL-12 and anti-inflammatory cytokines such as IL-4 and IL-10. Within the anti-inflammatory immunological profile, IL-4 (genic region 5q31.1) and IL-10 (genic region 1q31-q32) stand out, since these interleukins suppress macrophage activity. IL-10 blocks production of inflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-12, and TNF-α, which reduce TCD4⁺ proliferation, directing the immunologic response toward antibody production; this may cause the inability of the host to remove the M. leprae infection (2–4).

Many publications correlate the genetic variability of the host with its susceptibility to developing leprosy (4–10). Specifically, for the IL10 gene, different pathologies have shown an association with the single nucleotide polymorphisms (SNPs) A-1082G, C-819T, and C-592A (11–16). Malhotra et al. suggested that leprosy resistance in the Indian population was associated with a haplotype in the IL10 promoter region (11). Ates et al. reported the ACC haplotype (−1082, −819, and −592) as a resistance factor for tuberculosis in the Turkish population (12). Other studies used the same markers to associate susceptibility or resistance in viral disease (13, 14) and gastrointestinal disorders (15, 16).

Furthermore, differences observed in human populations appear to be important for proper interpretation of these association study results (17, 18). Therefore, genomic ancestry controls in association studies using ancestry informative markers (AIMs), especially in populations with a high degree of interethnic mixing, should be performed (19). Within this context, haplotypes formed by three SNPs of the IL10 gene (A-1082G, C-819T, and C-592A) were investigated to better understand the mechanism of susceptibility and protection involving the ability to combat bacillary growth and leprosy development in a mixed Brazilian population.

MATERIALS AND METHODS

Cases and controls. The subjects were 138 leprosy patients who attended the Dr. Marcello Candia Reference Unit in the Sanitary Dermatology center of the State of Pará (UREMC) in Marituba (Pará, Brazil). Those patients were grouped into paucibacillary (TT and BT; PB = 30) and multibacillary (BL and LL; MB = 108) groups. In UREMC, there are around 40,000 consultations per year in different medical specialties such as leprology, dermatology, ophthalmology, and orthopedics, besides nursing, physical therapy, and other health professional sessions. Since 2002, UREMC has registered between 308 and 472 leprosy patients per year (average, 408 cases per year). The control sample was composed of 162 unrelated individuals, without leprosy or any other chronic disease, from the same geographic area.
TABLE 1 Clinical and demographic variables for leprosy cases in the comparison between control, multibacillary, and paucibacillary groups

| Variable                        | Case (n = 138) | Control (n = 162) | Multibacillary (n = 108) | Paucibacillary (n = 30) | P\(^d\) |
|---------------------------------|---------------|-------------------|--------------------------|------------------------|--------|
| Gender (no. male/no. female)\(^a\) | 92/46         | 62/100            | 78/30                    | 14/16                  | 0.002  |
| Age (yr)\(^b\)                  | 43.35 ± 1.83  | 38.39 ± 1.64      | 45.73 ± 2.15             | 34.77 ± 2.77           | 0.002  |
| African ethnicity frequency\(^c\) | 0.304        | 0.266             | <0.001                   | 0.270                  | 0.749  |
| European ethnicity frequency\(^c\) | 0.407        | 0.405             | 0.998                    | 0.450                  | 0.479  |
| Amerindian ethnicity frequency\(^c\) | 0.288        | 0.328             | <0.001                   | 0.280                  | 0.951  |

\(^a\) Significance determined by Fisher’s exact test.

\(^b\) Significance determined by Student’s t test.

\(^c\) Significance determined by Mann-Whitney test.

\(^d\) Values in bold indicate variables that statistically significantly differ.

**Ethical aspects.** The project was approved by the Research Ethics Committee of the Universidade Federal do Pará (UFPA; approval no. 197/07).

**Collection of samples, DNA extraction, and quantification.** From each individual was collected 5 ml of peripheral blood with the anticoagulant EDTA. The DNA was extracted using the phenol-chloroform method as in the work of Sambrook et al. (20) and quantified with a NanoDrop1000 spectrophotometer (Thermo Scientific NanoDrop 1000; NanoDrop Technologies, Wilmington, DE).

**Analysis of polymorphisms.** The analyses applied real-time PCR with TaqMan probes conducted in a 7500 Real-Time PCR system (Life Technologies, CA, USA). The genotyping PCR of all three polymorphisms (A-1082G rs1800896, C-819T rs1800871, and C-592A rs1800872) was performed with 3.5 l of Master Mix, 0.175 l of DNA. The final mix was amplified with the following program: 10 min at 95°C, 40 cycles of 15 s at 92°C, and 1 min at 60°C.

**Analysis of genetic ancestry.** The ancestry analysis was performed as in the work of Santos et al. (19) using a panel of 48 autosomal ancestry informative markers (AIMs). Three multiplex PCRs were performed, each with 16 markers, followed by electrophoresis on ABI-Prism 3130 sequencer and analysis using GeneMapper ID v.3.2 (Life Technologies, CA, USA). The individual proportions of European, African, and Amerindian genetic ancestry were estimated using STRUCTURE software 2.3.3, assuming three parental populations (Europeans, Africans, and Amerindians), and using 200,000 runs for the burn-in period and 200,000 Markov chain Monte Carlo repetitions after burning (21–24).

**Statistical analysis.** Linkage disequilibrium (LD; \(r^2\) and \(D^\prime\) statistics) was analyzed by Arlequin software v.3.1 (25). PHASE v.2.1.1 software (26–28) was applied to obtain the haplotype frequencies. The chi-square test (\(\chi^2\)) and Fisher’s exact test were used to compare the categorical variables (gender), while comparisons of the quantitative variables (age) were evaluated using Student’s t test, and comparisons of the ancestry estimates, between cases and controls and between multibacillary (MB) and paucibacillary (PB) subjects, were evaluated using the Mann-Whitney test.

The association of haplotypes in the IL10 gene was tested by multiple logistic regression controlling for different variables (gender, age, and ethnicity), between leprosy patients and control individuals, as well as multibacillary (MB) versus paucibacillary (PB) patients. Statistical significance was defined as a two-tailed \(P\) value of \(\leq 0.05\). All of the evaluations were made using the commercial software SPSS v18. The association between leprosy cases and controls, adjusted for population stratification, was performed using the STRAT software with 100,000 simulations (22). STRAT software utilizes the STRUCTURE output to test for association in the presence of population stratification based on individual ancestry information.

**RESULTS**

One hundred thirty-eight leprosy patients (108 MB and 30 PB) and 162 control individuals were analyzed. Table 1 shows the clinical and demographic variables. The average age was 43.35 ± 1.83 years for the cases and 38.39 ± 1.64 years for the controls. The average age among the individuals with multibacillary leprosy was 45.73 ± 2.15 years, whereas the average age for individuals with paucibacillary leprosy was 34.77 ± 2.77 years.

The male gender was predominant in the case group, while the majority of the control group was female. Among the multibacillary and paucibacillary patients, there were predominances of males and females, respectively.

From the standpoint of genomic ancestry, it was observed that the ethnic composition of the case group was 30.4% African,
40.7% European, and 28.8% Amerindian, while in the control group, the composition was 26.6% African, 40.5% European, and 32.8% Amerindian. Among the multibacillary patients, 27% were of African ancestry, 45% of European ancestry, and 28% of Amerindian ancestry. The paucibacillary patients were 28% African, 46% European, and 26% Amerindian. Figure 1 shows the individual estimates of the interethnic mixture between cases and controls and between multibacillary and paucibacillary leprosy.

The results showed significant differences when the cases were compared against controls in relation to the following clinical and demographic variables: gender (P = 0.002), age (P = 0.044), African ethnicity (P < 0.001), and Amerindian ethnicity (P < 0.001) (Table 1). In comparative analyses between multibacillary and paucibacillary leprosy, only gender (P = 0.015) and age (P = 0.002) were found to be significant (Table 1).

Linkage disequilibrium was found for the SNPs A-1082G, C-819T, and C-592A of the IL10 gene (r² = 0.5407, P < 0.001, and D’ = 1.000, P < 0.001). A total of four haplotypes were observed: ATA, ACC, GCA, and GCC. The most frequent haplotypes were (i) −1082A/−819T/−592A (ATA) for the cases (multibacillary and paucibacillary) and (ii) −1082A/−819C/−592C (ACC) among the controls (see Table S1 in the supplemental material). There was no statistical significance for the multiple logistic regression analyses after adjustment for gender, age, and ethnicity among cases versus controls or among multibacillary versus paucibacillary patients (Table 2).

**Table 3** summarizes the distribution of the genotypes and IL10 production profiles with their respective frequencies and multiple logistic regression analyses. Significance was not established for the case-versus-control analyses nor for paucibacillary versus multibacillary leprosy for the haplotype sets ATA/ATA, ATA/ACC, ATA/GCA, ATA/GCC, ACC/GCA, GCA/GCC, and GCC/GCC.

The haplotype genotype ACC/ACC showed significant protective results against the development of leprosy (P = 0.021; odds ratio [OR] [95% confidence interval (CI)] = 0.290 [0.085 to 0.823]). This genotype was observed in the low-production profile of IL-10. The genotype ACC/GCC (P = 0.003; OR [95% CI] = 0.220 [0.504 to 0.040]) was also found to be a significant protective factor against the development of the disease. This genotype is distributed in the medium-production profile of IL-10.

**DISCUSSION**

The present study used a panel of 48 AIMs that are capable of precisely distinguishing, with low statistical error and cost, the genetic contributions of Africans, Europeans, and Amerindians to a mixed population (19). This control was important for consolidating the analyses of the susceptibility to and severity of leprosy in relation to IL10.

The data on ancestry showed a significantly different contribution (P < 0.001) between cases (leprosy patients) and controls, in relation to African ethnicity (30.4% versus 26.6%) and Amerindian ethnicity (28.8% versus 32.8%). These results suggest a loss of

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**TABLE 2** Analysis of haplotype frequencies by multiple logistic regression in case versus control and multibacillary versus paucibacillary groups

| SNP       | Frequency of haplotypes | Frequency of haplotypes                                      |
|-----------|-------------------------|-------------------------------------------------------------|
|           | Case        | Control       | OR (95% CI) |
| A-1082G   | C-819T      | C-592A        |             |
| A         | T           | A             | 0.340       | 0.269       | 0.634       | 1.179 (0.599–2.322) | 0.352       | 0.217       | 0.679       | 1.201 (0.564–2.866) |
| A         | C           | C             | 0.246       | 0.363       | 0.279       | 0.689 (0.351–1.352) | 0.250       | 0.183       | 0.293       | 0.631 (0.267–1.489) |
| G         | C           | A             | 0.105       | 0.010       | 0.642       |               | 0.111       | 0.133       | 0.713       | 0.830 (0.308–2.237) |
| G         | C           | C             | 0.262       | 0.266       | 0.271       | 0.681 (0.344–1.349) | 0.264       | 0.200       | 0.177       | 1.860 (0.755–4.580) |

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**TABLE 3** Analysis of haplotype and genotype profiles for the production of IL10 in case versus control groups and multibacillary versus paucibacillary groups by multiple logistic regression

| Genotype | Case | Control | P* | P STRAT | OR (95% CI) |
|----------|------|---------|----|---------|-------------|
| Low production | 57 (41.3) | 70 (50.7) | 0.412 | 0.752 (0.380–1.486) |
| ATA/ATA  | 16 (11.6) | 14 (10.1) | 0.647 | 0.789 (0.287–2.172) |
| ATA/ACC  | 27 (19.8) | 35 (25.4) | 0.749 | 1.153 (0.480–2.770) |
| ACC/GCA  | 7 (5.1) | 21 (15.2) | 0.021 | 0.290 (0.085–0.823) |
| Avg production | 59 (42.8) | 55 (39.8) | 0.999 | 0.996 (0.504–1.968) |
| ATA/GCA  | 1 (7.0) | 0 (0.0) | 0.792 | 1 (9.0) |
| ATA/GCC  | 32 (23.2) | 25 (18.1) | 0.691 | 1.181 (0.519–2.688) |
| ACC/GCA  | 15 (10.9) | 0 (0.0) | 0.650 | 1 (9.3) |
| ACC/GCC  | 9 (6.5) | 30 (21.7) | 0.003 | 1.33E+06 |
| High production | 22 (15.9) | 13 (9.5) | 0.227 | 1.871 (0.677–5.167) |
| GCA/GCC  | 16 (11.6) | 1 (0.7) | 0.640 | 13 (12.0) |
| GCC/GCC  | 6 (4.3) | 12 (8.8) | 0.128 | 0.367 (0.101–1.333) |

**Note:** Multiple logistic regression adjusted for the independent variables age and gender.
contribution from Amerindian genes and an increased contribution from African-ancestry genes in the case group compared to the estimates found for the control population of northern Brazil (19).

The variability in haplotypes of IL10 associated with leprosy in different ethnic groups can be explained by genetic ancestry of the populations, since the African population shows a more widespread distribution of IL10 haplotypes, and so acquires a higher susceptibility to leprosy, than the Caucasian and Asian populations (29). Therefore, our hypothesis of a correlation between genetic factors and susceptibility suggests that an increased African component in the ancestry of leprosy patients indicates a high frequency of genes that influence host susceptibility for disease.

Pereira et al. (30) and Zeng et al. (31) found that the polymorphisms A-1082G, C-819T, and C-592A of the IL10 gene were in linkage disequilibrium. The combined analysis showed the formation of seven haplotypes, of which ATA, ACC, and GCC had been previously identified in leprosy patients by Franceschi et al. (9).

Trajkov et al. (32) found the haplotype ATC to have a positive association with an individual’s susceptibility to tuberculosis, while the other haplotypes were observed only in the study of diseases not related to leprosy, such as the GTA haplotype, found by Wu et al. (33), in healthy individuals susceptible to silicosis; ACA, which was observed by Lung et al. (34) to be associated with schizophrenia; and GCA, in studies on peripheral arterial disease (35) and diabetes (36). In the present study, no significant difference was found for the haplotypes ACC and GCC despite their high frequency (Table 2), as previously suggested by Ates et al. (12).

The literature shows a strong correlation of the allele −1082G with the overexpression of IL10; on the other hand, the allele −1082A was associated with the low expression of IL10. For example, the genotype −1082GG confers overexpression of IL10, while the −1082GA and −1082AA genotypes confer intermediate and low expression of IL10, respectively (31, 37–39). According to the work of Foss (40), IL10 shifts the immune response for production of antibodies; thus, the lower the IL10 production, the higher the inflammatory cell response that protects against leprosy. In the present study, the ACC/ACC and ACC/GCC sets of haplotypes (low production and average production of IL10, respectively) provided significant protection against the development of the pathology.

Because ancestry proportions differ between leprosy patients and controls (Table 1), the association between sets of haplotypes, chosen from the multiple logistic regression analyses, was performed using the STRAT software (Table 3) (41). After population structure correction, the ACC/ACC set (P = 0.021; $P_{STRAT} = 0.002; OR [95% CI] = 0.290 [0.085 to 0.823]) and the ACC/GCC set (P = 0.003; $P_{STRAT} = 1.30E-5; OR [95% CI] = 0.220 [0.504 to 0.040]) show significant associations with protection against the development of leprosy. These results are consistent with the work of Chaves and Rodrigues (37) and Zeng et al. (31) in relation to the IL10 production profile. Therefore, these results suggest that the haplotypes formed by polymorphisms A-1082G, C-819T, and C-592A (haplotypes ACC/ACC and ACC/GCC) of IL10 are closely related and serve as a protective factor against leprosy in a mixed Brazilian population.

ACKNOWLEDGMENTS

Special thanks go to the donors of samples, who enabled this study to be carried out.

We thank also CNPQ (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FINEP (Financiadora de Estudos e Projetos—Ministério de Ciência e Tecnologia), PROPEP/UFPA (Universidade Federal do Pará), and FADESP (Fundação de Amparo e Desenvolvimento da Pesquisa).

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