Reviewer's report

Title: HLA-DR and HLA-DQ alleles in Southern Brazilian patients: markers for leprosy susceptibility and resistance.

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Reviewer: Milton O Moraes

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The paper entitled “HLA-DR and HLA-DQ alleles in Southern Brazilian patients: markers for leprosy susceptibility and resistance” by Silva et al describes the association of HLA DRB1, DQA1 and DQB1 alleles and clinical subtypes of leprosy corroborating previous findings and also describes the association with rare alleles such as DQB1*0606 in the Brazilian population.

The paper is a well designed although few patients and controls are enrolled. The paper is acceptable in the present form, however; at least power calculation of the sample size is necessary to improve the manuscript. In any case, experimental design is nice, although statistical analysis could also be improved and a few other points need clarification.

Major Issues

English needs revision

The major problem of the study is the number of patients and controls used because HLA is a multiallelic locus creating several categories with few patients. It is likely that some of the associations found are a result of type-I statistical error. Thus, it is encouraged that the authors increase the number of controls (at least) and also carry out power calculations to estimate the accuracy of the statistical analysis.

Authors failed to mention whether Ridley and Jopling was used to classify patients. What are the numbers of BL, BB, BT patients? It is unlikely that almost 30% of the patient population is TT. What criteria were used to distinguish TT from BT patients? Considering some new data in the literature (Alcais et al 2007, Nat Genet; Pereira et al 2008, Genes and Immun), statistical adjustments for age and sex could be performed. A better description of the recruited patients is suggested, especially considering ethnicity.

It is necessary that authors define whether they are testing HLA association with leprosy per se or with clinical subtypes. To test for association to leprosy per se, one would compare patients to controls, while to test for association with clinical subtypes one would have to stratify patients into their subgroups (lepromatous, tuberculoid and borderline) and compare between subgroups and to controls separately. Since authors compare either leprosy patients or subgroups of patients with controls it seems that they are assuming two different hypotheses of leprosy susceptibility. One deals with a susceptibility to the leprosy bacillus
irrespective of the clinical form they will develop later (leprosy per se). The other indicates that they are different diseases that develop independently. In my opinion these hypothesis are mutually exclusive. It is strongly suggested that authors use only leprosy per se as a comparison class. It will also help in the problem of classification of the patients and solve the problem of carrying out multiple comparisons (test patients as a group and later as another subgroup).

The authors should indicate if is there any genetic study of populations in the region (Southern Brazil) that helps understand admixture. If cases and controls were not matched ethnically a bias can be observed. This is crucial since among Brazilians DRB1*1602 is highly frequent in Amerindian ancestry population and DRB1*09 is frequent in African ancestry. It is supposed that the Southern Brazilian population is predominantly Caucasoid. The question remains: is there any correlation between morphological criteria (hair, skin, etc) and the presence of these alleles?

Alleles DQB1*0606 and DQB1*0504 (especially 0606) are rare alleles and few papers reported their frequency. Authors could confirm this finding using another typing method.

Minor issues
The first time the authors present results as numbers, they should include beforehand the type of data; for example (mean, +/- SD, 43, 28.2%).

The type of anticoagulant used to collect the blood samples wasn’t mentioned.

The full references of the PCR-SSP kit employed should be included in the description.

The full reference of the Arlequin software should be presented (the company or author’s name, issue date, country and city).

Authors should clarify what they called “patients per se”. I suppose that they refer to patients with leprosy independent of the clinical form.

Introduction, pg 3, third paragraph: “In located form and less severe Tuberculoid” the authors said located but I guess they mean localized. Also the sentence needs review. I suggest: “In localized and less severe form (tuberculoid).”

“cell immune response”: I suppose the authors meant cellular or cell-mediated.

Pc values should be included in the supplementary table.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

'I declare that I have no competing interests'