Reviewer’s report

Title: Association study of the HLA-DRB1 locus reveals the first evidence for the association of HLA-DRB1*15 and DRB1*09 with leprosy and the impact of DRB1*09 on the onset of disease in Chinese population

Version: 3 Date: 22 May 2009

Reviewer: Milton O Moraes

Reviewer’s report:

The second version of the paper “Association study of the HLA-DRB1 locus reveals the first evidence for the association of HLA-DRB1*15 and DRB1*09 with leprosy and the impact of DRB1*09 on the onset of disease in Chinese population” by Zhang et al is definitely improved after the modifications made by the authors. But some issues still need discussion.

A new table comparing clinical forms with leprosy is presented (table 3 2nd version). This is a specific request of other referee, and has been used for HLA associations with leprosy for a long time. The problem is that this type of comparison brings a question towards the model to understand genetic susceptibility of leprosy. Authors answered to reviewer #1 that in their opinion the two-step genetic susceptibility model is applied, (examples of this description can be seen in Mira et al (2004) and reviewed in Alcais (2005). In this model, in a first stage, genes could influence leprosy outcome per se. To test that, one needs to compare patients to controls. In the next stage, patients will develop a disseminated (LL) or a localized (TT) form of leprosy. Considering this model, it does not make sense to compare the two subgroups (MB and PB) separately with controls, which is presented in table 3. The way it is presented now it seems that authors 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 there are different diseases that develop independently. These hypothesis are contrasting and it could be solved by i) suppressing the table or ii) comparing PB vs MB.

Concerning age, the authors stated that “Answer: the analysis proposed by the reviewer is usually used for evaluating the effect of age on the genetic association of DNA polymorphisms, aiming to verify that the identified genetic association is not due to the ‘co-founding’ effect of age. In our case, we are interested in knowing whether the identified genetic risk allele plays any role in differential clinical presentation of the disease, age-onset in this case. We think that our method is appropriate for this purpose”. I did not understand the difference between a “genetic association is not due to the cofounding effect of age” and “the identification of genetic risk allele in differential clinical presentation”. The question is basically the same: if you stratify patients for age categories do you see the effect in younger or older people? I suggest that age and sex are used to adjust P-values in one comparison using logistic regression
or multivariate analysis.

Minor issues:
An English revision is still necessary
Some misspelling words needs correction for example: pg. 9- Competeing interest
Pg 6- PCR-SSOP-Liuminex

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
'I declare that I have no competing interests'