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: 2 Date: 10 March 2009

Reviewer: Marcelo Mira

Reviewer’s report:

The manuscript reports a population-based (case-control) candidate gene association study on leprosy phenotypes and the HLA-DRB1 locus. In general terms, the study is well designed and well conducted. The most interesting finding was positive evidence for age-dependent association between the HLA-DRB1*09 allele and leprosy.

However, upon careful reading of the manuscript, several issues have risen, as described below, that this reviewer kindly asks the authors to address:

1. Major compulsory revisions

1.1 The case group is strongly biased towards the male gender – almost the entire group is composed by males. The authors state that the control group was matched by gender. In this case, would it be more adequate to report association between leprosy and HLA-DRB1 alleles in a MALE leprosy population? Maybe the issue should be explored in the discussion, since gender is a well known independent risk factor for leprosy susceptibility;

1.2 The control group is composed by blood donors. How can the authors assure homogenous exposure of these individuals to M. leprae – or at least, the same level of exposure that the case group has been subjected to?

1.3 The authors mention the diagnostic criteria for leprosy but do not address what criteria were adopted to define clinical forms of disease - how did the authors defined a multibacillary and a paucibacillary case of leprosy?

1.4 Why did the authors use the Fisher’s exact test for such a large population sample? Usually this strategy for association analysis is applied to small sample sizes (which is not the case of this report) at a considerable cost in loss of power.

1.5 Did the authors test genotyping/allelic distribution for Hardy-Weinberg Equilibrium?

1.6 Due to the presence of extensive – and poorly understood – linkage disequilibrium across the HLA gene cluster, it is possible that the alleles reported in association with leprosy are in LD with other variants of the same locus. Particularly important would be to consider the possibility of LD between the HLD-DRB1 and the LTA-TNFA loci, given the interesting age effect reported, in accordance with what was recently reported for LTA variants and leprosy in three different populations. Did the authors test their finding, in particular the DRB1*09
age-dependent association, for independence from the LTA (or other HLA genes)?

2. Minor essential revisions

2.1 The third column of Table 1, describing the allele frequencies of HLA-DBR1 variants on the case group does not add up to 100%.

2.2 The manuscript will greatly benefit from major English revision, preventing mistakes such as, for example, "... Leprosy was once prevalent in the worldwide..." and "World Healthy Organization" (both on page 1) and several others detected throughout the text.

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

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:

'I declare that I have no competing interests'