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

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Reviewer: Dimitri S Monos

reviewer's report:

Major Compulsory Revisions

1. There is a fundamental issue that needs to be explained and justified. Two completely different forms of Leprosy can develop in the susceptible human host. On the one end of the spectrum is the tuberculoid form or paucibacillary leprosy; while on the other end is the lepromatous or multibacillary leprosy. These two forms representing different immune responses to the same Mycobacterium leprae most likely are characterized by two distinct mechanisms, the one eliciting an effective T-cell response (tuberculoid form), while the other is characterized by a different immune response that does not eliminate the mycobacterium, the disease is disseminating and progressive. In this study the authors pull all subjects of the two forms in one group, seeking HLA associations in this one group that includes patients with both forms. Any kind of identified association would pose a problem in terms of explaining what type of immune response is associated with the particular HLA polymorphism. Would be the effective immune response that eliminates the mycobacterium (tuberculoid) or would be a response that induces T regulatory cells and promotes non-responsiveness or no T-cell responses at all and therefore the lepromatous form? The authors will need to provide a good rational for their analysis; why they pull all samples together and if they do what is the meaning of their findings.

2. In the second phase of their analysis they split the two groups of Leprosy patients and compared the two groups against each other but not against the controls. The analysis will need to include these comparisons also. Data should be presented even if there are no associations at the typing level provided by Luminex.

3. The HLA typing has been performed by the Luminex technology that provides low to intermediate resolution typing. That means that the typing is not performed at the allelic level and therefore it is difficult with this kind of typing to look for associations at the amino acid level. However given earlier reports for the significance of positively charged residues (Arginine) in pocket 4 of the HLA DR molecule in tuberculoid leprosy (J. Exper. Med. 183: 829-836, 1996), the authors should try to examine as to whether some of the probes used in the Luminex platform react with sequences that would code for arginine in DRbeta 13, 70 or 71 positions. The authors can then evaluate the number of individuals that are reactive with these probes in each of the three groups (control, TL and LL) and
make the three comparisons between C and TL, control and LL and TL and LL. No corrections are required at this point as they specifically ask this particular question of differential frequencies of arginines in the different groups.

4. The authors are encouraged to examine their population and report not only allele frequencies but also the frequency of the individuals positive for the different HLA specificities. HLA and disease association studies are usually reporting frequencies of individuals positive for a particular specificity because HLA molecules are codominant and the functional unit in a disease is the patient, so makes sense to ask the question as to how many patients are positive for a particular HLA and compare it to the control group.

Minor Essential Revisions

5. The manuscript needs editing to improve the English. The name of the technology is Luminex not Liuminex. The total number of patients is 305 not 315 as mentioned in the “Statistical Analysis” section.

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

**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