Author's response to reviews

Title: HLA-DR and HLA-DQ alleles in patients from the south of Brazil: markers for leprosy susceptibility and resistance

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Author's response to reviews: see over
COVERING LETTER

BMC Infectious Diseases

Subject: Resubmission of manuscript (original paper)

June 20, 2009

Dear Editor:

We would like to resubmit the following manuscript for possible publication:

HLA-DR and HLA-DQ alleles in Southern Brazilian patients: markers for leprosy susceptibility and resistance.
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Point-by-point response to the concerns:

- We affirm that the manuscript has been revised according to editor and reviewer comments and to journal style.

- Reviewer 1:
This manuscript require the Major Compulsory Revisions before the acceptation.
1. Regarding the Abstract section:
   • Page 2, lines 20-22: The Authors should be supplemented the Results section with the significant DQ frequency values before Bonferroni correction.
   • Page 2, line 22-24: The Authors have rewritten the Conclusion section: the Authors should be supplement with association particular stages of Leprosy with particular HLA-DR16 alleles.

Answer: In abstract: The Results section was supplemented with the significant DQ frequency values before Bonferroni correction. The Conclusion section was modified
according to referee. According to referee 2, there was modification between the
groups that were compared.

2. Regarding the Methods section:
• The Authors should be supplement this section with information concerning
  number of heterozygotes or homozygotes.
• In my opinion, the Authors should be multiply p value by number of tested loci
  inside each locusi, not all loci.
**Answer:** There were not homozygotes for significant results. We multiplied p value
  by number of tested loci.

3. Regarding the Results section:
• In my opinion, the Authors should be add the subtitles.
• What a connection the current results with a new classification of subgroups of
  leprosy?
**Answer:** Subtitles were added. There is not connection the current results with a
  new classification of subgroups of leprosy.

4. Regarding the Discussion section:
• Page 9, lines 13-18: Are these results the Author’s or Rani et al. ?
• Page 9, lines 30-32: The Authors should be connect the linkage disequilibrium
  with obtained results.
**Answer:** Discussion section was modified.

5. Regarding the Conclusion:
• The Authors have rewritten the Conclusion section: the Authors should be
  supplement with association particular stages of Leprosy with particular
  HLA-DR16 alleles.
**Answer:** Conclusion was modified.

6. Regarding the Tables:
• Tables 1-3 should be significantly rewritten: In my opinion the Authors should
  be introduce the frequency of all tested alleles: n, %, p with only marked
  significant pc values in all tested subgroups and marked significant OR and CI
  values. Once more, I also suggest that main headline inside Table 3 is wrong. In
  the Legend of Table 3 is marked pc>0.05????should be marked only significant
  pc<0.05!!!
**Answer:** Suggestions were accepted.

7. Regarding the English:
• The manuscript requires language improvements. The Authors very often used
  sign”;” before however in the manuscript.
**Answer:** The manuscript was reviewed by a native from England: Peter Grimshaw.

Reviewer 2:
1. The authors in the introduction stated that “WHO classifies leprosy patients into
   three groups. Patients presenting a single skin lesion are classified as
single-lesion paucibacillary cases, all cases presenting five or fewer skin lesions are classified as paucibacillary leprosy (PB) and patients presenting six or more skin lesions plus detectable M. leprae are classified as multibacillary (MB) cases.”

I guess that WHO does not use, for treatment purposes, the detection of M. leprae in MB patients. Only skin lesions are used. Also for treatment, WHO does not distinguish single lesions or PB patients. A reference needs to be added and amendments (if any) need to be made:

Answer: We agree. This section was rewritten.

2) One of the points raised in the first review concerned classification of patients. Now, it is clear by the authors’ answer that they do not use R&J classification since they do not have BT, BB, and BL patients. Although this classification (probably Madrid) does not impact drastically the results, it is strongly suggest a careful revision of patients classification in view of R&J. It is necessary to further compare the results with other papers published in the literature not only for this paper but also for other data generated with these DNA samples.

Answer: Suggestions were accepted.

3) Also, authors failed to support evidences of why they choose to compare LL vs TT; LL vs controls; TT vs controls and controls vs patients. It is important to notice that all these comparisons introduce bias and needs an extra level of Bonferroni correction in a way that all P values needed to be correct with increased stringency. Thus, it would be easier to compare only PB vs MB patients (because this includes the large proportion of borderline patients) and controls vs. patients. If authors choose to maintain the analyses as it is, they need to present P-corrected for extra comparisons. Authors should state in the introduction or in the discussion their hypothesis of leprosy resistance and susceptibility to support their choice of comparisons.

Answer: We agree. We have compared Leprosy per se with controls and LL vs. TT. According to referee 1, we have multiplied p value by number of tested loci for decreasing the stringency.

4) The authors mentioned that the high resolution PCR-SSP typing was used only to alleles DRB1*. SSO-Luminex kit (LABType SSO DQA1/DQB1, RSSO2Q, One Lambda) is considered to be low/median resolution typing method.

Answer: We have considered low resolution typing results for DQA1 and DQB1.

5) English still needs minor revision.

Answer: The manuscript was reviewed by a native from England: Peter Grimshaw.

Thank you for your revision.