Reviewer’s report

Title: Clinical and genetic markers associated with tuberculosis, HIV-1 infection, and TB/HIV immune reconstitution inflammatory syndrome outcomes

Version: 0 Date: 10 May 2019

Reviewer: Caroline Tiemessen

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

The authors describe a study investigating the association of HLA-B alleles and KIR genotypes with outcomes of TB, HIV-1 infection and immune reconstitution inflammatory syndrome (IRIS). Patients were from Rio de Janeiro, Brazil - followed from 2006 to 2016 - and constituted 4 groups of patients: Grp1 - TB+/HIV+ (n=88; 11 with IRIS), Grp2 - HIV+ (n=24), Grp3 - TB+ (n=24) and Grp4 - healthy individuals (n=26).

The following findings were reported:
With TB as an outcome, KIR2DS2 associated with risk, while HLA-B*08 and female gender, and absence of KIR2DL3 associated with protection against TB.
With IRIS as an outcome - HLA-B*41, KIR2DS2, CD8 count ≤ 500 associated with an increased risk of IRIS in TB/HIV coinfected patients. Associations of HLA-B*41 and KIR2DS2 with IRIS have previously not been reported.

There are some major errors in accuracy of documenting the KIR genotypes - see major concerns.

Specific comments:
In the introduction reference 4 is referred to (line 124/125) as a study linking host genetics to IRIS pathogenesis - this study does not include genetics but reports IL-18 levels as a biomarker. Appropriate references for the few host genetic studies that may have been done should be included. Which genes have been studied, what did they show?

Line 129 also states no biomarker to predict IRIS - does this refer to the studies referred to in the same paragraph describing clinical factors associated with IRIS. Reference 4 referred to above suggests IL-18 levels as a possible biomarker.

Methods, line 162. Group 2 and 3 starting cART and anti-TB treatment - details of the ART and TB drugs/regimens should be described.

Line 267 - Inhibitory genes were more frequent than activating genes - how is this calculated? Supplementary Table S5 - it would be helpful to include a column for total genes, number inhibitory genes and number activating genes. It should also be indicated which are AA and Bx genotypes - may be worth grouping. Please see major concern section below.
Line 282 - note that absence of KIR2DL3 (stated as protective against TB in the HIV groups comparison) would indicate KIR2DL2-only carriers (genes of the same locus) - and implies Bx genotypes and therefore more activating genes. The majority of KIR2DL3 genotypes would be the dominant AA1 genotype. However, the opposite outcome of KIR2DL2 associated with TB (tendency) shows when combining groups 1 and 3 vs Groups 2 and 4. I'm not sure this makes sense. This requires some explanation.

The HLA C alleles would also be important to determine, and analyse the C1 and C2 allotypes in relation to the inhibitory KIRs they bind.

Correct: "All de groups" headings of Supplementary Tables - to "All the groups"

Supplementary Table S1 - state what "other" routes of transmission are as a footnote

Major concerns:
The genotype ID allocations - these are erroneous. These all need to be checked. For example AA1 genotype - the most prevalent genotype worldwide - does not have 3DS1, 2DS2 or 2DS3 as indicated. Other spot checks show there is some mix up in showing representation of genes according to their genotype IDs. This therefore also raises concerns of all analyses done for the KIR genes. For example - it is hard to imagine how an association of KIR2DS2 with TB outcome could be possible if 158 of 162 individuals all have KIR2DS2. The 3 individuals without this gene each have a unique genotype (0.62% each), so one individual is also missing (with KIR2DS2 absence). Table 2 represents the figures very differently - expect these are more likely the the correct ones. Another example: Bx63 has 2DL5 and 2DS3 missing, figure shows 2DL3 and not 2DS3 missing. I suspect the error may be in labelling of columns for the KIR genes. However, without knowing all reporting and subsequent analyses need to be checked.

It is stated (line 273) that there was no statistical difference between groups and then refers to Supplementary Table 5 - which provides the descriptions of KIR genotype prevalence in the combined total group. Please clarify if you mean comparisons of AA and Bx groupings between Groups 1,2,3 and 4 - if so should indicate Supplementary Table S2. If is this comparison then even if not significant - there is quite a shift in representation of the AA and Bx genotypes in the TB group vs the other groups that deserves mention. Again all analyses need to be checked based on concerns raised above.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Unable to assess

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal