Reviewer's report

Title: Analysis of eight genes modulating interferon gamma and human genetic susceptibility to tuberculosis: a case-control association study

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Reviewer: Catherine Stein

Reviewer's report:

This paper presents a thorough analysis of 8 candidate genes hypothesized to influence IFN-g response, in their association with TB disease in a South African population. This is a relatively large study, which is one of its strengths. The conclusion of the abstract states that this study “highlights the importance of using larger sample sizes” – this point should actually be further emphasized in the text, because it is a very important point and likely explanation for discrepancy of results across published studies.

Minor Essential Revisions:

Most importantly, this study makes the assumption that all the individuals in the study population have latent M. tuberculosis infection, based on the high incidence of TB in South Africa. However, studies have shown that some individuals, albeit a minority, do not acquire latent Mtb infection despite prolonged and persistent exposure to infectious TB cases. Thus, it is not appropriate to state that this study examined the association of these SNPs in “progression from latent infection to active disease”, and it is a limitation of this study that tuberculin skin testing or interferon-gamma response assays were not conducted to test for latent Mtb infection.

The power analysis presented is unclear. In the Methods section, a power analysis is presented, stating that there is 80% power to detect an odds ratio = 2.15. (What is meant by 95% confidence – is this an #=0.05? This should be rephrased.) Later, in Additional Table 2, there are power calculations provided with many different odds ratios. Why are these odds ratios smaller than 2.15? This should be clarified.

Additional Table 1 is a very nice table. The discussion of it is a little spotty – some SNPs are emphasized, others not so much (and study populations not mentioned). Also, the Uganda study did include a haplotype analysis, and found an association between an IL10 haplotype and TB.

Minor discretionary revisions:

It is unclear how WNT5A and FZD5 are involved in IFNg modulation. At least a reference for these genes should be provided.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.