Reviewer’s report

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

Version: 1 Date: 25 March 2010

Reviewer: Hazel Dockrell

Reviewer’s report:

Reviewers report to authors

This paper reports a carefully performed and rigorously analysed study of genetic associations of eight genes involved in genes that are hypothesised to regulate interferon gamma. The previously reported associations did not replicate, possibly because of the larger sample size used here than in some earlier studies, or as a result of more stringent correction for multiple testing, with the exception of one association with a haplotype in IL-12B that was only significant if not adjusted for permutation testing.

Minor essential revisions

1. For readers not familiar with this type of genetic analysis, the text of the first sentence of the Abstract Results section on page 2 and of the Conclusions section on page 12 "which was not globally significant" should be qualified to make its meaning clearer to non-specialists.

2. The Conclusions section of the Abstract should also be qualified as to why larger sample sizes are needed (presumably to obtain clear evidence that a particular association is or is not present in a particular population). The text on page 11 gives a better sense as to why previously reported associations may not be valid, such due to small sample size, a lack of stringent correction for multiple testing as used here, or a lack of association with reactivation rather than primary disease in a very highly endemic setting, but also highlights the possibility of ethnic-specific associations, which must remain a possible explanation for such differences.

3. On page 4, some additional references might be added in addition to ref 18 to back up the statement that "current experimental data suggest that IFNg is the best correlate of protection against TB", as well as a few references to some of those studies in other species such as mice and cattle that do not support the hypothesis that magnitude of the IFNg response can be used as a correlate of protection, even if its production is necessary for control of infection.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests