Reviewer’s report

Title: Polymorphisms in IL-1beta, Vitamin D Receptor Fok1, and Toll-like Receptor 2 Are Associated with Extrapulmonary Tuberculosis

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Reviewer: Thomas Hawn

Reviewer’s report:

Motsinger-Rief et al examine the role of candidate gene polymorphisms and susceptibility to TB. The paper is well written and presents data with a statistical technique that is not common and may offer some advantages over existing techniques. Although interesting, the data is somewhat difficult to interpret in its current format. In addition, the small sample size is a serious limitation for any negative conclusions of the study.

Major Comments.

1. Study Design: The small sample size is a major limitation of this study. As illustrated in Table 6, the power of this study is extremely limited to detect anything except major associations. Given that most of the selected candidate genes have previously been shown to have smaller effects than those that can be detected in this cohort, the value of the studies in the current manuscript is severely compromised and cannot be properly be considered a validation sample. Although the authors acknowledge this limitation, the fact remains that this severely limits any negative findings from this study.

2. Statistical analysis: Multifactor dimensionality reduction (MDR) is not a standard technique used in genetic association studies. Given its statistical complexity, a full review by a genetic statistician may be helpful. Although the technique appears to present some advantages, its use in such a small sample set may not take advantage of its strengths. For example, the authors state that this technique enables analysis of gene-gene interactions. Such an analysis is not practically possible with such a small cohort, which is small even for assessing single SNP associations. The MDR data is difficult to analyze and compare to more traditional ways of presenting genetic data. For example, no odds ratios or genotype frequencies are presented in Tables 4 and 5. At a minimum, a more traditional display of data (with odds ratios, allele, and genotype frequencies) alongside the MDR analysis would be helpful for this reviewer to assess the strength of the association.

Specific points:

1. For the single locus association tests in Table 4, what model is used for analysis? Comparisons of alleles or genotypes? Is an allele trend test used or a dominant or recessive model? Why doesn’t the MDR analysis also find associations with IL-1beta393 and VDR Fok1.
2. Table 5: what does average balanced accuracy mean? Or average prediction error? Or cross-validation consistency? Given the lack of familiarity that most readers have with MDR, a more detailed explanation of terms and how the data compares to a conventional analysis would be helpful.

3. Extrapulmonary phenotype: The extrapulmonary cases are composed of small numbers of many different types. The pathogenesis may be very different among these types—particularly lymphatic vs miliary vs meningeal vs all other. Such heterogeneity among the extrapulmonary cases may limit any conclusions.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

NO