Author's response to reviews

Title: Association between Tumor necrosis factor alpha-238G/A polymorphism and tuberculosis susceptibility: a meta-analysis study

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Dear Dr Tonilynn Manibo,

Please find attached a revised version of our manuscript “Association between Tumor necrosis factor alpha-238G/A polymorphism and tuberculosis susceptibility: a meta-analysis study”, which we would like to resubmit for publication as a research article in BMC infectious diseases.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown using yellow highlight for additions, and strikethrough font for deletions. In accordance with reviewer Vladyslav Nikolayevskyy’s suggestion, the changes we’ve made are as follows:

1. 19 excluded studies are exactly talking about polymorphisms of TNF-α and TB susceptibility, but unfortunately, none of them are relevant to -238 site. We added the information of other polymorphisms of TNF-α into the “Background” section, and clarified this situation in the “Selection process” section accordingly;

2. We deleted “HIV” in the “exclusion criteria 4”. Among three studies which provided HIV status, only HIV-negative cases were included in our meta-analysis, and this has been added into the “Characteristics of eligible studies” section. Otherwise, we amended the subgroup analysis and mentioned them in the “limitations” section correspondingly;

3. We reconduted the analyses through putting EPTB into the “other TB” group in the subgroup analysis, and then leaving out smear-confirmed TB in the sensitive analysis. No significant changes had been found among culture-confirmed TB and no substantial difference had been identified between TB types. The “limitations” section was amended as “the subgroup analyses were only implemented among some explicitly described population due to the lack of original studies. Studies conduct among Non-Asian population, EPTB patients and HIV-positive TB patients were needed in the future”;

4. We invited Professor Meng to revise our study of grammatically and stylistically incorrect, and thus, she was added into the authors;

5. In the Discussion section, we deleted some repetition of what has already been said in the Background and Results sections.

In accordance with reviewer Sergey Nejentsev’s suggestion, the changes we’ve made are as follows:

1. Two studies as examples of studies that reported positive association between TNF -238 and TB were excluded for they are inconsistency with HWE in controls, and we clarified it in the “Selection process” section;
2. We described some limitations in the “limitations” section about how well the original studies performed, and which may explain why well-designed studies with large sample size are needed in the future. Besides, we clarified some limitations of one SNP study in Para 2 of the “Discussion” section, and other polymorphisms with TNF may be the real one influencing the susceptibility to TB, thus, studies with multiple SNPs should be considered. In addition, among nine studies, only three studies were conducted among Non-Asian population and one study entirely targets EPTB, so we suggested the researchers could make up for the gap in this field. All of the consideration are based on the important role of TNF-\(\alpha\) to control TB;

3. We deleted the text results which have been already shown in Table 3;

4. We invited Professor Meng to revise our study of grammatically and stylistically incorrect, which was presented in the lastest version.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC infectious diseases.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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