Meta-Analysis

Association between interleukin-8 –251A/T polymorphism and the risk of tuberculosis: A meta-analysis

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Abstract

Objective: The relationship between interleukin-8 (IL8) –251A/T polymorphism and tuberculosis (TB) risk remains controversial. Therefore, the present meta-analysis was performed by retrieving relevant studies from the available literature.

Methods: We comprehensively searched three databases to identify eligible literature on the relationship of IL8 –251A/T polymorphism with TB risk, calculated pooled odds ratios (OR) with 95% confidence intervals (CI), and subsequent evaluated the heterogeneity and publication bias.

Results: We found that IL8 –251A/T polymorphism increased TB risk (AA vs. TT: OR = 2.86, 95%CI: 1.46–5.60; AT vs. TT: OR = 1.64, 95%CI: 1.15–2.34; dominant model: OR = 1.88, 95%CI: 1.24–2.86; recessive model: OR = 1.77, 95%CI: 1.17–2.69). Subgroup analyses based on race revealed that the IL8 –251A/T polymorphism might be associated with the risk of TB in African but not Asian individuals.

Conclusion: The IL8 –251A/T polymorphism might be related to the risk of TB. Nevertheless, large-scale studies should be performed to confirm the role of IL8 –251A/T polymorphism on TB risk.

Keywords

Tuberculosis, interleukin-8 gene, genetic variant, meta-analysis, IL8, IL8 –251A/T polymorphism

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Introduction

Tuberculosis (TB), an infectious disorder caused by Mycobacterium tuberculosis (MTB), is recognized as a major cause for
single infection source–associated mortality worldwide. Nevertheless, the precise etiology and pathogenesis of TB remain unclear. The World Health Organization has estimated that about one-third of the global population is burdened with TB infection, but only 10% of infected individuals will develop clinical disease. A number of factors can cause infection risk and disease progression of TB, including malnutrition, smoking, diabetes, alcohol use, socioeconomic status, and environmental pollution. Moreover, an increasing number of studies have shown the vital role of diverse genetic factors on host vulnerability to TB.

Interleukin 8 (IL-8), an inflammatory cytokine of the chemokine superfamily with functional and structural correlation, was first discovered in 1987. It has been shown to participate in the promotion of early host defense responses. The effects of IL-8 on human TB have become a particular research hotspot globally. Pathological as well as clinical observations have revealed obvious elevations of IL-8 levels in cerebrospinal fluid, bronchoalveolar lavage fluid, and tuberculous pleural exudate. Additionally, some studies have shown higher plasma levels of IL-8 in patients who die from TB compared with levels in survivors. The generation and release of IL-8 by structure cells as well as leukocytes has been further revealed in response to MTB or its components.

The IL-8 gene (IL8) is located on chromosome 4q13-q21, and comprises 4 exons, 3 introns, and a proximal promoter region. A common single nucleotide polymorphism (SNP) has been identified at locus −251, in the promoter region, with subsequent studies showing a correlation between the IL8 −251A/T polymorphism and IL-8 secretion or protein expression. A previous meta-analysis demonstrated that the IL8 −251A/T polymorphism was correlated with tumor risk.

The relationship of IL8 −251A/T polymorphism with TB risk has been reported in various studies, but with varied outcomes across studies. Case–control studies with relatively limited sample size might be inadequate to comprehensively illustrate a complex relationship because of their insufficient statistical power. In contrast, meta-analysis is a useful method for analyzing complicated data from case–control studies. Herein, this meta-analysis aimed to explore the association of IL8 −251A/T polymorphism with TB risk by collecting all relevant and accessible articles currently available.

Materials and methods

Publication search

We searched PubMed, Web of Science, and the Chinese National Knowledge Infrastructure (CNKI) databases (including publications from 2000 to 2019) using the following keywords and subject terms: “interleukin-8” or “IL-8,” “polymorphism” or “allele,” and “tuberculosis.” References of the included studies were also screened. For literature with overlapping data, studies with the largest sample sizes were selected. Moreover, references from primary or review literature were manually screened to identify additional related studies. Figure 1 shows the PRISMA flow chart of excluded and included studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) case-control studies assessing the correlation between IL8 −251A/T polymorphism and TB risk; (2) subjects clinically diagnosed with TB; and (3) populations with accessible odds ratio (ORs) with 95% confidence intervals (CI) or sufficient information to calculate OR and CI. However, studies
were eliminated if they lacked control or usable information.

**Data extraction**
All possible articles were independently reviewed by two investigators, followed by data extraction. Discrepancy was settled by discussion with another investigator. The following data were retrieved from every paper: region, number of cases and controls, first author, genotype frequencies in cases and controls, publication year, and evidence for Hardy-Weinberg equilibrium (HWE) in controls.

**Statistical analysis**
The chi-square goodness-of-fit test was used to assess the HWE of controls in every study. The correlation strength of the \( IL8 -251A/T \) polymorphism with TB risk was assessed by ORs along with 95% CIs calculated separately for the codominant model (AA vs TT; AT vs TT), the dominant model (AA+AT vs TT), and the recessive model (AA vs AT+TT). The \( I^2 \) test was used to determine the effect of heterogeneity; \( I^2 \), ranging from 0% to 100%, indicates the proportion of inter-study variability that could be attributed to heterogeneity instead of random chance. A value of \( I^2 > 50\% \) was
suggestive of heterogeneity and the application of a random-effects model; otherwise, a fixed-effects model was used. In addition, sensitivity analysis was conducted by removing a single study and analyzing the remaining data. Begg’s funnel plot was used to assess publication bias. STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used for statistical analyses. A $P$-value $< 0.05$ implied statistical significance.

## Results

### Characteristics of included studies

As shown in Figure 1, we identified 344 studies exploring the correlation of $IL8$ –251A/T polymorphism with TB vulnerability. Of these, five articles with seven case–control studies met the inclusion criteria, including 1,355 controls and 1,292 cases for pooled analysis.\(^{15-19}\) The study features were given in Table 1. In brief, all included studies were published in English. The source of controls was mostly healthy individuals. The HWE test performed on genotype distribution of the controls was consistent with HWE except for the study of Ma et al.\(^{15}\) In terms of race, two studies included Asian populations, two included African populations, one included Caucasians, and one was a mixed population.

### Meta-analysis

The major outcomes of this pooled analysis are shown in Table 2, and the correlation of $IL8$ –251A/T polymorphism with TB risk is shown in Figure 2 in the form of forest plots. Our study revealed that $IL8$ –251A/T polymorphism significantly enhanced TB risk (AA vs. TT: $OR = 2.86$, 95%CI: 1.46–5.60, $P = 0.00$; AT vs. TT: $OR = 1.64$, 95%CI: 1.15–2.34, $P = 0.02$; dominant model: $OR = 1.88$, 95%CI: 1.15–2.94, $P = 0.00$; recessive model: $OR = 1.37$, 95%CI: 1.17–2.69, $P = 0.02$). Because of the possible effects of confounding factors on overall outcomes, a subgroup analysis was carried out. By race stratification, we showed that $IL8$ –251A/T polymorphism was related to TB in Africans (AA vs. TT: $OR = 3.02$, 95%CI: 1.47–6.20, $P = 0.05$; AT vs. TT: $OR = 1.79$, 95%CI: 1.17–2.69, $P = 0.02$; dominant model: $OR = 1.86$, 95%CI: 1.17–2.69, $P = 0.02$; recessive model: $OR = 1.72$, 95%CI: 1.06–2.76, $P = 0.02$). Because of the possible effects of confounding factors on overall outcomes, a subgroup analysis was carried out. By race stratification, we showed that $IL8$ –251A/T polymorphism was related to TB in Africans (AA vs. TT: $OR = 3.02$, 95%CI: 1.47–6.20, $P = 0.05$; AT vs. TT: $OR = 1.79$, 95%CI: 1.17–2.69, $P = 0.02$; dominant model: $OR = 1.86$, 95%CI: 1.17–2.69, $P = 0.02$; recessive model: $OR = 1.72$, 95%CI: 1.06–2.76, $P = 0.02$).

### Table 1. Study selection and subject characteristics of included studies in meta-analysis.

| First author | Year | Country | Ethnicity | Cases | Controls | Genotypes for cases | Genotypes for controls | $P$ for HWE |
|--------------|------|---------|-----------|-------|----------|--------------------|------------------------|-------------|
| Ma\(^{15}\)  | 2003 | USA     | Caucasian | 106   | 107      | TT, AT, AA         | TT, AT, AA             | 0.98        |
| Ma\(^{15}\)  | 2003 | USA     | African   | 180   | 167      | 8, 59, 113         | 23, 50, 94             | 0.00        |
| Cooke\(^{16}\) | 2004 | Gambia  | African   | 363   | 320      | 287, 69, 7         | 260, 57, 3             | 0.95        |
| Yang\(^{17}\) | 2010 | China   | Asian     | 167   | 167      | 33, 86, 48         | 68, 79, 20             | 0.69        |
| Lindenau\(^{18}\) | 2014 | Brazil  | Mixed     | 38    | 58       | 11, 19, 8          | 30, 24, 4              | 0.79        |
| Ma\(^{19}\)  | 2016 | China   | Asian     | 438   | 536      | 144, 219, 75       | 188, 260, 88           | 0.91        |

HWE, Hardy–Weinberg equilibrium.
TT: OR = 1.479, 95%CI: 1.07–2.07, P = 0.05; dominant model: OR = 1.72, 95%CI: 1.13–2.63, P = 0.00; recessive model: OR = 2.01, 95%CI: 1.14–3.55, P = 0.01).

**Publication bias**

To assess whether our findings were stable, sensitivity analysis was conducted by sequentially omitting a single study at a time. Pooled ORs were not significantly affected by any individual study (Figure 3). Begg’s funnel plot was used to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Figure 4).

**Discussion**

IL-8, a member of chemokine family, mainly participates in initiating and amplifying acute and chronic inflammatory processes. Thus, it is feasible to speculate that variations in the *IL8* gene might regulate TB risk. The relationship of *IL8* –251A/T polymorphism with TB susceptibility was first reported in 2003 and was subsequently shown in different populations. Nevertheless, the outcomes remained inconsistent, without consensus on the relationship of *IL8* –251A/T with TB risk, even within populations. Because it is rarely possible to determine the effects of a gene polymorphism on TB based on a single study with a relatively small sample size, the present meta-analysis was conducted by retrieving all eligible studies to more accurately assess the correlation between *IL8* polymorphism and TB risk.

In total, 1,292 cases and 1,355 controls were included to analyze whether *IL8* –251A/T polymorphism was correlated with TB risk, revealing significant association of *IL8* –251A/T polymorphism with TB risk. Subgroup analysis by ethnicity demonstrated that the *IL8* –251A/T polymorphism was correlated with TB risk in Africans but not in Asians, suggesting a possible role of ethnic differences in genetic backgrounds and the environment in which...
they lived. Only one paper studied a Caucasian population, and further studies on Caucasians are needed to clarify these results. Distribution of alleles deviating from HWE might contribute to inter-study heterogeneity; however, subgroup analysis by including studies conforming to HWE did not change our conclusions, indicating that our outcome was robust. Sensitivity analysis was performed by removal of single studies and analyzing the remaining data. These results revealed that our meta-analysis was realistic and believable. There was no evidence of publication bias. Because the eligible study number was small in this

Figure 2. Forest plot for meta-analysis of the association between the IL8-251A/T polymorphism and TB risk. Data points and horizontal lines indicate ORs and 95%CI, respectively; diamonds indicate I² values. IL8, interleukin 8 gene; TB, tuberculosis; OR, odds ratio; CI, confidence interval.
meta-analysis, these results need further investigation.

The mechanism underlying the correlation between \( IL8 -251A/T \) polymorphism and TB risk remains unclear. The \( IL8 -251A \) allele is directly related to enhanced IL-8 transcription ability. IL-8 is generated in the lungs in response to MTB.

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**Figure 3.** Sensitivity analysis of the association between the \( IL8 -251A/T \) polymorphism and TB risk. \( IL8 \), interleukin 8 gene; TB, tuberculosis; CI, confidence interval.

**Figure 4.** Begg’s funnel plot analysis to detect potential publication bias for \( IL8-251A/T \) polymorphism. \( IL8 \), interleukin 8 gene; TB, tuberculosis; logOR, logarithm of the odds ratio; s.e., standard error.
infection. The highly secreted IL-8 might promote inflammation by promoting apoptosis of polymorphonuclear leukocytes. Moreover, the enhanced expression of IL-8 attracts excessive leukocytes to the location of the lesion, causing massive tissue destruction by producing elastases, proteases, and free radicals.15

This meta-analysis has certain limitations. First, it was based on six studies with relatively small sample sizes, which reduces the statistical power, especially for subgroup analysis. Second, because of the lack of detailed information, such as subtyping of TB, in individual studies, we were unable to conduct additional subgroup analyses to adjust for these possible confounding factors. Third, we only selected articles published electronically in three databases; therefore, some pertinent articles not included in these databases or unpublished articles with negative results may have been missed. Finally, gene–environment and gene–gene interactions were not considered in this study.

This meta-analysis demonstrated that IL8 –251A/T polymorphism might enhance TB risk. Nevertheless, well-designed and large-scale studies in line with the HWE test are warranted to confirm these outcomes.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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