Association between the IL-6 gene polymorphism and tuberculosis risk: a meta-analysis

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Background: The gene polymorphism of interleukin-6 (IL-6) has been shown to be implicated in tuberculosis susceptibility in many studies, but with conflicting results. This study aimed to provide more accurate estimation of the relationship between IL-6 gene polymorphism and tuberculosis risk through a meta-analysis.

Method: A literature search was performed in PubMed, EMBASE, and other databases. Data were retrieved, and pooled odds ratio (OR) with 95% CI were calculated. Statistical analyses were performed by using STATA 12.0.

Results: Twelve publications with 2635 cases and 3049 controls were included. The pooled analysis demonstrated significant evidence of association between IL-6 (-174G/C) and low risk of tuberculosis in dominant model (CC+GC vs GG: OR =0.693, 95% CI 0.581–0.826, p<0.001). Subgroup analysis got similar results for IL-6 (-174G/C) in Asians and Latinos, but the significance did not exist in Caucasians. IL-6 (-572C/G) polymorphism was also associated with low risk of tuberculosis in dominant model (CC+GC vs GG: OR =0.719, 95% CI 0.577–0.896, p=0.003). No publication bias was detected in either of the polymorphisms.

Conclusion: In summary, IL-6 -572 C/G polymorphism may be associated with a decreased risk of tuberculosis, and C allele is the protective factor against tuberculosis for IL-6 -174G/C among Asians and Latinos, but not in Caucasian population.

Keywords: interleukin-6, rs1800795, rs1800796, TB

Introduction

Tuberculosis remains the main cause of mortality and morbidity worldwide, especially in developing countries.1,2 The precise etiology and pathogenesis of tuberculosis is still inconclusive. However, among those infected with Mycobacterium tuberculosis, only 10% develop active tuberculosis, and most of infected individuals remain latently infected, implying that each stage of the host response to M. tuberculosis may be under genetic control.3 Growing number of reports have demonstrated that various host genetic factors are critical in susceptibility to tuberculosis.4,5

Cytokines play a significant role in host susceptibility and development of tuberculosis.6 For instance, the polymorphism of interleukin (IL)-10 and interferon (IFN)-γ were reported to be associated with pleural tuberculosis.7 Similarly, Hussain et al reported that suppressed T-cell-derived IFN-γ but greater monocyte-derived IL-6 and IL-10 production might be associated with pulmonary tuberculosis susceptibility.8 Lopez-Maderuelo et al found that IFN-γ (+874) A allele significantly increased the risk of tuberculosis.9 IL-6 is a pro-inflammatory cytokine secreted by monocytes, endothelial...
cells and fibroblasts, which is able to stimulate B and T lymphocytes, and regulate immune response to tuberculosis.\(^{10}\) It is found to be essential for generating protective Th1 immune responses which is necessary for the resistance to \textit{M. tuberculosis} infection.\(^{11,12}\) Precedently, several studies have shown that the \textit{IL}-6 polymorphism is significantly associated with a number of diseases, such as sepsis, coronary heart disease, and systemic lupus erythematosus, in which it plays an important role in the etiology.\(^{13–15}\) With regard to tuberculosis, two positions of \textit{IL}-6 gene polymorphism, -174G/C (rs1800795) and -572C/G (rs1800796), were reported to be related to tuberculosis risk in different populations.\(^{16–18}\) However, the results of these studies were variable and inconclusive. Since meta-analysis is a powerful tool for analyzing cumulative data from individual studies, the sample sizes of which are small and the statistical power low,\(^{19,20}\) two recently published meta-analysis reviews investigated the relationship between -174G/C polymorphism and risk of tuberculosis based on the results of studies performed before 2012.\(^{21,22}\) However, 5 years have passed, thus a meta-analysis based on the most current published independent studies was performed in the current review, which may provide a comprehensive assessment of the associations of both \textit{IL}-6 (-174G/C) and \textit{IL}-6 (-572C/G) gene polymorphisms with the risk of tuberculosis.

**Materials and methods**

**Search strategy**

Databases, including PubMed, EMBASE, Wanfang, VIP, and CNKI, were systematically searched for publications regarding the association between the \textit{IL}-6 gene polymorphism and tuberculosis risk up to October 2016. The search terms were set as follows: (“\textit{Interleukin}-6” or “\textit{IL}-6” or “rs1800795” or “rs1800796”) and (“polymorphism” or “variant” or “mutation” or “SNP”) and “tuberculosis.” Articles were also identified using the related articles function in PubMed. References within the identified articles or review articles were also searched manually.

**Quality assessment**

Quality of the included studies was evaluated with a standard method recommended by Thakkinstian et al.\(^{23}\) The assessment was carried out according to the following variables: representativeness of cases and controls, credibility of controls, specimens of cases determining genotypes, Hardy–Weinberg equilibrium (HWE) in controls, and total sample size. A quality score was ultimately obtained by summing each component giving a range from 0 (the lowest) to 15 (the highest), the higher the publication scored, the better quality it is, and vice versa, and studies with scores $\geq 10$ were classified as high-quality studies, whereas studies with scores $<10$ were considered as low-quality studies.

**Inclusion and exclusion criteria**

Articles were included in this meta-analysis if they met the following criteria: 1) they were case–control clinical studies published in English or Chinese; 2) they evaluated the \textit{IL}-6 gene polymorphism and tuberculosis risk; 3) they comprised sufficient data (genotype frequency for cases and controls) to estimate an odds ratio (OR) with its 95% confidence interval (95% CI). The exclusion criteria included the following: 1) they were abstracts and reviews; 2) there were studies without sufficient data reported. When publications involved the same or overlapping data sets, only the study with the largest number of participants was included.

**Data extraction**

Data of all eligible publications were extracted according to the inclusion and exclusion criteria by two independent investigators (HW and CP). A consensus was reached in case of disagreement. The following characteristics were collected from each study: first author, year of publication, study design, country, ethnicity, sample size, alleles, and \textit{IL}-6 genotype distributions in both cases and controls. If necessary information could not be obtained from the original article, we contacted the corresponding author via the email listed.

**Statistical analysis**

With the purpose of assessing the associations between the \textit{IL}-6 gene polymorphisms and tuberculosis risk, pooled OR with corresponding 95% CI was calculated based on allele contrast (C vs G), co-dominant (CC vs GG), dominant (CC+GC vs GG), and recessive (CC vs GC+GG) models. A fixed-effects or random-effects model was used for pooling data according to the results of heterogeneity examination, which was checked by a $\chi^2$-based Q statistic test. When $p<0.05$, OR was calculated by the random-effects model, otherwise the fixed-effects model was applied. The significance of the pooled OR was determined by a $z$-test, and $p<0.05$ was considered statistically significant.

Subgroup analysis was also conducted to determine whether there was an association between the \textit{IL}-6 gene polymorphism and tuberculosis risk in different ethnicities. Sensitivity analysis was performed by individually removing the included studies to assess the stability of results. Publication bias was analyzed by Begg’s funnel plots and Egger’s test.\(^{24}\) HWE was tested by Pearson’s $\chi^2$ test ($p<0.05$ means
deviated from HWE). All statistical tests were performed by STATA 12.0 software (StataCorp, College Station, TX, USA) two-sided, and \( p < 0.05 \) was considered statistically significant.

**Results**

**Study characteristics of included studies**

A total of 12 publications with 2635 cases and 3049 controls were justified eligible according to inclusion criteria.\(^7\),\(^17\),\(^18\),\(^25\)–\(^33\) Figure 1 outlines the selection and inclusion process of publications.

Among the included publications, eight evaluated the association between the \( IL-6 \) (-174G/C) polymorphism and tuberculosis risk, with 959 cases and 1608 controls;\(^7\),\(^18\),\(^25\)–\(^30\) three focused on \( IL-6 \) (-572C/G) polymorphism, including 686 cases and 725 controls.\(^17\),\(^32\),\(^33\) One article assessed both \( IL-6 \) (-174G/C) and (-572C/G) with 495 cases and 358 cases,\(^18\) and it was treated as two independent studies in the present meta-analysis. Consequently, 13 studies were available for analyzing the association between \( IL-6 \) gene polymorphism and tuberculosis risk, nine (8 publications) of them were conducted in Asians,\(^7\),\(^17\),\(^18\),\(^25\),\(^27\)–\(^32\),\(^33\) while two were in Caucasians,\(^26\),\(^28\) and two were in Latinos.\(^7\),\(^31\) Ten studies (9 publications) recruited pulmonary tuberculosis patient,\(^17\),\(^18\),\(^25\)–\(^32\) three investigated other types of tuberculosis such as tuberculosis pleurisy, renal tuberculosis, tuberculous lymphadenitis, and central nervous system tuberculosis.\(^7\),\(^26\),\(^33\) The genotype distributions in the controls of four studies were not consistent with HWE.\(^7\),\(^25\),\(^17\),\(^30\) In the 13 studies (12 publications), 10 are with quality score \( \geq 10 \), suggesting the reliability of our results. The general characteristics of each study included in this meta-analysis are summarized in Table 1. Genotype distributions and HWE examination results are listed in Table 2.

**Quantitative data synthesis**

**\( IL-6 \) (-174G/C) polymorphism and tuberculosis risk**

We analyzed the heterogeneity of four genetic models: allele contrast (C vs G), co-dominant model (CC vs GG), dominant (CC+GC vs GG), and recessive (CC vs GC+GG) models. The values of \( \chi^2 \) were 7.98, 8.09, 11.26, and 9.71, respectively \( (p=0.281, 0.324, 0.188, \text{ and } 0.206, \text{ respectively}) \). Thus, all data were synthesized using the fixed-effects model. Overall, OR was 0.693 \( (95\% \text{ CI } 0.581–0.826) \) and the test for overall effect \( z \) value was 4.09 \( (p < 0.001) \) for CC+GC vs GG (Figure 2). We also analyzed the other three models: C vs G model: OR = 0.714 \( (95\% \text{ CI } 0.619–0.825) \), \( z = 4.59, p < 0.002 \); CC vs GG model: OR = 0.506 \( (95\% \text{ CI } 0.349–0.734) \), \( z = 3.59, p < 0.001 \);
**Table 1** Characteristics of the case–control studies included in the present meta-analysis

| Study            | Year | Country | Ethnicity | Gene polymorphisms | Tuberculosis/control | Genotyping method | Quality score |
|------------------|------|---------|-----------|--------------------|----------------------|-------------------|---------------|
| Amirzargar et al | 2006 | Iran    | Asian     | IL-6 -174          | 40/119               | PCR-SSP           | 9             |
| Oral et al       | 2006 | Turkey  | Caucasian | IL-6 -174          | 81/49                | PCR-SSP           | 9             |
| Henao et al      | 2006 | Colombia| Latino    | IL-6 -174          | 190/135              | PCR-SSP           | 10            |
| Selvaraj et al   | 2008 | India   | Asian     | IL-6 -174          | 160/183              | PCR              | 12            |
| Trakjov et al    | 2009 | Macedonia| Caucasian| IL-6 -174          | 75/301               | PCR-SSP           | 11            |
| Ansari et al     | 2011 | Pakistan| Asian     | IL-6 -174          | 102/166              | ARMS PCR          | 11            |
| Zhang et al      | 2012 | China   | Asian     | IL-6 -174          | 495/358              | PEMS             | 11            |
| Hu et al         | 2015 | China   | Asian     | IL-6 -174          | 120/480              | ARMS-PCR          | 12            |
| Milano et al     | 2016 | Southern Brazil| Latino| IL-6 -174          | 191/175              | PCR              | 12            |
| Zhang et al      | 2012 | China   | Asian     | IL-6 -572          | 495/358              | PEMS             | 11            |
| Sun et al        | 2008 | China   | Asian     | IL-6 -572          | 142/135              | PCR-RFLP          | 9             |
| Feng et al       | 2014 | China   | Asian     | IL-6 -572          | 191/191              | PCR              | 10            |
| Shen et al       | 2014 | China   | Asian     | IL-6 -572          | 353/399              | PEMS             | 11            |

**Table 2** Distributions of IL-6 genotype and allele among tuberculosis patients and controls

| Study           | IL-6 -174 | IL-6 -572 |
|-----------------|-----------|-----------|
|                 | C/C   | G/C   | G/G   | C/C | G/C | G/G | C/C | G/C | G/G | HWE chi-square | HWE p-value |
| Amirzargar et al | 6     | 4     | 13    | 23  | 10  | 71  | 38  | 21  | 59  | 91  | 8.24      | 0.004     |
| Oral et al      | 11    | 8     | 3     | 55  | 17  | 38  | 12  | 13  | 32  | 57  | 7.32      | 0.007     |
| Henao et al     | 3     | 2     | 11    | 106 | 31  | 26  | 13  | 27  | 39  | 123 | 5.15      | 0.023     |
| Selvaraj et al  | 8     | 4     | 31    | 36  | 152 | 132 | 25  | 144 | 47  | 103 | 3.25      | 0.071     |
| Zhang et al     | 13    | 9     | 4     | 74  | 10  | 56  | 32  | 172 | 47  | 103 | 1.00      | 0.281     |
| Hu et al        | 8     | 4     | 4     | 66  | 53  | 180 | 247 | 258 | 182 | 85  | 0.67      | 0.412     |
| Zhang et al     | 6     | 4     | 43    | 123 | 15  | 55  | 94  | 55  | 309 | 85  | 2.63      | 0.105     |
| Sun et al       | 24    | 8     | 152   | 319 | 31  | 125 | 202 | 200 | 790 | 187 | 8.04      | 0.004     |
| Feng et al      | 13    | 2     | 83    | 21  | 17  | 112 | 6   | 159 | 125 | 146 | 3.25      | 0.071     |
| Shen et al      | 153   | 38    | 157   | 43  | 179 | 171 | 49  | 463 | 243 | 529 | 0.67      | 0.412     |

Abbreviations: ARMS PCR, amplification refractory mutation system polymerase chain reaction; PCR, polymerase chain reaction; PCR-SSP, polymerase chain reaction-sequence-specific primer; PEMS, primer-extension mass spectrometry; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; IL, interleukin.

<0.001; CC vs GC+GG model: OR =0.570 (95% CI 0.397–0.819), z=3.04, p=0.002, as listed in Table 3.

Additionally, subgroup analysis was carried out by ethnicity for IL-6 (-174G/C). IL-6 (-174G/C) polymorphism was not significantly associated with tuberculosis in Caucasian patients under the four genetic models. However, in Asian and Latino patients, the results indicated that there were significant associations between IL-6 (-174G/C) polymorphism and tuberculosis under all genetic models, similar to overall text effect (Figure 3). A summary of results from these comparisons is listed in Table 4.

**IL-6 (-572C/G) polymorphism and tuberculosis risk**

Based on the examination results of heterogeneity ($\chi^2$=7.03, p=0.071), a fixed-effects model was applied to pool the OR under dominant model (CC+GC vs GG), and the OR was 0.719 (95% CI 0.577–0.896), with a z value of 2.93 (p=0.003), the forest plot is shown in Figure 4. The results are summarized in Table 3.

**Sensitivity analysis and publication bias**

In order to evaluate the influence of single studies on overall estimates, sensitivity analyses were carried out for four genetic models by removing each study in turn. No obvious changes were found, which suggested that our results were stable in these models.

Begg’s funnel plots and Egger’s test were performed to evaluate the publication bias qualitatively and quantitatively. Figure 5A shows the funnel plots for IL-6 (-174G/C). The shape of the funnel plots seemed symmetrical, and Egger’s
test did not find obvious publication bias (CC+GC vs GG, \( p = 0.714 \)). Figure 5B shows the funnel plots of IL-6 (-572C/G); similarly, Egger’s test for all models also suggested the absence of publication bias (CC+GC vs GG, \( p = 0.423 \)).

**Discussion**

To date, numerous studies have evaluated the effects of gene polymorphism on tuberculosis risk and confirmed that host susceptibility to tuberculosis was associated with genetic factors.34,35 With regard to IL-6, the results were paradoxical and some studies failed to identify the association. Recently, several systematic reviews focused on the relationship between -174G/C or -572C/G polymorphism and risk of tuberculosis;21,22,36 however, the enrolled studies and subjects were limited. In order to increase the statistical power and generate an absolute conclusion, we performed this meta-analysis to integrate the results from parallel studies regarding the association between IL-6 gene polymorphism (-174G/C and -572C/G) and tuberculosis risk.

In this meta-analysis, we evaluated the association between IL-6 (-174G/C and -572C/G) polymorphisms and tuberculosis risk under the allele comparison, co-dominant, recessive, and dominant models, respectively. There was an association between IL-6 (-174G/C) and low tuberculosis risk under allele contrast (for C vs G: OR = 0.714, 95% CI 0.619–0.825, \( p < 0.001 \)) and dominant models (for CC+GC vs GG: OR = 0.506, 95% CI 0.349–0.734, \( p < 0.001 \)), and also in recessive and co-dominant model (CC vs GC+GG: OR = 0.719, 95% CI 0.577–0.896, \( p = 0.003 \)), and co-dominant model (CC vs GG: OR = 0.577–0.896, \( p = 0.003 \)) and co-dominant model (CC vs GG: OR = 0.713, 95% CI 0.517–0.984, \( p = 0.039 \)), which suggested that the CC+GC carriers have a 29% decreased risk of tuberculosis compared with those with GG. Recently, Sun...
### Table 3: Summary of results from different comparative genetic models for IL-6

| SNP N | TB/control | C vs G | CC vs GG | CC+GC vs GG | CC vs GC+GG |
|-------|------------|--------|----------|-------------|-------------|
|       |            | OR (95% CI) | Heterogeneity* | p-value | OR (95% CI) | Heterogeneity | p-value | OR (95% CI) | Heterogeneity | p-value | OR (95% CI) | Heterogeneity | p-value |
| -572 C/G | 4 (1181/1083) | 0.956 (0.760–1.203) | 0.703 (0.517–0.984) | 0.039 (0.577–0.896) | 0.003 (0.683–1.962) |
| -174 G/C | 9 (1454/1966) | 0.714 (0.619–0.825) | 0.506 (0.349–0.734) | 0.693 (0.581–0.826) | 0.570 (0.397–0.819) |

Note: *Represents $\chi^2$.

Abbreviations: TB, tuberculosis; N, number of studies; OR, odds ratio; CI, confidence interval; IL, interleukin.

### Table 4: Subgroup analysis of different comparative genetic models for IL-6 -174G/C

| Subgroup by ethnicity | C vs G | CC vs GG | CC+GC vs GG | CC vs GC+GG |
|-----------------------|--------|----------|-------------|-------------|
|                       | OR (95% CI) | Heterogeneity* | p-value | OR (95% CI) | Heterogeneity | p-value | OR (95% CI) | Heterogeneity | p-value |
| Caucasian 2 156/350  | 0.917 (0.666–1.262) | 0.594 (0.397–1.606) | 0.528 (0.622–1.423) | 0.800 (0.407–1.574) |
| Asian 5 917/1306  | 0.717 (0.582–0.883) | 0.002 (0.253–0.851) | 0.013 (0.546–0.896) | 0.541 (0.301–0.972) |
| Latino 2 309/310  | 0.605 (0.469–0.780) | 1.50 (0.281) | <0.001 (0.415) | 0.003 (0.415–0.781) |

Note: *Represents $\chi^2$.

Abbreviations: TB, tuberculosis; N, number of studies; OR, odds ratio; CI, confidence interval; IL, interleukin.
et al reported similar findings that -572C/G polymorphism was related to the decreased risk of tuberculosis (CC vs GC; OR = 0.71, 95% CI 0.55–0.90); compared with this review, we enrolled two more studies in the current study, and we got some new points through the co-dominant model (CC vs GG). Nevertheless, what should be addressed is that the role of IL-6 in tuberculosis is complicated. It has been reported that IL-6 played a critical role in protection against murine M. tuberculosis infection, while it has also been suggested to downregulate macrophage microbicidal activity and promote...
the growth of *Mycobacterium avium* in vitro. Additionally, environmental factors may interact with gene polymorphism and influence tuberculosis susceptibility. How to adjust the environmental effects on tuberculosis risk is still being investigated. More studies should be performed to investigate the mechanism how *IL-6* polymorphism regulates *IL-6* production and plays a role in tuberculosis susceptibility.

Ethnicity is one of the considerable factors for tuberculosis risk with controversial conclusions in previous studies. Therefore, we conducted subgroup analyses based on ethnicity in *IL-6* (-174G/C), but not in *IL-6* (-572C/G), as all studies investigating *IL-6* (-572C/G) in this meta-analysis were performed in Asian population. The significant associations between *IL-6* (-174G/C) polymorphism and tuberculosis risk were found in Asians and Latinos, but no obvious association was observed in Caucasian population, suggesting that ancestral genetic factors in different ethnic populations may have an impact on tuberculosis risk.

Heterogeneity and publication bias should be taken into consideration while interpreting the results of a
meta-analysis. The heterogeneity in our meta-analysis existed in IL-6 (-572C/G), but not in overall or subgroup analyses of IL-6 (-174G/C). Several factors may be used to explain the heterogeneity, such as genetic background of cases and controls, diverse genotype distributions of IL-6 in different ethnicities which suggest that they are always subjected to natural selection.40 Besides, the uneven selection criteria for cases and controls in different original studies have also contributed to this heterogeneity. According to our inclusion and exclusion criteria, only four studies involved the association between IL-6 (-572C/G) and tuberculosis risk, all of which were conducted in Asian population. Thus, the reason for the heterogeneity may be attributed to the moderate number of studies and the absence of studies conducted in populations other than Asians. Referring to -174G/C polymorphism, our meta-analysis enrolled studies performed in Asians (five studies), Caucasians (two studies), and Latinos (two studies), which might make our conclusion inapplicable for the other populations. In addition, only two studies were conducted in Caucasians or Latinos, respectively. Therefore, more studies will be needed in the future to evaluate the relationship between IL-6 polymorphism and tuberculosis risk in different population, especially in Africans which were not enrolled in the current review. In this meta-analysis, publication bias was analyzed by Begg’s funnel plots and Egger’s test, and no significant publication bias was detected, suggesting that our results are reliable. However, more studies should be performed to verify the results of our meta-analysis.

Limitations should be pointed out in our meta-analysis. First, after strict search strategy and study selection, only limited numbers of publications were included. There are possibilities that certain articles were missed in this study, due to database or language limitation, which may bias the results. In the present meta-analysis, we included only publications in English or Chinese. Although we did not detect any publication bias, it is possible that including relevant studies in other languages or unpublished studies which had null outcomes may alter our results.

Second, due to the limited number of studies included, we did not exclude studies in which the genotype distributions in controls were not consistent with HWE. Large-scale and well-designed case–control studies should be done to estimate the accurate association between the IL-6 and tuberculosis risk in the years to come.

Lastly, the studies included in the meta-analysis were conducted in Caucasian, Asian, and Latino patients, which may not represent the associations in ethnicities worldwide. Meanwhile, due to the limitation of original information, the influence of gene–gene interactions or environmental factors was not considered in this meta-analysis. Last but not least, the current genotyping method may cause errors, which should be paid attention to in clinical explanation.

However, it is worthwhile to mention several highlights of this study. First, this was the first meta-analysis to assess the relationship between the IL-6 (-572C/G) polymorphism and tuberculosis risk. Second, heterogeneity, stability of results, and publication bias in this meta-analysis were all well investigated, indicating a correct methodology. Also, strict inclusion and exclusion criteria were followed to limit the potential bias among studies.

Taken together, our results suggested that in Asian and Latino population, IL-6 -572C/G polymorphism decreased the risk of tuberculosis, and C allele was a protective factor against tuberculosis for IL-6 -174G/C polymorphism, which may not be in Caucasian population. In future, additional case–control studies should be performed to validate our findings.

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Author contributions
All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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