Review Article

Association between IL-6 gene polymorphisms and susceptibility of tuberculosis: evidence based on a meta-analysis

Yaping Sun¹, Meihua Wang²

¹Department of Tuberculosis, Hangzhou Red Cross Hospital, Hangzhou, Zhejiang, China; ²Department of Respiration, Chunan First People’s Hospital, Hangzhou 310024, China

Received September 30, 2016; Accepted December 20, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: The present study aimed to investigate the association of IL-6 gene polymorphisms with tuberculosis (TB) susceptibility. There were inconsistent findings from previous studies on this topic. The aim of this study was to perform a meta-analysis to investigate the relationship between IL-6 -174G/C, G/A nt565 and -572C/G polymorphisms and TB risk. PubMed and Embase databases were searched for publications until September 2016 for eligible studies on IL-6 gene polymorphisms. The data from relevant studies were extracted and used to calculate pooled odd ratios (ORs) and 95% confidence intervals (95% CI). A total of 8 studies were included in this meta-analysis. There was a significant association between IL-6 -174G/C polymorphism and TB risk in the total population (CC vs GG: OR=0.67, 95% CI=0.43-1.05; CG vs GG: OR=0.72, 95% CI=0.57-0.90; Dominant model: OR=0.71, 95% CI=0.57-0.88; Recessive model: OR=0.77, 95% CI=0.50-1.19). In the subgroup analysis by ethnicity, the IL-6 -174G/C polymorphism was associated with TB risk in Asians. No association was found for IL-6 G/A nt565 polymorphism. For the IL-6 572C/G polymorphism, a significant correlation with TB risk was determined (GG vs CC: OR=0.84, 95% CI=0.25-2.84; GC vs CC: OR=0.71, 95% CI=0.55-0.90; Dominant model: OR=0.70, 95% CI =0.55-0.88; Recessive model: OR=0.96, 95% CI=0.26-3.56). In conclusion, the meta-analysis results suggest that IL-6 -174G/C and -572C/G polymorphisms might be associated with the risk of TB. No significant association was observed between the IL-6 G/A nt565 polymorphism and TB risk.

Keywords: Interleukin-6, tuberculosis, meta-analysis

Introduction

Tuberculosis (TB) remains a challenge among migrants despite a steady decrease in TB incidence worldwide in the last decade [1]. According to a 2013 World Health Organization (WHO) report, 9 million people were infected with TB and 1.5 million deaths were attributed to TB [2]. Recent studies show that one-third of the population is infected with Mycobacterium tuberculosis, but only one-tenth of infected individuals will ever develop active TB [3]. However, the underlying nosogenesis of TB infection remains unclear. Previous studies indicate that the risk of developing tuberculosis is strongly influenced by genetic factors [4]. So far, gene polymorphisms of SLC11A1, vitamin D receptor, and tumor necrosis factor-alpha have been identified as genetic risk factors that increases TB susceptibility [5-7].

Interleukins are vital components of the immune system, and interleukin deficiency may lead to autoimmune disease or immune deficiency. Interleukin-6 (IL-6) is an key inflammatory cytokine produced by different cells including adipocytes, endothelial cells, fibroblasts, myocytes and white blood cells [8]. Previous studies found that IL-6 may play a key role in the inflammatory response to microbial invasion and diseases, including tuberculosis [9, 10]. Proinflammatory cytokine production is affected by specific gene polymorphisms [11]. The gene encoding IL-6 is located on chromosome 7p21, and contains 6 exons with a 1.3-kb coding sequence (size 6119 base pairs). Most studies have focused on the promoter region of the IL-6 gene as many polymorphisms are identified in this region, including -174G/C (NCBI ID: rs1800795), G/A nt565 (NCBI ID: rs1800797) and -572C/G (NCBI rs1800796).
IL-6 gene polymorphisms and tuberculosis

Some studies linked the IL-6 174G>C polymorphism to susceptibility to coronary heart disease and cancer [12, 13].

To date, large numbers of epidemiological studies have been performed to examine the relationship between the IL-6 gene polymorphisms and the risk of TB, but different studies reached different conclusions. The differences in results may be due to a possible small effect of the polymorphism on TB risk and the relatively small sample sizes in the published studies. Therefore, we performed a systematic review and meta-analysis in this study to evaluate the associations between IL-6 gene polymorphisms and TB susceptibility.

Material and methods

Selection of studies

We searched all publications in the PubMed and EMBASE databases via the internet without language limitation. The following terms were used as searching keywords: “Interleukin-6 or Interleukins”, “polymorphism or polymorphisms”, “174G/C”, “G/A nt565”, “-572C/G” and “tuberculosis (TB)”. The references lists

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Cases</th>
<th>Controls</th>
<th>Genotypes for cases</th>
<th>Genotypes for controls</th>
<th>P for HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral et al</td>
<td>2006</td>
<td>Turkey</td>
<td>Caucasian</td>
<td>81</td>
<td>49</td>
<td>CC</td>
<td>GG</td>
<td>0.01</td>
</tr>
<tr>
<td>Henao et al</td>
<td>2006</td>
<td>Colombia</td>
<td>Mixed</td>
<td>190</td>
<td>135</td>
<td>CG</td>
<td>CC</td>
<td>0.69</td>
</tr>
<tr>
<td>Amirzargar et al</td>
<td>2006</td>
<td>Iran</td>
<td>Asian</td>
<td>40</td>
<td>119</td>
<td>GG</td>
<td>AA</td>
<td>0.43</td>
</tr>
<tr>
<td>Selvaraj et al</td>
<td>2008</td>
<td>India</td>
<td>Asian</td>
<td>160</td>
<td>183</td>
<td>GC</td>
<td>AG</td>
<td>0.97</td>
</tr>
<tr>
<td>Trajkov et al</td>
<td>2009</td>
<td>Macedonia</td>
<td>Caucasian</td>
<td>75</td>
<td>301</td>
<td>CC</td>
<td>GG</td>
<td>0.07</td>
</tr>
<tr>
<td>Ansari et al</td>
<td>2011</td>
<td>Pakistan</td>
<td>Asian</td>
<td>97</td>
<td>166</td>
<td>GG</td>
<td>GC</td>
<td>0.95</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>495</td>
<td>358</td>
<td>GG</td>
<td>GC</td>
<td>0.09</td>
</tr>
<tr>
<td>Feng et al</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>191</td>
<td>191</td>
<td>GC</td>
<td>CC</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Figure 1. Detailed process of study selection.
from major textbooks, review studies and included studies were identified through manually searched to identify other potentially eligible articles.

Inclusion and exclusion criteria

The following inclusive criteria were used to select relevant articles: (1) evaluating the interrelation between IL-6 gene 174G>C, G/A nt565 and -572C/G polymorphisms and TB, (2) case-control study, (3) the papers must provide the data of sample size, distribution of alleles, and genotype data included to allow calculation of the odds ratio (ORs) and 95% confidence intervals (CIs), (4) the most recent study was selected if included studies used the same patient or control data. The major reasons for study exclusion were the following: duplicate research articles, research protocols, commentaries, editorials, letters, and books were excluded from the systematic review.

Data extraction

Two investigators independently selected the studies and extracted the data from the articles, and conflicting or uncertainties were resolved via discussion and reaching consensus. The following data were extracted: first author’s surname, year of publication, race of the study population, country where the study was conducted, the number of cases and controls for each genotype, and if the gene distribution of the controls were in compliance with Hardy-Weinberg Equilibrium (HWE).

Statistical analysis

Meta-analysis was performed using the Stata 12.0 software (Stata Corporation, College Station, TX, USA).
IL-6 gene polymorphisms and tuberculosis

Station, TX, USA). The odds ratio (OR) corresponding to the 95% confidence interval (95% CI) was used to assess the correlation between IL-6 gene polymorphisms (174G>C and G/A nt565) and TB under a homozygote comparison (AA vs aa), a heterozygote comparison (AA vs Aa), a dominant model and a recessive model between groups. In this study, the dominant model was defined as Aa+aa vs AA, where “A” and “a” are the major and minor alleles, respectively, and the recessive model was defined as aa vs AA+Aa [14]. For the effect models, $I^2$ was considered the standard (when $I^2$<50%, the fixed effect was applied; otherwise, the random effect was selected) [15]. Subgroup analyses were performed by stratification of race. Funnel plot and Egger’s regression asymmetry test were calculated to assess publication bias.

Results

Characteristics of included studies

The study selection process is shown in Figure 1. According to the inclusion criteria, eight qualified case-control studies were included in the

![Figure 2: Meta-analysis of the relationship between the -174G/C polymorphism in the IL-6 gene and TB risk.](image-url)
IL-6 gene polymorphisms and tuberculosis

Quantitative analysis

IL-6 -174G/C: The main results of meta-analysis of the IL-6 -174G/C polymorphism and TB risk were present in Table 2. In pooled analysis using data from all 7 studies, a significant association was found between the IL-6 -174G/C polymorphism and TB risk (see Figure 2: CC vs GG: OR=0.67, 95% CI=0.43-1.05; CG vs GG: OR=0.72, 95% CI=0.57-0.90; Dominant model: OR=0.71, 95% CI=0.57-0.88; Recessive model: OR=0.77, 95% CI=0.50-1.19). In subgroup analyses stratified by ethnicity, statistically significant association was observed in Asians CC vs GG: OR=0.69, 95% CI=0.32-1.48; CG vs GG: OR=0.61, 95% CI=0.44-0.85; Dominant model: OR=0.63, 95% CI=0.46-0.86; Recessive model: OR=0.93, 95% CI=0.44-1.97). Sensitivity analysis was performed by omission of non-HWE studies and the final result was not altered, indicating the result of meta-analysis has statistical significance (Table 2).

IL-6 G/A nt565: The main results of meta-analysis of the IL-6 G/A nt565 polymorphism and TB risk were summarized in Table 2. The results of pooling all studies showed that the IL-6 G/A nt565 polymorphism was not associated with TB susceptibility (see Figure 3: AA vs GG: OR=1.36, 95% CI=0.66-2.80; AG vs GG: OR=1.06, 95% CI=0.69-1.62; Dominant model: OR=1.11, 95% CI=0.74-1.66; Recessive model: OR=1.34, 95% CI=0.67-2.69).

IL-6 -572C/G: The results of meta-analysis of the IL-6 -572C/G polymorphism and TB risk were summarized in Table 2. Overall, there were significant associations of the IL-6 -572C/G polymorphism and TB risk when all the eligible studies were pooled into the meta-analysis (see Figure 4: GG vs CC: OR=0.84, 95% CI=0.25-2.84; GC vs CC: OR=0.71, 95% CI=0.55-0.90; Dominant model: OR=0.70, 95% CI=0.55-0.88; Recessive model: OR=0.96, 95% CI=0.26-3.56).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of included articles. The shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry in the allele model, which implied that the publication bias was low in our meta-analysis (all P>0.05).
IL-6 gene polymorphisms and tuberculosis

**Discussion**

Tuberculosis has been a prevalent disease worldwide for many years. It remains poorly understood why only some people, and not others, developed to this illness. Many investigations have confirmed that inherited genetic factors strongly influence susceptibility to TB [24, 25]. IL-6 is a multifunctional cytokine that regulates immune reactions and is regarded as an endogenous pyrogen that induces fever in patients with infection. The -174G/C, -572C/G and G/A nt565 single nucleotide polymorphisms in the IL-6 gene were found to be associated with IL-6 promoter activity, leading to inter-individual variations in cytokine production [26]. Genetic studies showed that IL-6 polymorphisms in the promoter region were associated with TB risk, and a number of studies have been performed to investigate that association. However, the results of these previous studies have been inconsistent. These inconsistencies may partly be attributed to the insufficient power of the included studies, a minimal effect of the polymorphism on TB risk, or false-positive results. Here, we have performed a meta-analysis to evaluate the association between the IL-6 gene polymorphisms and risk of TB.

Our meta-analysis systemically assessed the association between IL-6 gene polymorphisms (-174G/C, G/A nt565 and -572C/G) and the susceptibility to TB. For the IL-6 -174G/C polymorphism, the meta-analysis indicated a significant association between this variant and TB susceptibility among the total population. Because the result may be affected by ethnicity, we performed a race-related subgroup analysis, and the results revealed that the IL-6 -174G/C polymorphism is associated with the risk of TB in Asians but not in Caucasians, suggesting a possible role of ethnic differences in genetic backgrounds and the environment in which they lived in. Deviation of allelic distributions from HWE may contribute to between-study heterogeneity, so we next performed sen-

---

**Figure 4.** Meta-analysis of the relationship between the -572C/G polymorphism in the IL-6 gene and TB risk.
sitivity analysis by limiting this meta-analysis to those articles that are consistent with HWE. We found the same result when those studies were removed, lending support to our conclusions. For the IL-6 G/A nt565 polymorphism, no evidence was found for association, but the IL-6 -572C/G polymorphism was associated with the risk of TB in the general population. In our analysis, there was evidence of heterogeneity between studies. This may be due to some factors, including the selection of methods, definition of cases, and limited sample sizes. Due to the limited number of relevant articles, it is not possible to perform further analysis in this meta-analysis.

There are still some limitations in this meta-analysis. First, the number of published studies was not sufficiently large for a comprehensive analysis, and some articles with few subjects may not have enough statistical power to identify the real association. Second, all the included articles in the current meta-analysis were published in English, therefore publication bias may exist. Third, the overall conclusions were based on unadjusted ORs, a more precise estimation should be adjusted by age, environmental, and other possible confounding factors.

In conclusion, the present meta-analysis demonstrated that IL-6 -174G/C and -572C/G polymorphisms may be associated with the risk of TB. Analysis of the data for the IL-6 G/A nt565 polymorphism did not reveal a substantial contribution to TB susceptibility. Further large-scale and well-designed studies are required to confirm these results.

Acknowledgements
This study was supported by Grants from the Medical and Health Science and Technology Plan of Zhejiang Province (2016KYB245).

Disclosure of conflict of interest
None.

Address correspondence to: Meihua Wang, Department of Respiration, Chunan First People's Hospital, North Huanhu Road, Hangzhou 310024, China. E-mail: wangmeihuasd@163.com

References
[15] Lee YH, Choi SJ, Ji JD, Song GG. Associations between the angiotensin-converting enzyme insertion/deletion polymorphism and suscep-
IL-6 gene polymorphisms and tuberculosis


