Association between Interleukin-18-137G/C Gene Polymorphisms and Tuberculosis Risk in Chinese Population: A Meta-Analysis

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Abstract

This study was to investigate the relationship between IL-18-137G/C polymorphism and TB risk by meta-analysis. The literatures about the IL-18-137G/C polymorphism and risk of tuberculosis were selected from four English databases and four Chinese databases. Data were extracted from the studies by two independent reviewers. Statistical analysis was executed using Revman 5.3 and Stata 11.0 software. A total of 5 studies with 558 TB patient and 720 controls were included in this meta-analysis. The results showed that-137G/C polymorphisms in the IL-18 gene were associated with TB risk in China when taking comparisons of the G allele vs. C allele (OR=1.49, 95% CI=1.21-1.84, P=0.0002), GG vs. GC+X:OR=1.84, P=0.0002), GG vs. GC+X:OR=1.63 vs. GC+CC:OR=1.13-1.70, P=0.003; GG vs. GC+CC:OR=1.31-1.91, P=0.0008; GG vs. GC+CC:OR=2.02, 95% CI=1.33-3.07, P=0.0010). This study provides the evidence that the allele G of IL-18-137G/C polymorphism was closely associated with TB risk in China.

Keywords: Interleukin 18; Gene polymorphism; Tuberculosis; Meta-analysis

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (MTB), and is a serious public health problem that has caused 1.6 million deaths every year over the world, especially in Asia and Africa [1-4]. However, only 10% of people infected with Mycobacterium tuberculosis may develop into clinical disease, which indicates that some factors can devote to the pathogenesis of tuberculosis, including host immune response and gene environment interactions [4,5]. The genetic influence on TB infection has had a series of studies which mainly related to the associations between gene polymorphism and TB risk [6]. They entirely demonstrated that host genetic factors were connected with TB susceptibility.

The interleukin -18 (IL-18) genes, which is located at chromosome 11q22.2-22.3 with six exons and five introns, is called interferon (IFN)-γ-inducing factor affiliated to IL-1 family secreted by plenty of immune cells, such as monocytes, dendritic cells, activated macrophages, and Kupffer cells [7-9]. IL-18 has been recognized as an essential role in resistant immunity against tuberculosis, and possesses a-137G/C polymorphisms in the promoter region which showed a critical influence on tuberculosis [10-12]. The function of IL-18-137 gene region can regulate the different transcriptions. Several case-control studies have been carried out to confirm whether IL-18-137G/C polymorphisms is correlated to susceptibility to tuberculosis. The results showed some differences between districts, population, and nations [13-21]. In order to get a more dependable conclusion, those relevant case-control data were extracted for a meta-analysis to be performed.

Results

Study selection process and characteristics

Twenty-nine potentially relevant studies were filtered from our publication’s search, and four case-control articles about IL-18-137G/C polymorphism met the inclusion criteria, of which four studies derived from China. The remaining four papers were integrated, a gross of 558 cases and 720 controls were included into the final meta-analysis. The detail characteristics of the eligible literature were presented in Tables 1 and 2.

Quantitative data synthesis

The meta-analysis results demonstrated that the pooling statistical analysis of all models showed some association between IL-18-137G/C polymorphisms and TB susceptibility in Chinese people (G allele vs. C allele: OR=1.49, 95% CI=1.21-1.84, P=0.0002; GG vs. CC: OR=1.63 95% CI=1.04-2.57, P=0.03; GC vs. CC: OR=1.60, 95% CI=1.04-2.46, P=0.03; GG vs. GC+CC: OR=1.60, 95% CI=1.24-2.06, P=0.0003) (Figure 1).
A significant relationship was found in the subgroup of Chinese adults under allele model and recessive model (G allele vs. C allele: OR=1.32, 95% CI=1.03-1.70, P=0.03; GG vs. GC+CC: OR=1.39, 95% CI=1.01-1.91, P=0.04) (Figure 2). Moreover, significantly increased risk of TB was presented in G allele in Chinese children: allele model (G allele vs. C allele: OR=1.91, 95% CI=1.31-2.78, P=0.0008) (Figure 3), recessive model (GG vs. GC+CC: OR=2.02, 95% CI=1.33-3.07, P=0.0010), while no association was observed in homozygous model (GG vs. CC: OR=1.47, 95% CI=0.90-2.40, P=0.12; OR=2.95, 95% CI=0.82-10.69, P=0.16).

**Figure 2:** Subgroup forest plot of the association between IL-18 G/C polymorphisms and TB susceptibility for allele test (G vs. C) in Chinese adults.

**Publication bias**

Both Beggs funnel plot and Egger’s linear regression test were performed to reveal the publication bias of the included studies. No significantly statistic evidence of publication bias was observed in allelle model and any of the genetic contrast by Egger’s test funnel plot (all P>0.05). Furthermore, the Beggs funnel plots have no obvious asymmetry under all of genetic models among Chinese (all P>0.05). But

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**Table 2:** Main age information of population that was included in the studies.

| First author | Year | Country | Ethnicity | Provence | Type of tuberculosis | The diagnosis of TB patient | Controls | Genotyping method | HIV status | Sample size |
|--------------|------|---------|-----------|----------|----------------------|----------------------------|----------|-------------------|------------|-------------|
| Lai YB [18]  | 2013 | China   | Asian     | Jie Yang | PTB                  | Clinical symptoms, sputum positive, and X-ray, X-ray, and unrelated to TB patients | PCR-     | Negative          | 122/107    |
| Wang CY a [19]| 2007a| China   | Asian     | Chong Qing | PTB                  | National Diagnostic Criteria of TB | Health controls | PCR-SSP          | Unknown    | 91/167      |
| Wang CY b [19]| 2007b| China   | Asian     | Chong Qing | PTB                  | National Diagnostic Criteria of TB | Health controls | PCR-SSP          | Unknown    | 32/82       |
| Liang ZH [20]| 2009 | China   | Asian     | Shen Zen  | PTB                  | Clinical symptoms, sputum positive, and X-ray | Never infected TB, unrelated to TB patients | PCR-SSP          | Unknown    | 200/197     |
| Zhou C [21]  | 2008 | China   | Asian     | Chong Qing | PTB                  | National Diagnostic Criteria of TB | Healthy examination | PCR-SSP          | Negative    | 113/167     |

**Table 1:** Main characteristics of the studies were included in the meta-analysis.

| First author | Case | Population | Average age | Proportion of gender | Control | Population | Average age | Proportion of gender |
|--------------|------|------------|-------------|----------------------|---------|------------|-------------|----------------------|
| Lai YB [18]  | Adults | 33.4 ± 10.2 | Unknown     | Adults               | 32.6 ± 9.8 | unknown    |
| Wang CY a [19]| Children | 7 ± 4.77 | 47:44:00    | Children             | 5.6 ± 3.5 | 89:78      |
| Wang CY b [19]| Adults | 44 ± 3.6  | 22:10       | Adults               | 41 ± 1.5  | 46:36:00   |
| Liang ZH [20]| Adults | 33 ± 10.7 | 112:88      | Adults               | 31 ± 9.3  | 112:85     |
| Zhou C [21]  | Children | 8 ± 5.6   | 1:01        | Children             | 4.7 ± 2.9  | 1:01       |
Egger’s test was not applied in comparison of Indian due to the inadequate studies. The funnel figures are not appeared due to there are less than 10 pieces of studies. Detailed information of meta-analysis is listed in Tables 3 and 4.

Figure 3: Subgroup forest plot of the association between IL-18 G/C polymorphisms and TB susceptibility for allele test (G vs. C) in Chinese children.

Table 3: Baseline characteristics of the 6 eligible studies for the analysis of IL-18-137G/C polymorphisms and tuberculosis.

| First author | Year | Country | Ethnicity | Source of controls | Genotype of the IL-18-137C/G | Sample size(case/control) |
|--------------|------|---------|-----------|-------------------|-----------------------------|-------------------------|
| Lai YB [18]  | 2013 | China   | Asian     | PB                | G/G vs. C/G; C/C           | 122/107                 |
| Wang CY a [19]| 2007 | China   | Asian     | PB                | G/G vs. C/G; C/C           | 91/167                  |
| Wang CY b [19]| 2007 | China   | Asian     | PB                | G/G vs. C/G; C/C           | 32/82                   |
| Liang ZH [20] | 2009 | China   | Asian     | PB                | G/G vs. C/G; C/C           | 200/197                 |
| Zhou C [21]  | 2008 | China   | TB        |                   | G/G vs. C/G; C/C           | 113/167                 |

Table 4: Determination of the genetic effects of IL-18 polymorphisms on TB in subgroup analysis.

| Allele model | Homozygous model | Dominant model | recessive model |
|--------------|------------------|---------------|----------------|
| -137G/C      | G allele vs. C allele | GG vs. CC | GG vs. GC+CC |
| Chinese      | 1.48 (1.20-1.83)  | 0.0022 1.63 (1.04-2.57) 0.03 | 1.60 (1.04-2.46) 0.03 |
| Chinese adult| 1.32 (1.03-1.70)  | 0.03 1.47 (0.90-2.40) 0.12 | 1.49 (0.94-2.36) 0.09 |
| Chinese children| 1.91 (1.31-2.78) | 0.0008 2.95 (0.82-10.69) 0.1 | 2.52 (0.70-9.09) 0.16 |

Discussion

TB is a chronic infection disease caused high morbidity and mortality in Asia and internationally. Many researchers have confirmed that a series of cytokines take possession of critical roles in development of tuberculosis development [13,14]. Furthermore, several studies have revealed genetic marks of the IL-18 gene promoter region correlating to TB risk and susceptibility, although the outcome
of TB is regulated by the environment and mycobacteria [15]. IL-18 is an essential regulatory as well as pro-inflammatory cytokine; it is an effective resistance to the intracellular infection when production of IL-18 increases by pathogen. The several polymorphisms associated with TB risk have been identified in the range of promoter region, such as -137G/C, +105A/C, -607A/C, -372C/G [16,17]. But less statistical analysis has been used to get the inconclusive association between IL-18-137G/C polymorphism and TB susceptibility. Meta-analysis is a powerful method to provide further evidences for reconciling the controversial points.

This meta-analysis was based on 5 literatures containing 6 studies with 723 cases and 893 controls. The statistically significant results shown in comparisons of G versus C, GG versus CC, GG+GC versus CC, and GG versus CC+GC suggest that G allele of IL-18-137G/C polymorphism was significantly associated with increased risk of TB in the general Asian population according to overall studies' statistics. In the subgroup analysis by nationality, significant associations were discovered in Chinese adult and children but not in Indian, more studies should be needed to confirm our results. All in all, we found a significant association between IL-18-137G/C polymorphisms and TB risk in Chinese population under allele model, homozygous model, dominant model, and recessive model.

Some definite potential limitations should be considered in this meta-analysis when confronting with our results. First, only published literatures were included in this meta-analysis, but did not seek as well as get available unpublished and on-going studies. It is also possible that some of unpublished studies and written or published papers in other language which might meet the inclusion criteria were missed, although our statistic of publication bias was not significant. Second, no original data about gene-gene and gene-environment interactions from these studies were obtained, however, gene-gene and gene-environment interactions also could be factors contributing to the risk of TB. Third, under the subgroup analyses, there were not enough relevant studies found in other countries, most of case-control studies were searched from Chinese, and the result might just be applicable to Chinese population or Asia. Fourth, the control individuals of the included studies could not be confirmed whether they had latent TB infection which could develop into active TB in future. In conclusion, the meta-analysis conducted that the allele G of the IL-18 -137G/C polymorphisms might be associated with increased risk for TB infection in Asia area, especially in Chinese population. More studies with large sample sizes and multi-centers should be included to validate our preliminary findings.

Materials and Methods

We analyzed literatures using the four English databases (PubMed, Embase, Science Direct, Ovid) and four Chinese databases (CNKI, WangFang, CBM, CNKI, FMJS) to search studies involving MESH terms “Tuberculosis, Pulmonary” and “Polymorphism, Single Nucleotide” or “SNP” combined with “Interleukin*18” or “IL-18”. Data were extracted independently by two reviewers according to the inclusion and exclusion standard, and reached a compromise on items mentioned above. If any disagreement based on criteria, the group came to agreement through discussions and inducing a third party. The necessary data were collected from each literature, including first author's name, year of the publication, country, the ethnicity, genotyping method, and total number of sample size, case-control detail, the number of IL-18-137G/C genotypes and alleles for case and control.

Criteria for considering studies for this review

All included studies had to comply with following criteria: (1) publications concentrate on the IL-18-137G/C promoter polymorphisms and TB risk; (2) case-control studies diagnosis should meet the international criteria; (3) total sample size ≥ 100 (case +control) (4) the genotype quantity should be available for evaluating the odds ratio (OR) with 95% confidence interval (CI) and P value. The exclusion criteria were (a) non-case-control, (b) meta-analysis, (c) animal researches, (d) studies without genotype frequency.

Data extraction

Data were extracted independently by two reviewers according to the inclusion and exclusion standard, and reached a compromise on items mentioned above. If any disagreement based on criteria, the group came to agreement through discussions and inducing a third party. The necessary data were collected from each literature, including first author's name, year of the publication, country, the ethnicity, genotyping method, and total number of sample size, case-control detail, the number of IL-18-137G/C genotypes and alleles for case and control.

Data collection and analysis

The pooled odds ratio (OR) with its 95% confidence interval (CI) was used to appraise the strength of the relationship between the IL-18 polymorphisms and TB risk. The significance of the pooled OR was determined by the Z-test, in which P<0.05 was considered significant. The pooled ORs were calculated for allele model (G allele versus C allele), dominant model (GG+GC versus CC), recessive model (GG versus GC+CC). The studies' heterogeneity was assessed by the Chi-square-based Q-test and the inconformity of index I (2). Heterogeneity assumption was regarded to be statistically significant if P<0.10. When P ≥ 0.10, the pooled statistical analysis was calculated by the fixed-effect model, otherwise, a random-effect model was also used. To evaluate the age-level of Chinese population's effects, subgroup analyses were performed by age group. Review manager 5.0 program provided by the Cochrane Library and Stata (Version 11.0, Stata Corporation) were used to perform all the statistical analysis.

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Author Contributions Statement

• 1 L.Q.S. collected the papers about this meta-analysis and wrote the manuscript including analysed the results.
• 2 H.Z. and X.L.H. reviewed and evaluated the papers for this meta-analysis review.
• 3 Z.L. J.R.Y. and C.P.X. reviewed and evaluated the papers.
• 4 F.K.B. and A.H.I. conducted the manuscript and as corresponding authors.

References

1. Shijubo N, Shigehara K, Okamura H, Kurimoto M, Abe S, et al. (2000) Increased levels of circulating interleukin-18 in patients with advanced tuberculosis. Am J Respir Crit Care Med. 161: 1786-1789.
2. Sasindran SJ, Torrelles JB (2011) Mycobacterium Tuberculosis Infection and Inflammation: what is Beneficial for the Host and for the Bacterium?. Front Microbiol 2:1-18.
3. Gracie JA, Robertson SE, McInnes LB (2003) Interleukin-18. J Leukoc Biol 73: 213-224.
4. Azad AK, Sadee W, Schlesinger LS (2012) Innate immune gene polymorphisms in tuberculosis. Infect Immun 80: 3343-3359.
5. Alagarasu K, Harishankar M, Vidyarani M, Nisha Rajeswari D, Narayanan PR, et al. (2008) Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis. Cytokine 43: 26-33.
6. Na MJ, Paik TH, Kim HJ, Park JK, Jo EK, et al. (2002) IL-18 production in human pulmonary and pleural tuberculosis. Scand J Immunol 56: 611-618.
7. Thorand B, Benjamin EJ, Blankenberg S, Koenig W, Schnabel RB, et al. (2015) Molecular Characterization of the NLRC4 Expression in Relation to Interleukin-18 Levels. Circ Cardiovasc Genet 115: 1-19.
8. Dinarello CA (1999) IL-18: A TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. J Allergy Clin Immunol 103: 11-24.
9. Dungan LS, Sutton CE, Basdeo SA, Fletcher JM, Mills KH, et al. (2011) Caspase-1-processed cytokines IL-1beta and IL-18 promote IL-17 production by gammadelta and CD4 T cells that mediate autoimmunity. J Immunol 186: 5738-5748.
10. Chung JH, Kim JW, Seok H, Lew BL, Sim WY, et al. (2014) Association between interleukin 18 polymorphisms and alopecia areata in Koreans. J Interferon Cytokine Res 34: 349-353.
11. Lee YM, Chang CL, Kim YS, Lee MK, Park SK, et al. (2011) Association between the interleukin-18 promoter polymorphism and pulmonary tuberculosis in a Korean population. Int J Tuberc Lung Dis 15: 1246-1251.
12. Birbain N, Singh J, Jindal SK (2013) Protective role of IL-18 -137G/C polymorphism in a North Indian population with asthma: a pilot study. Cytokine 61: 188-193.
13. Yin JJ, Selvaraj P (2010) Genetic susceptibility in tuberculosis. Respirology 5: 241-256.
14. Moller M, Wit E, Hoal EG (2010) Past, present and future directions in human genetic susceptibility to tuberculosis. FEMS Immunol Microbiol 58: 3-26.
15. Yue J, Lian YY, Zhao YL, Wang HX, Liu LR, et al. (2011) Relationship between single nucleotide polymorphism of interleukin-18 and susceptibility to pulmonary tuberculosis in the Chinese Han population. Microbiol Immunol 55: 388-393.
16. Giedraitis V, He B, Huang WX, Hillert J (2001) Cloning and mutation analysis of the human IL-18 promoter: a possible role of polymorphisms in expression regulation. J Neuroimmunol 112: 146-152.
17. Woo JS, Chae SW, Lee SH, Kang HJ, Hwang SJ, et al. (2006) Interleukin-18/-607 gene polymorphism in allergic rhinitis. Int J Pediatr Otorhinolaryngol 70: 1085-1088.
18. Lai Y, Chen D (2013) Association between IL-18 promoter polymorphism and tuberculosis susceptibility for chinese population of JiYang GuangDong. Med J 34: 2553-2555.
19. Wang C (2007) Association of polymorphisms of IL-18 and IL-18a gene promoter with susceptibility to tuberculosis in ChongQing[thesis]. Chongqing Med Univ.
20. Liang Z, Yang H, Fen T, Wanf F, Xuu X (2009) Relationship between polymorphisms of interleukin-18 gene promoter region and susceptibility to pulmonary. Pract Med 25: 2939-2941.
21. Zhou C (2008) Association between IL-18-137G/C promoter polymorphism about protein expression and TB susceptibility in ChongQing children of Chinese. J ChongQing Medical Univ. 33, 1029-1033.