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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.06, P=0.0003). It was also significant in the subgroup analysis of Chinese adults (G allele *vs.* C allele: OR=1.32, 95%=CI 1.03-1.70, P=0.003; GG *vs.* GC+CC: OR=1.39, 95% CI=1.01-1.91, P=0.04) and Chinese children (G allele *vs.* C allele: OR=1.91, 95% CI=1.31-2.78, 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: Interlukin 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 Asian 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 extrons 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+CC *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).

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			Control		
	Population	Average age	Proportion of gender	Population	Average age	Proportion 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	8.6 ± 5.6	1:01	Children	4.7 ± 2.9	1:01

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

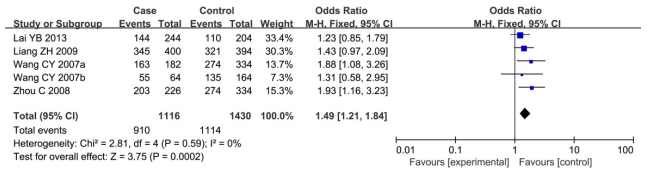

Figure 1: Forest plots of the association between the IL-18-137G/C polymorphisms and TB susceptibility for allele test (G *vs.* C) in Chinese population.

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=0.1) and dominant model (GC+GG *vs.* CC: OR=1.49, 95% CI=0.94-2.36, P=0.09; OR=2.52, 95% CI=0.70-9.09, P=0.16).

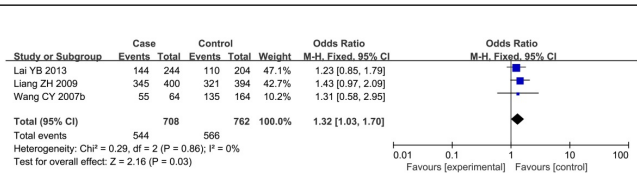

Figure 2: Subgroup forest plot of the association between IL-18 G/C polymorphisms and TB susceptibility for allele test (G *vs.* C) in Chinese adults.

Publication bias

Both Begg's 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 allele model and any of the genetic contrast by Egger's test funnel plot (all P0.05). Furthermore, the Begg's funnel plots have no obvious asymmetry under all of genetic models among Chinese (all P0.05). But

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.

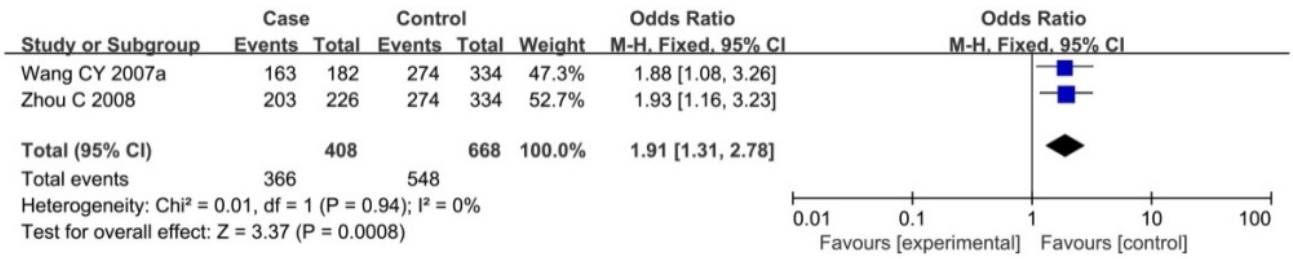

Figure 3: Subgroup forest plot of the association between IL-18 G/C polymorphisms and TB susceptibility for allele test (G *vs.* C) in Chinese children.

First author	Year	Country	Ethnicity	Source of controls	Genotype of the IL-18-137C/G												
					Cases						Control						Sample size(case/control)
					G/G		G/C		C/C		G/G		G/C		C/C		
					N	%	N	%	N	%	N	%	N	%	N	%	
Lai YB [18]	2013	China	Asian	PB	57	46.7	30	24.6	35	28.7	45	42.1	20	18.7	42	39.3	122/107
Wang CY a[19]	2007a	China	Asian	PB	91	83.49	17	15.6	1	0.01	113	0.68	48	0.29	6	0.34	91/167
Wang CY b[19]	2007b	China	Asian	PB	24	0.75	7	0.22	1	0.31	56	0.68	23	0.28	3	0.04	32/82
Liang ZH [20]	2009	China	Asian	PB	154	77	37	18.5	9	4.5	135	68.5	51	25.9	11	5.6	200/197
Zhou C [21]	2008	China	Asian	TB	92	81.4	19	16.8	2	1.8	113	67.7	48	28.7	6	3.6	113/167

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

	Allele model		Homozygous model		Dominant model		recessive model	
	OR (95%)	P	OR (95%)	P	OR (95%)	P	OR (95%)	P
-137G/C	G allele *vs.* C allele		GG *vs.* CC		GC+GG *vs.* CC		GG *vs.* GC+CC	
Chinese	1.48 (1.20-1.83)	0.0002	1.63 (1.04-2.57)	0.03	1.60 (1.04-2.46)	0.03	1.60 (1.247-2.06)	0.0003
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	1.39 (1.01-1.91)	0.04
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	2.02 (1.33-3.07)	0.001

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

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 cytokines; 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 statis`tic 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". We had no restriction to language, time period, sample size, and publication type.

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 radio (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 discusses 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% confident 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 P0.05 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 P0.10. 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 the manuscript.
- 4 F.K.B. and A.H.L. conducted the manuscript and as corresponding authors.

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