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META-ANALYSIS

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Arg753Gln Polymorphisms in Toll-Like Receptor 2 Gene are Associated with Tuberculosis Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Numerous epidemiological studies have reported the association between polymorphisms of Toll-like receptor 2 (TLR2) and susceptibility to tuberculosis (TB). However, the results remain inconclusive. Therefore, we performed a quantitative meta-analysis to evaluate associations between the polymorphism of Arg753Gln of the TLR2 gene and susceptibility to TB.

Material/Methods: Three databases (PubMed, CNKI and Embase) were systematically searched for eligible studies. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) as our index were used to assess the relation between the TLR2 gene Arg753Gln polymorphism and risk of TB. Overall and subgroup analyses were conducted according to the available information.

Results: With a detailed selection, 7 eligible studies with 1486 cases and 1322 controls were identified in our meta-analysis. There was a significant difference between TLR2 gene Arg753Gln polymorphism and the risk of TB (additive model: P<0.01, OR=2.89, 95% CI: 2.13–3.91; GA *vs.* GG: P<0.01, OR=2.92, 95% CI: 2.09–4.08). Interestingly, subgroup analysis based on ethnicity indicated that TB risk was significantly increased in Asians (additive model: P<0.01, OR=3.17, 95% CI: 2.31–4.35; GA *vs.* GG: P<0.01, OR=3.29, 95% CI: 2.32–4.68); by contrast, there was no association found in whites (additive model: P=0.40, OR=0.57, 95% CI: 0.15–2.13; GA *vs.* GG: P=0.40, OR=0.57, 95% CI: 0.15–2.13).

Conclusions: Our meta-analysis provides evidence that the TLR2 gene Arg753Gln polymorphism is a risk factor to TB, especially in Asian populations.

MeSH Keywords: Genes, vif • Polymorphism, Genetic • Tuberculosis, Pulmonary

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Background

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is still great a serious health problem throughout the world. It is reported that approximately 2 million people die of this disease annually [1]. Another study showed that one-third of the population around the world is infected by *Mycobacterium tuberculosis*, but only one-tenth of infected individuals developed active TB [2]. Furthermore, TB mainly occurs in the developing countries of Asia and Africa [3,4], which indicates the occurrence of TB may have specific regional differences. Therefore, we have reason to suspect that apart from environmental factors, genetic variability may also participate in the advancement of this infection. This view has been verified in previous studies, and several gene polymorphisms have been reported to be associated with TB susceptibility [2,5,6].

Toll-like receptors (TLRs) are a family of mammalian cell-surface proteins that play an essential role in regulation of inflammatory reactions and activation of the adaptive immune response. This protein family can mediate cellular responses to microorganisms to eliminate the harmful effects of pathogens. Among the various TLRs, TLR2 can recognize the most diverse set of pathogens, such as peptides derived from *Borrelia*, *Mycoplasma*, *Treponema*, and *M. tuberculosis* [7,8]. When this receptor is blocked, the response of cell the to mycobacterial peptides is influenced. This gene is located on the long arm of chromosome 4 (4q32) [9], in which many single-nucleotide polymorphisms (SNPs) have been identified. Among the various SNPs, Arg753Gln (rs5743708, G2258A) of TLR2 is best characterized by functional studies, and its effect on the development of TB has recently received increased attention. This novel polymorphism in TLR2 gene, leading to a substitution of arginine to glutamine at residue 753, results in a decreased response of macrophages to bacterial peptides, and ultimately causes an attenuated immune response in the host [8].

A number of published studies have evaluated the relationship between the TLR2 Arg753Gln polymorphism and the susceptibility to TB, but the results are inconsistent. It is still unclear whether the TLR2 Arg753Gln polymorphism is a risk factor for TB. Therefore, to derive a more precise estimation of the relationship between the TLR2 Arg753Gln polymorphism and the risk of TB, we performed this meta-analysis by combining the data from case-control studies to reach more convincing results.

Material and Methods

Study selection and inclusion criteria

We systematically searched for relevant studies in PubMed, Embase, and Chinese National Knowledge Infrastructure (CNKI) databases (the last search was updated on December 10, 2014), using the following keywords ("polymorphism" OR "SNPs" OR "Single Nucleotide Polymorphism") and ("Toll-Like Receptor 2" OR "TLR2" OR "TLR2 Receptor") and ("Tuberculosis" or "TB") without language limitations. Reference lists cited in this study were also searched by 2 independent reviewers (H. Wu and Y. Li) until no new references were found.

The eligibility criteria were: (1) the studies explored the association between TLR2 polymorphisms (Arg753Gln) and TB susceptibility, (2) the studies are case-control studies, (3) the articles must provide sufficient data of outcome about odds ratios (ORs) with the corresponding 95% confidence intervals (CIs), and (4) when multiple studies were based on the same data, the study with the largest sample size was selected. Excluded criteria were: (1) review, case editorial, report, or comment; (2) duplicated studies, and (3) animal studies.

Data extraction

Two investigators (H. Wu and Y. Li) independently extracted data. Controversy was resolved by discussion. The main characteristics of articles were listed as follows: first author's name, year of publication, country, ethnicity, source of controls, goodness-of-fit of Hardy-Weinberg equilibrium (HWE) in control group, sample types of TB, total number of cases and controls, and the distribution of genotypes in the cases and controls.

Statistical analysis

The ORs and corresponding 95% CIs were analyzed to evaluate the associations between the *TLR2 gene* Arg753Gln polymorphisms and TB risk. The pooled ORs were calculated in the dominant model (AA + GA *vs.* GG), the recessive model (AA *vs.* GA + GG), and the additive model (G *vs.* A). Moreover, pooled estimates were also calculated for the pair-wise comparisons (allele GA *vs.* GG, and allele AA *vs.* GG). Heterogeneity among the studies was evaluated by the chi-square-based Q-test and I^2 test [10,11]. A significant result produced by the Q test ($P<0.10$ or $I^2>50\%$) it means heterogeneity exists across articles, and the random-effects model was used to measure the pooled OR; otherwise, the fixed-effects model was used. Subgroup analysis was mainly conducted based on the ethnicity and source of controls, which were used to investigate and explain the heterogeneity among the studies. In addition, Hardy-Weinberg equilibrium (HWE) was also tested in the control group, which was calculated using a chi-square test if genotype data were available. We also conducted sensitivity analysis to evaluate the stability of the results by excluding each study in turn.

Publication bias was analyzed by several methods. A funnel plot was used to analyze publication bias qualitatively. Egger's and

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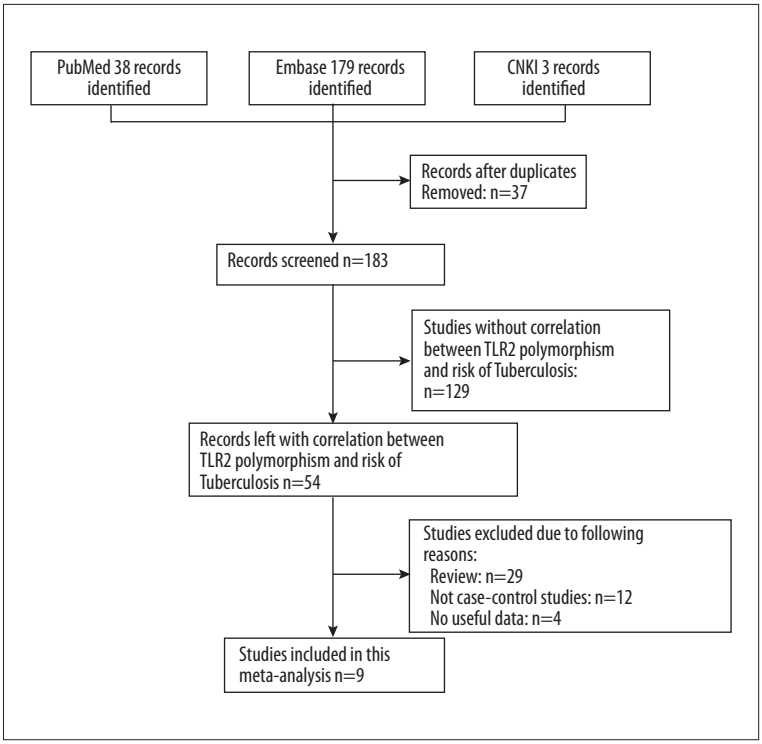

Figure 1. Flow diagram of the selection of eligible studies.

Begg's tests were used to analysis publication bias quantitatively. P<0.05 was statistically significant [12,13]. Furthermore, for the possible publication bias, the trim and fill method, which estimates the number and results of potential missing studies resulting from publication bias, was also used to estimate publication bias. All data were performed with RevMan 5.0 software and STATA 11.0 software.

Results

Selection and characteristics of studies

Our search strategy found 220 individual records, of which 9 studies met our inclusion and exclusion criteria [14–22]. However, 2 studies [16,18] among these 9 original studies failed to detect the A allele and were dropped. Finally, 7 eligible studies with 1486 cases and 1322 controls were included in the meta-analysis, and the details of the selection process are shown in Figure 1. Table 1 lists the main characteristics of studies included in this meta-analysis. The HWE was tested in each study, and all including studies met the HWE expectations except for 1 [14]. Furthermore, due to the limitation of the original data, AA genotype frequency was so low that only 2 models (additive model and GA *vs*. GG) could be used to evaluate the association between TLR2 gene Arg753Gln polymorphisms and TB risk.

Meta-analysis

The main results of the meta-analysis are shown in Table 2. There was a significant difference between TLR2 gene Arg753Gln polymorphism and the susceptibility to TB (additive model: P<0.01, OR=2.89, 95% CI: 2.13–3.91, Figure 2A; GA *vs*. GG: P<0.01, OR=2.92, 95% CI: 2.09–4.08, Figure 2B). Heterogeneity was small in these 2 genetic models (P>0.05) and the fixed-effects model was used. Subgroup analysis based on ethnicity indicated that TB risk was significantly increased in Asian populations (additive model: P<0.01, OR=2.82, 95% CI: 2.01–3.96; GA *vs*. GG: P<0.01, OR=3.02, 95% CI: 2.25–4.60). In contrast, no association was found in white populations (additive model: P=0.40, OR=0.57, 95% CI: 0.15–2.13; GA *vs*. GG: P=0.40, OR=0.57, 95% CI: 0.15–2.13). Subgroup analysis based on source of controls also showed a discrepant result. Compared to a negative outcome from the subgroup of population based controls (additive model: P=0.71, OR=1.41, 95% CI: 0.23–8.66; GA *vs*. GG: P=0.67, OR=1.55, 95% CI: 0.20–11.87), a positive outcome was found in the subgroup of hospital-based controls (additive model: P<0.01, OR=3.13, 95% CI: 2.02–4.85; GA *vs*. GG: P<0.01, OR=2.44, 95% CI: 1.34–4.44). In addition, a stratified analysis was also performed because 1 study [14] deviated from HWE. When we removed it and conducted the analysis, a similar significant result was found (additive model: P<0.01, OR=2.82, 95% CI: 2.01–3.96; GA *vs*. GG: P<0.01, OR=3.02, 95% CI: 2.25–4.60). The heterogeneity in most subgroup analysis was not significant, and the fixed-effects model was used. However, the population-based controls subgroup

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Table 1. Characteristics of the eligible studies in the meta-analysis.

Author	Year	Country	Ethnicity	Source of controls	HWE of controls	Sample types	Sample size		Case					Control				
							Case	Control	G	A	GG	GA	AA	G	A	GG	GA	AA
Sánchez	2012	Colombia	White	Population-based	0.907	PTB	466	300	929	3	463	3	0	596	4	296	4	0
Dalgic	2011	Turkey	Asian	Hospital-based	0.608	PTB+ EPTB	198	200	350	46	152	46	0	386	14	186	14	0
Ma	2010	China	Asian	Hospital-based	N	PTB	543	544	1086	0	543	0	0	1088	0	544	0	0
Etokebe	2010	Croatian	White	Hospital-based	0.961	PTB	103	105	205	1	102	1	0	209	1	104	1	0
Xue	2009	China	Asian	Population-based	0.972	PTB	205	203	409	1	204	1	0	405	1	202	1	0
Biswas	2009	India	Asian	Hospital-based	N	PTB	100	100	200	0	100	0	0	200	0	100	0	0
Ogus	2004	Turkey	Mixed	Hospital-based	0.0003	PTB+ EPTB	151	116	261	41	124	13	14	221	11	107	7	2
Selvaraj	2010	South India	Asian	Hospital-based	0.972	PTB	193	199	385	1	192	1	0	387	1	198	1	0
Jin	2007	China	Asian	Population-based	0.233	PTB	170	199	269	71	99	71	0	367	31	168	31	0

PTB – pulmonary tuberculosis; EPTB – extrapulmonary tuberculosis.

Table 2. Pooled Analysis of the Association between the TLR2 Arg753Gln polymorphism and TB risk.

Genetic model	Subgroup	Case	Control	I^2 (%)	P_h	Analysis model	P	OR (95%CI)	Begg's test	Egger's test
G *vs.* A	Total	2972	2634	24	0.25	F	<0.01	2.89 [2.13, 3.91]	0.368	0.035
	Total*	2670	2402	36	0.17	F	<0.01	2.82 [2.01, 3.96]		
	White	1138	810	0	0.64	F	0.40	0.57 [0.15, 2.13]		
	Asian	1834	1824	0	0.82	F	<0.01	3.17 [2.31, 4.35]		
	Hospital-based	1700	1636	0	0.71	F	<0.01	3.13 [2.02, 4.85]		
	Population-based	1272	998	82	0.02	R	0.71	1.41 [0.23, 8.66]		
GA *vs.* GG	Total	1486	1322	48	0.07	F	<0.01	2.92 [2.09, 4.08]	0.764	0.040
	Total*	1335	1206	46	0.10	F	<0.01	3.22 [2.25, 4.60]		
	White	569	405	0	0.64	F	0.40	0.57 [0.15, 2.13]		
	Asian	917	917	20	0.29	F	<0.01	3.29 [2.32, 4.68]		
	Hospital-based	850	823	11	0.34	F	<0.01	2.44 [1.34, 4.44]		
	Population-based	636	499	85	0.009	R	0.67	1.55 [0.20, 11.87]		

* One study (Ogus et al., 2004) was omitted because of deviation from HWE; CI – confidence interval; OR – odds ratio.

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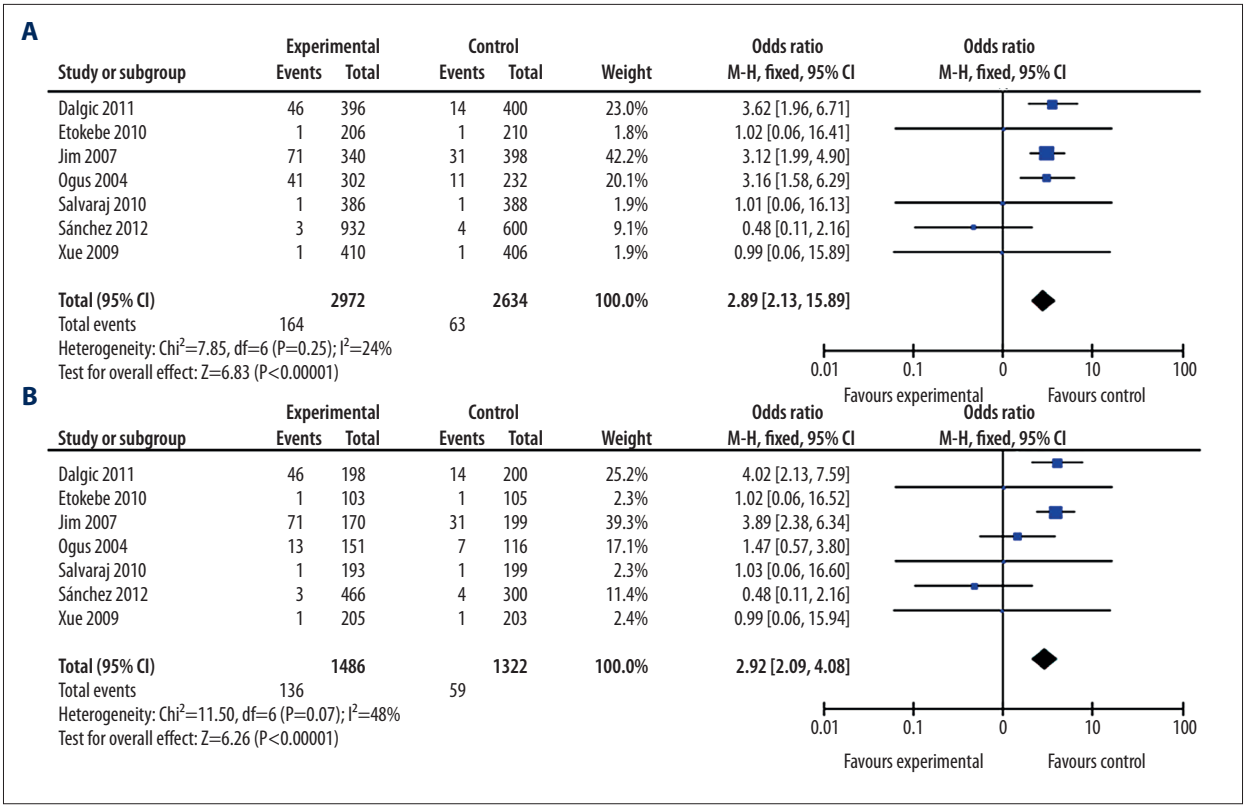

Figure 2. Meta-analysis for the association between TB risk and the TLR2 Arg753Gln polymorphism. (**A**) Meta-analysis of A *vs*. G (additive model) using the fixed-effects model. (**B**) Meta-analysis of GA *vs*. GG using the fixed-effects model.

showed higher heterogeneity, so that the random-effects model was used.

Sensitivity analysis and publication bias

Publication bias was detected based on the symmetry of funnel plots and Begg's and Egger's tests. The shape of funnel plots were asymmetrical, and the Egger's test showed P<0.05. However, Begg's test indicated no publication bias existed. Considering the conflicting results and the possible publication bias, the trim-and-fill method was used to estimate the publication bias [23]. Although this method indicated 2 potential studies missing, the final results were similar to the original findings after 2 virtual studies were appended (additive model: OR=2.875, 95% CI: 2.111–3.914; GA *vs*. GG: OR=2.922, 95% CI: 2.077–4.110), which indicated the stability of our results. Sensitivity analyses were performed to evaluate the effect of each study on the pooled OR. The results indicated that the results of the meta-analysis were stable and reliable.

Discussion

Many studies have attempted to reveal the association between various polymorphisms in TLR2 and susceptibility to TB [24–27]. However, the effective of 1 polymorphism, Arg753Gln in TRL 2, is still unclear [14–21]. Although many studies had attempted to explore this possible association, due to the influence of various factors and the differences of experimental design, a more credible and accurate outcome is still lacking. Therefore, in order to enhance this condition, we tried our best to accumulate the available case-control studies to perform this meta-analysis. Finally, 7 studies of the 9 with 1486 cases and 1322 controls were included to perform this quantitative analysis. Because of the lower frequency of the mutation genotypes (GA, AA), the other 2 studies [16, 18], which did not detect the mutation genotypes, were dropped. In particular, this is the first meta-analysis to evaluate the association between TLR2 Arg753Gln polymorphisms and susceptibility to TB.

For the overall data, our study indicated that the TLR2 Arg753Gln polymorphism increased the susceptibility to TB. The results were consistent with those of most previous studies [8,14,15,19,21]. This mutation in the TLR2 gene located at the very C terminus of TLR2 results a substitution of arginine to glutamine. It likely affects the signaling function of the molecule, rather than ligand binding [8]. This Arg753Gln polymorphism may reduce the ability to respond to bacterial peptides *in vitro* and finally leads to an increased susceptibility to TB.

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In the subgroup analysis, most of the subgroup results were consistent with the overall outcome (data not shown). However, the subgroup analysis based on ethnicity showed a discrepant outcome. A significant association was found in Asian populations, but a non-significant association was found in white populations. This result suggests that gene polymorphisms lead to ethnic-specific susceptibility to TB. However, because of the absence of data about other ethnicities, further investigations should include people of different ethnicities to clarify this issue. Furthermore, the subgroup analysis, which was stratified by the source of controls, also showed a discrepant outcome, with significantly increased TB risk observed in the hospital-based group but not the population-based group. In general, population-based controls more closely represent the general population. However, high heterogeneity existed in this population-based subgroup, which could reduce the reliability of this result. This high heterogeneity may be the cause of the discrepant outcome. Therefore, further research is needed to verify this point.

Publication bias is an important factor to consider in meta-analysis. Various methods were used to estimate publication bias in our study. Among these methods, although Egger's test showed that publication bias may be exist in our meta-analysis (P_{egger} <0.05), the trim-and-fill method was applied to adjust for the meta-analysis results by adding the potential missing studies. The adjusted results indicated that 2 potential studies were missing; however, the final results that the TLR2 Arg753Gln polymorphism was a risk factor to TB were not changed. Therefore, this had little influence on the results and demonstrated the robustness and credibility of this meta-analysis. Furthermore, sensitivity analyses were also conducted, and revealed that the results are stable and reliable.

This study has several limitations. First, the sample size was not large enough, and more original articles are needed to make our conclusions reliable and accurate. Second, the original articles provided data about Asians and whites only, so additional research in other ethnicities such as Africans should be performed. Third, most of the included studies lacked data on extra-pulmonary TB. Even if several studies explored pulmonary TB and extra-pulmonary TB, the separate data were mixed together. Furthermore, environment is closely related with the development of TB, and gene-environment interactions should be considered in future studies. Therefore, the results of the present meta-analysis should be interpreted with caution.

Conclusions

This meta-analysis provided evidence about the TLR2 gene Arg753Gln polymorphism and risk of TB, especially in Asian populations. Further research is needed to explain the inconsistent results in different ethnicities.

Competing interests

The authors declare no competing financial interests.

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