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Original Article

Association of toll-like receptor 2 gene polymorphism with susceptibility to pulmonary tuberculosis and tuberculous meningitis: a meta-analysis

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Abstract: Background: Toll-like receptor 2 (*TLR2*) gene plays an important role in the pathogenesis of pulmonary tuberculosis and tuberculous meningitis. The association between *TLR2* T597C polymorphism and the susceptibility to pulmonary tuberculosis has been extensively studied. However, the results of these studies remain inconsistent. Therefore, we performed a meta-analysis to evaluate the association between *TLR2* T597C polymorphism and the susceptibility to pulmonary tuberculosis and tuberculous meningitis. Methods: PubMed, Embase, CNKI, Wanfang, Weipu databases were searched for case-control studies on *TLR2* polymorphisms and the risks of tuberculosis, published up to Nov 31, 2014. To assess the strength of the association between *TLR2* polymorphism and pulmonary tuberculosis and tuberculous meningitis, the odds ratios (ORs) with 95% confidence intervals (CIs) were used. The meta-analysis of the associations between the *TLR2* T597C polymorphism and pulmonary tuberculosis and tuberculous meningitis were carried out under different genetic models. Results: Fourteen published studies with 4381 cases and 5082 controls were included. Overall, there are significant association between *TLR2* T597C polymorphism and the risk of tuberculosis (CC vs. TC OR = 1.26, 95% CI = 1.10-1.43; CC vs. TT OR = 1.20, 95% CI = 1.04-1.38; CC vs. TC+TT OR = 1.23, 95% CI = 1.08-1.39). When stratified by ethnicity, we found a significant association between this polymorphism and tuberculosis risks in Asian (CC vs. TC OR=1.23, 95% CI = 1.02-1.48; CC vs. TT OR = 1.22, 95% CI = 1.12-1.47; CC vs. TC+TT OR = 1.22, 95% CI = 1.02-1.46) and Caucasians (CC vs. TC OR = 1.31, 95% CI = 1.01-1.62; CC vs. TC+TT OR = 1.24, 95% CI = 1.01-1.52). We also found significant the association between this polymorphism and pulmonary tuberculosis (CC vs. TC OR = 1.16, 95% CI = 1.01-1.34) and the tuberculous meningitis (CC vs. TC OR = 3.16, 95% CI = 2.00-5.00; CC vs. TT OR = 3.56, 95% CI = 2.27-5.58; CC vs. TC+TT OR = 3.37, 95% CI = 2.19-5.19; CC+TC vs. TT OR = 1.36, 95% CI = 1.05-1.77; C vs. T OR = 1.52, 95% CI = 1.25-1.85), respectively. Conclusions: *TLR2* T597C polymorphism associated with the susceptibility to pulmonary tuberculosis and tuberculous meningitis.

Keywords: Toll-like receptor 2 T597C, *TLR2*, single nucleotide polymorphism, tuberculosis risk, pulmonary tuberculosis, tuberculous meningitis, meta-analysis

Introduction

According to WHO statistics report in 2010, about one third people in the world have infected with Mycobacterium tuberculosis, in some developing countries, adults who have carried Mycobacterium tuberculosis even up to 80%, about 5% to 10% of these carriers may develop to active tuberculosis. A number of genes participate in the progression from M. tuberculosis infection to tuberculosis diagnosis. Toll-like receptors (TLR) family plays essential roles in the innate responses against M. tuberculosis [3-5]. Toll-like receptors (TLRs) mediate the each stage of the inflammatory response, for example the first line of host defense and the immune activation [6-11]. Therefore, the polymorphisms of TLR1, *TLR2*, TLR4, TLR6 and TLR9 have been reported that they have the susceptibility to pulmonary tuberculosis (PTB) with distinct nationality [12-16]. In contrast, some studies showed that there was no association between the polymorphism of TLRs and the susceptibility to tuberculosis [16-19].

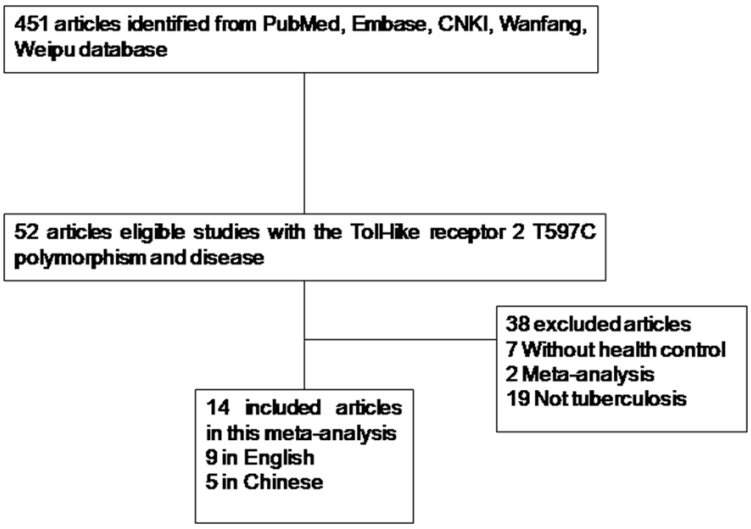

Figure 1. Flow diagram of study selection.

TLR2 gene locates in human's chromosome 4q32 and consists of 4 exons and 3 introns. It contains numerous polymorphisms, in vitro and in vivo studies; *TLR2* plays the critical role in the recognition of M. tuberculosis [20-22].

Up to now, a number of studies have evaluated the association between *TLR2* T597C (rs3804099) polymorphism and risk of different types of tuberculosis in diverse populations. However, results from published studies remain conflicting. Therefore, we performed a meta-analysis on all eligible case-control studies to elucidate the association between *TLR2* T597C polymorphism and the susceptibility to pulmonary tuberculosis and tuberculous meningitis.

Materials and methods

Literature search

We conducted literatures search by using the PubMed, Embase, CNKI, Wanfang, Weipu databases (update to Nov 31, 2014) with the following search terms: "*TLR2*" or "Toll-like receptor 2" and "polymorphism" or "polymorphisms" and "tuberculosis" or "pulmonary tuberculosis" or "tuberculous meningitis". In addition, the reference lists of reviews and retrieved studies were identified by manual search.

Inclusion and exclusion criteria

Basing on the published articles [23], the inclusion criteria were: (1) the study evaluated the association between *TLR2* polymorphism and pulmonary tuberculosis or tuberculous meningitis risk in human; (2) a case-control study; (3) the genotype distributions in both cases and controls were available for estimating the odds ratio with 95% confidence interval (CI) and *P* value; (4) the genotype distributions of cases and controls must be consistent with Hardy-Weinberg equilibrium (HWE). The main exclusion criteria of studies were as follows: (1) case reports, reviews, letters and editorial articles; (2) only have the case population; (3) duplicate of previous publication; and (4) the distribution of genotypes among controls are consistent with HWE.

Data extraction

The data were extracted from every eligible study by two authors independently, and then the authors discussed to reach a consensus. In each study, the first author's name, year of publication, country of origin, ethnicity, the definition of case, source of control selection and genotype frequencies in cases and controls were extracted.

Statistical analysis

For each study, the genotype distributions in the control group were first examined to determine if it is consistent with Hardy-Weinberg. The heterogeneity of each study was evaluated by the X^2 based Q-statistic which was considered statistically significant at *P* value < 0.10. To measure the percentage of variability in the studies that due to heterogeneity rather than chance, the I^2 value was used. If the I^2 value < 70%, the effects were assumed to be homogenous, the fixed-effects model was used (the Mantel-Haenszel method); otherwise, the random-effects model (DerSimonian and Laird method) were used [24-26]. The subgroup analysis by ethnicity was performed, to explore the source of heterogeneity. Hardy-Weinberg equilibrium (HWE) was also tested by Pearson's chi-square test. Comprehensively define the strength of associations between *TLR2* poly-

Table 1. Distribution of *TLR2* genotype and allele among Pulmonary Tuberculosis and Tuberculous Meningitis patients and controls

Auther	Year	Country	Disease	Race	Case	Control
Ma	2007	America	PTB	African American	339	194
Caws	2008	Vietnam	PTB	Asian	165	377
Caws	2008	Vietnam	TBM	Asian	141	377
Che	2010	China	PTB	Asian	115	156
Li	2011	China	PTB	Asian	122	262
Ma	2011	China	PTB	Asian	923	1033
Shi	2012	China	PTB	Asian	20	20
Shi	2012	China	TBM	Asian	9	20
Sun	2013	China	PTB	Asian	280	187
Thuong	2007	Vietnam	PTB	Asian	179	377
Thuong	2007	Vietnam	PTB+TBM	Asian	43	377
Thuong	2007	Vietnam	TBM	Asian	106	377
Xue	2010	China	PTB	Asian	215	230
Arji	2014	Moroccan	PTB	Caucasian	343	202
Etokebe	2010	Croatia	PTB	Caucasian	97	102
Ma	2007	America	PTB	Caucasian	555	224
Naderi	2013	Iran	PTB	Caucasian	174	177
Sa'nchez	2012	Colombian	PTB	Caucasian	465	300
Torres-García	2013	Mexican	PTB	Caucasian	90	90

morphism and tuberculosis risk, the ORs with 95% CIs were used. The ORs were evaluated for the homozygote model (CC vs. TT), heterozygote model (TC vs. TT and CC vs. TC), dominant model (CC+TC vs. TT), recessive model (CC vs. TC+TT), and the haploid model (C vs. T) comparison. The funnel plots, Begg's adjusted rank correlation test and Egger's regression asymmetry test were used to demonstrate the publication bias; and the significance level was set at $P < 0.05$. To assess the stability of the results, the sensitivity analysis was performed by sequentially excluding each study. All statistical analyses were performed by using the STATA11.0 (STATA Corporation, College Station, TX, USA) and the Revman5.2 Software (Cochrane Library Software, Oxford, UK).

Results

Literature search and studies characteristics

According to the inclusion and exclusion criteria (**Figure 1**), 14 publications [5, 18, 21, 22, 28-37] including 4381 cases and 5082 controls were included for this meta-analysis. The main characteristics of these studies are summarized in **Table 1**. There were 12 studies of Asian populations, 6 studies of Caucasians population, and 1 study of the African American population. In this analysis, two types of tuberculosis were addressed: 16 studies focused on pulmonary tuberculosis, and 4 studies on tuberculous meningitis. The diagnoses of most of the cases were based on clinical, sputum Acid Fast Bacillus (AFB) or pathology. Healthy subjects who matched for age and sex served as controls. Polymerase chain reaction (PCR) or Mass-Array was performed for genotypes.

Quantitative data synthesis

A total of fourteen case-control studies, including 4381 cases and 5082 controls, to evaluate the relationship between the *TLR2* T597C polymorphisms and the risks of pulmonary tuberculosis and tuberculous meningitis. A summary results about the association between *TLR2* T597C polymorphism and tuberculosis risk are shown, there are significant association were found between *TLR2* T597C polymorphism and the risk of tuberculosis (CC vs. TC OR = 1.26, 95% CI = 1.10-1.43; CC vs. TT OR = 1.20, 95% CI = 1.04-1.38; CC vs. TC+TT OR = 1.23, 95% CI = 1.08-1.39) (**Figures 2**-**4**).

Moreover, in the subgroup analysis by ethnicity, there were significant associations between *TLR2* T597C polymorphism and tuberculosis risk in Asian (CC vs. TC OR = 1.23, 95% CI = 1.02-1.48; CC vs. TT OR = 1.22, 95% CI = 1.12-1.47; CC vs. TC+TT OR = 1.22, 95% CI = 1.02-1.46) and Caucasians (CC vs. TC OR = 1.31, 95% CI = 1.01-1.62; CC vs. TC+TT OR = 1.24, 95% CI = 1.01-1.52).

Similarly, in the subgroup analysis by the type of tuberculosis, there are significant associations between *TLR2* T597C polymorphism and the susceptibility of pulmonary tuberculosis (CC vs. TC OR = 1.16, 95% CI = 1.01-1.34) or tuberculous meningitis (CC vs. TC OR = 3.16, 95% CI

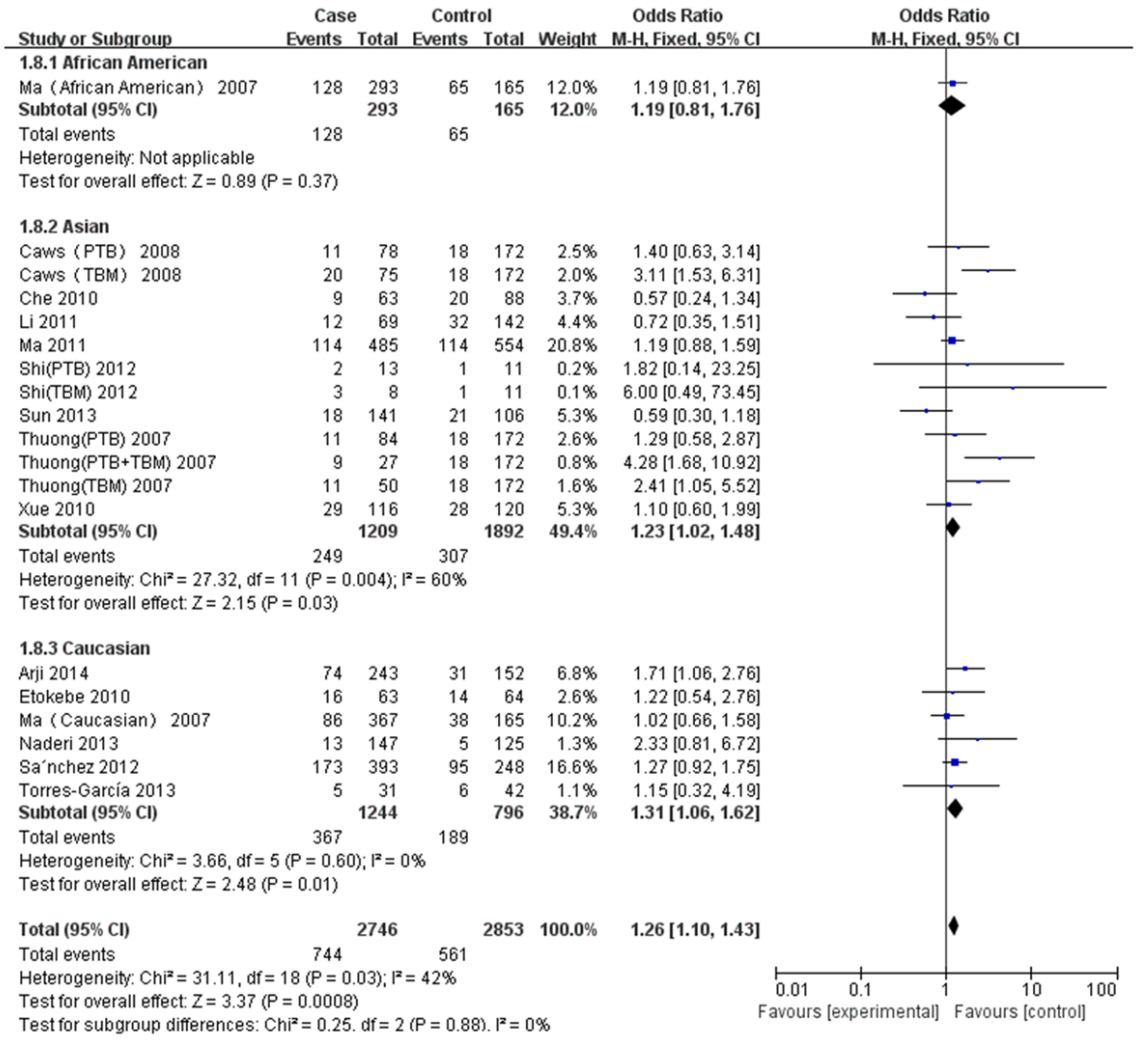

Figure 2. The association between *TLR2* T597C polymorphism and tuberculosis risk (CC vs. TC).

= 2.00-5.00; CC vs. TT OR = 3.56, 95% CI = 2.27-5.58; CC vs. TC+TT OR = 3.37, 95% CI = 2.19-5.19; CC+TC vs. TT OR = 1.36, 95% CI = 1.05-1.77; C vs. T OR = 1.52, 95% CI = 1.25-1.85), respectively.

Test of heterogeneity

In the overall analysis, the I^2 showed stable variation and the Q-statistic was significant under the models (CC vs. TCP = 0.03, I^2 = 42%; CC vs. TT P < 0.0001, I^2 = 64%; TC vs. TT P < 0.00001, I^2 = 79%; CC vs. TC+TT P = 0.001, I^2 = 57%; CC+TC vs. TT P = 0.03, I^2 = 42%; C vs. T P = 0.002, I^2 = 55%). In the subgroup analysis by ethnicity, the P and I^2 are different. In the subgroup analysis by tuberculosis, the P and I^2 are also different. In the subgroup of pulmonary tuberculosis, P and I^2 are (CC vs. TC P = 0.53, I^2 = 0%). And in the subgroup of tuberculous meningitis (CC vs. TC P = 0.79, I^2 = 0%; CC vs. TT P = 0.22, I^2 = 32%; CC vs. TC+TT P = 0.46, I^2 = 0%; CC+TC vs. TT P = 0.21, I^2 = 33%; C vs. T P = 0.10, I^2 = 52%), respectively.

Sensitivity analysis

By excluding each study at a time, we can estimate the influence of a single study on the overall meta-analysis. There are not any significant changes through the omission of any study. This indicated that the results of our meta-analysis were statistically reliable.

Publication bias

To assess the publication bias of the literatures, we used the Begg's funnel plot and

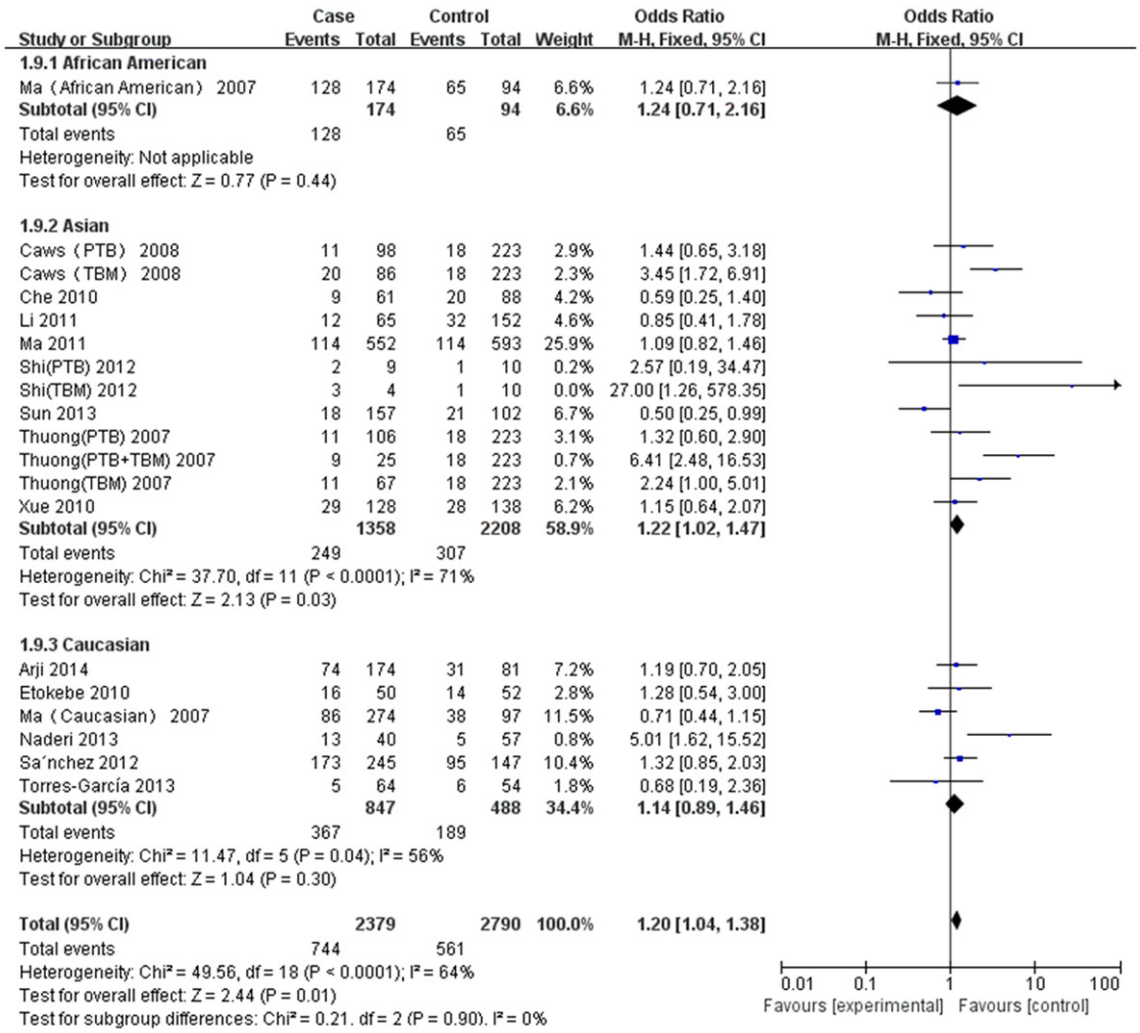

Figure 3. The association between *TLR2* T597C polymorphism and tuberculosis risk (CC vs. TT).

Egger's regression asymmetry test. We analyzed the symmetrical shapes of the Begg's funnel plot of *TLR2* T597C polymorphism; the Begg's funnel plot did not suggest any evidence of publication bias (**Table 2**). Meanwhile, the result of Egger's test also showed no publication bias.

Discussion

In the present meta-analysis, we show that *TLR2* T597C polymorphism is associated with susceptibility to pulmonary tuberculosis and tuberculous meningitis. In subgroup by ethnicity, we found significant associations between this polymorphism and tuberculosis risk in Asian and Caucasians.

The *TLR2* gene plays the important role in the pathogenesis of tuberculosis. Toll-like receptors (TLRs) involve in linking innate and adaptive immunity by recognizing the microbial patterns, and the proinflammatory immune response. Up to now, many studies have investigated whether the *TLR2* T597C polymorphism confers susceptibility to pulmonary tuberculosis and tuberculous meningitis. However, the results of the published studies were still controversial. Therefore we conducted this meta-analysis including in 4381 cases and 5082 controls from 14 case-control studies to evaluate the association between *TLR2* T597C gene polymorphism and the tuberculosis risks.

There is a significant association between *TLR2* T597C polymorphism and tuberculosis risks under the homozygote model (CC vs. TT), heterozygote model (CC vs. TC), and recessive model (CC vs. TC+TT) genetic model in the over-

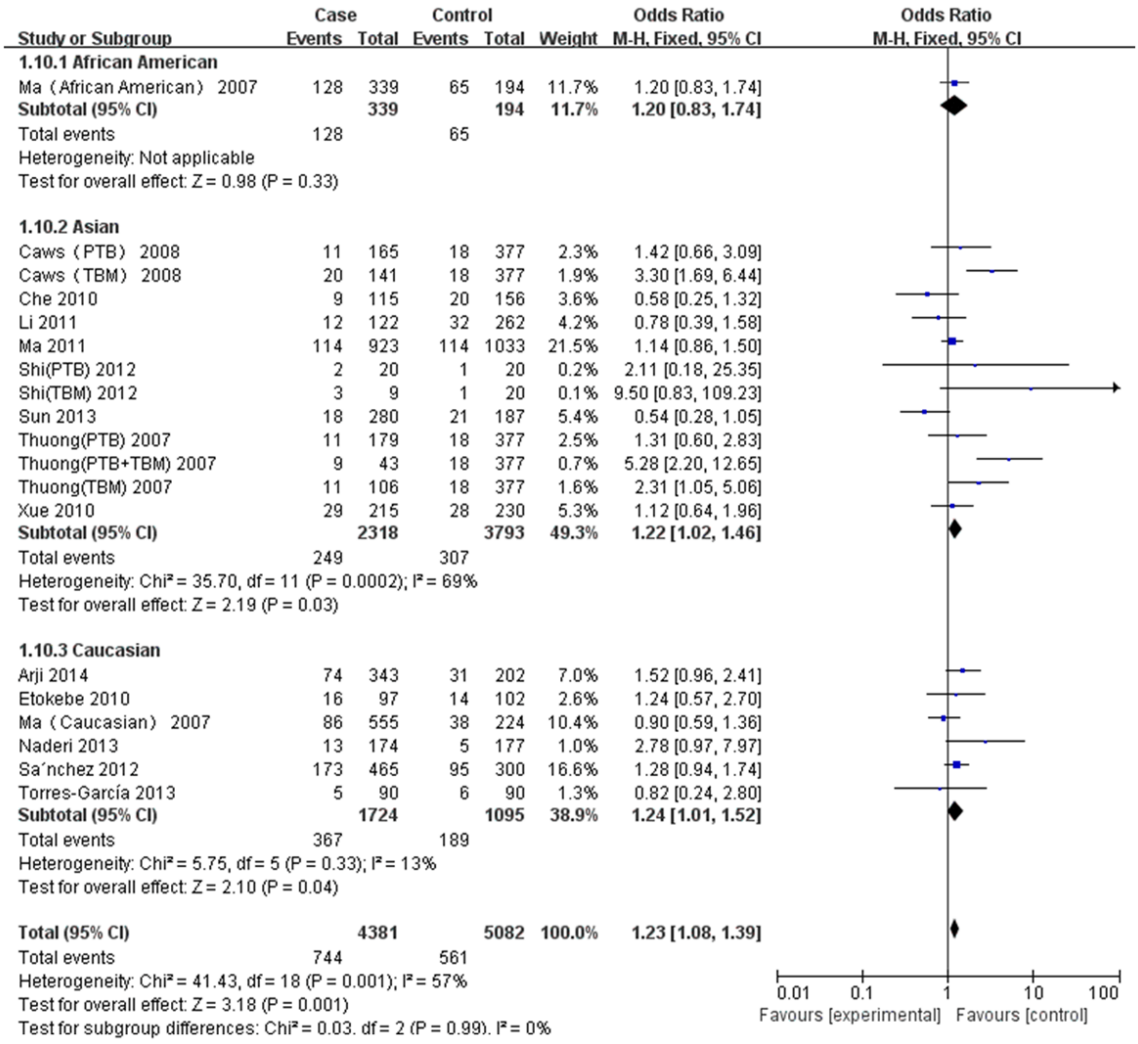

Figure 4. The association between *TLR2* T597C polymorphism and tuberculosis risk (CC vs. TC+TT).

Table 2. Summary of different model meta-analysis results

Genetic model	Participants (case/control)	OR [95% CI]	*P* value	I^2%	Effect mode	Begg's test P > |z|	Egger's test P > |t|
TC vs. TT	3647/4521	0.91 [0.72, 1.14]	< 0.00001	79	R	0.441	0.826
CC vs. TC	2746/2853	1.26 [1.10, 1.43]	0.03	42	F	0.162	0.215
CC vs. TT	2379/2790	1.20 [1.04, 1.38]	< 0.0001	64	F	0.050	0.102
CC vs. TT+TC	4381/5082	1.23 [1.08, 1.39]	0.001	57	F	0.108	0.183
TC+CC vs. TT	4381/5082	1.02 [0.93, 1.11]	0.03	42	F	0.093	0.152
C vs. T	8762/10164	1.06 [1.00, 1.13]	0.002	55	F	0.162	0.177

all population. In the subgroup analysis by ethnicity, we found that the *TLR2* T597C polymorphism is associated with tuberculosis risk in Asian and Caucasians. Similar to the total population, there are many genetic models shown this susceptibility. Compared with the T genotype, the C genotype was the recessive phenotype in human. Our meta-analysis suggests that individuals with the recessive phenotype (C genotype) appear to be associated with increased risk of tuberculosis, particularly with tuberculous meningitis. That indicates that the

TLR2 T597C polymorphism may contribute to pathogenesis of tuberculosis or mediate immune process, and also exert a regulatory effect of *TLR2* gene expression.

The heterogeneity was found in all comparisons in our meta-analysis. To get more complete and accurate detail of the precious data, we try to use the random-effect models. The results are stable when analysis their sensitivity, which does not change the results of the meta-analysis. Meanwhile, there are no publication biases for the risks of tuberculosis in the *TLR2* T597C polymorphism studies.

There were certain limitations in our meta-analysis. First, all the included studies were from Caucasians, Asian and African American populations in 8 country, further studies are necessary to contain more findings of other ethnic populations and nationality. Second, the synergistic effect of the gene has not been premeditated in our study. Third, tuberculosis is a multifactorial disease; the immune response has a pivotal position in the human resisting against the Mycobacterium tuberculosis. The environmental and genetic factors may contribute. Due to lack of original data, we could not evaluate the potential interactions of gene-gene and gene-environment.

In conclusion, *TLR2* T597C polymorphism is associated with susceptibility to pulmonary tuberculosis and tuberculous meningitis. Future studies with more stringent design and a larger sample size are required to further validate this conclusion.

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Disclosure of conflict of interest

None.

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References

[1] Pan H, Yan BS, Rojas M, Shebzukhov YV, Zhou H, Kobzik L, Higgins DE, Daly MJ, Bloom BR and Kramnik I. Ipr1 gene mediates innate immunity to tuberculosis. Nature 2005; 434: 767-772.

[2] Yim JJ and Selvaraj P. Genetic susceptibility in tuberculosis. Respirology 2010; 15: 241-256.

[3] Azad AK, Sadee W and Schlesinger LS. Innate immune gene polymorphisms in tuberculosis. Infect Immun 2012; 80: 3343-3359.

[4] Bafica A, Scanga CA, Feng CG, Leifer C, Cheever A and Sher A. TLR9 regulates Th1 responses and cooperates with *TLR2* in mediating optimal resistance to Mycobacterium tuberculosis. J Exp Med 2005; 202: 1715-1724.

[5] Chen YC, Hsiao CC, Chen CJ, Chin CH, Liu SF, Wu CC, Eng HL, Chao TY, Tsen CC, Wang YH and Lin MC. Toll-like receptor 2 gene polymorphisms, pulmonary tuberculosis, and natural killer cell counts. BMC Med Genet 2010; 11: 17.

[6] Akira S, Takeda K and Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol 2001; 2: 675-680.

[7] Iwasaki A and Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nat Immunol 2004; 5: 987-995.

[8] Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol 2001; 1: 135-145.

[9] Ozinsky A, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, Schroeder L and Aderem A. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. Proc Natl Acad Sci U S A 2000; 97: 13766-13771.

[10] Schnare M, Barton GM, Holt AC, Takeda K, Akira S and Medzhitov R. Toll-like receptors control activation of adaptive immune responses. Nat Immunol 2001; 2: 947-950.

[11] Underhill DM and Ozinsky A. Toll-like receptors: key mediators of microbe detection. Curr Opin Immunol 2002; 14: 103-110.

[12] Kobayashi K, Yuliwulandari R, Yanai H, Naka I, Lien LT, Hang NT, Hijikata M, Keicho N and Tokunaga K. Association of TLR polymorphisms with development of tuberculosis in Indonesian females. Tissue Antigens 2012; 79: 190-197.

[13] Thada S, Valluri VL and Gaddam SL. Influence of Toll-like receptor gene polymorphisms to tuberculosis susceptibility in humans. Scand J Immunol 2013; 78: 221-229.

[14] Velez DR, Wejse C, Stryjewski ME, Abbate E, Hulme WF, Myers JL, Estevan R, Patillo SG, Olesen R, Tacconelli A, Sirugo G, Gilbert JR, Hamilton CD and Scott WK. Variants in toll-like receptors 2 and 9 influence susceptibility to pulmonary tuberculosis in Caucasians, African-Americans, and West Africans. Hum Genet 2010; 127: 65-73.

[15] Zaki HY, Leung KH, Yiu WC, Gasmelseed N, Elwali NE and Yip SP. Common polymorphisms in TLR4 gene associated with susceptibility to pulmonary tuberculosis in the Sudanese. Int J Tuberc Lung Dis 2012; 16: 934-940.

[16] Zhang Y, Jiang T, Yang X, Xue Y, Wang C, Liu J, Zhang X, Chen Z, Zhao M and Li JC. Toll-like receptor-1, -2, and -6 polymorphisms and pulmonary tuberculosis susceptibility: a systematic review and meta-analysis. PLoS One 2013; 8: e63357.

[17] Biswas D, Gupta SK, Sindhwani G and Patras A. *TLR2* polymorphisms, Arg753Gln and Arg677Trp, are not associated with increased burden of tuberculosis in Indian patients. BMC Res Notes 2009; 2: 162.

[18] Sanchez D, Lefebvre C, Rioux J, Garcia LF and Barrera LF. Evaluation of Toll-like receptor and adaptor molecule polymorphisms for susceptibility to tuberculosis in a Colombian population. Int J Immunogenet 2012; 39: 216-223.

[19] Tian T, Jin S, Dong J and Li G. Lack of association between Toll-like receptor 4 gene Asp299Gly and Thr399Ile polymorphisms and tuberculosis susceptibility: a meta-analysis. Infect Genet Evol 2013; 14: 156-160.

[20] Berrington WR and Hawn TR. Mycobacterium tuberculosis, macrophages, and the innate immune response: does common variation matter? Immunol Rev 2007; 219: 167-186.

[21] Etokebe GE, Skjeldal F, Nilsen N, Rodionov D, Knezevic J, Bulat-Kardum L, Espevik T, Bakke O and Dembic Z. Toll-like receptor 2 (P631H) mutant impairs membrane internalization and is a dominant negative allele. Scand J Immunol 2010; 71: 369-381.

[22] Ma X, Liu Y, Gowen BB, Graviss EA, Clark AG and Musser JM. Full-exon resequencing reveals toll-like receptor variants contribute to human susceptibility to tuberculosis disease. PLoS One 2007; 2: e1318.

[23] Zhang K, Cheng D, Yi L, Shi H and Zhen G. Association between angiotensin I-converting enzyme gene polymorphism and susceptibility to cancer: a meta analysis. Int J Clin Exp Pathol 2014; 7: 6291-6300.

[24] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[25] Laird NM and Ware JH. Random-effects models for longitudinal data. Biometrics 1982; 38: 963-974.

[26] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[27] Munafo MR, Clark TG and Flint J. Assessing publication bias in genetic association studies: evidence from a recent meta-analysis. Psychiatry Res 2004; 129: 39-44.

[28] Arji N, Busson M, Iraqi G, Bourkadi JE, Benjouad A, Bouayad A, Mariaselvam C, Salah S, Fortier C, Amokrane K, Marzais F, Boukouaci W, Krishnamoorthy R, Charron D, El AR and Tamouza R. Genetic diversity of *TLR2*, TLR4, and VDR loci and pulmonary tuberculosis in Moroccan patients. J Infect Dev Ctries 2014; 8: 430-440.

[29] Caws M, Thwaites G, Dunstan S, Hawn TR, Lan NT, Thuong NT, Stepniewska K, Huyen MN, Bang ND, Loc TH, Gagneux S, van Soolingen D, Kremer K, van der Sande M, Small P, Anh PT, Chinh NT, Quy HT, Duyen NT, Tho DQ, Hieu NT, Torok E, Hien TT, Dung NH, Nhu NT, Duy PM, van Vinh CN and Farrar J. The influence of host and bacterial genotype on the development of disseminated disease with Mycobacterium tuberculosis. PLoS Pathog 2008; 4: e1000034.

[30] Li S. Research on the association of *TLR2* and TIRAP gene polymorphism with susceptibility to tuberculosis in Chinese Han population. MA thesis, Jinlin Agricultural University, China 2011.

[31] Ma MJ, Liu W and Cao WC. Host susceptibilty genes of tuberculosis. Chin J Epidemiol 2011; 32: 650-656.

[32] Naderi M, Hashemi M, Hazire-Yazdi L, Taheri M, Moazeni-Roodi A, Eskandari-Nasab E and Bahari G. Association between toll-like receptor2 Arg677Trp and 597T/C gene polymorphisms and pulmonary tuberculosis in Zahedan, Southeast Iran. Braz J Infect Dis 2013; 17: 516-520.

[33] Shi YJ, Wang Q, Guan YQ, Wang XJ, Wang JX and Jiang HS. Associativity of T597C polymorphisms of Toll-like receptors 2 gene with susceptibility to tuberculous meningitis in Han population of southern China. Journal of Xinxiang Medical College 2012; 29: 253-256.

[34] Sun HM. TIRAP and *TLR2* gene polymorphism and susceptibility of Mycobacterium tuberculosis. MA thesis, Hebei Medical University, China 2013.

[35] Thuong NT, Hawn TR, Thwaites GE, Chau TT, Lan NT, Quy HT, Hieu NT, Aderem A, Hien TT, Farrar JJ and Dunstan SJ. A polymorphism in human *TLR2* is associated with increased susceptibility to tuberculous meningitis. Genes Immun 2007; 8: 422-428.

[36] Torres-Garcia D, Cruz-Lagunas A, Garcia-Sancho FM, Fernandez-Plata R, Baez-Saldana R, Mendoza-Milla C, Barquera R, Carrera-Eusebio A, Ramirez-Bravo S, Campos L, Angeles J, Vargas-Alarcon G, Granados J, Gopal R, Khader SA, Yunis EJ and Zuniga J. Variants in toll-like receptor 9 gene influence suscepti-

bility to tuberculosis in a Mexican population. J Transl Med 2013; 11: 220.

[37] Xue Y, Zhao ZQ, Wang HJ, Jin L, Liu CP, Wang Y and Li JC. Toll-like receptors 2 and 4 gene polymorphisms in a southeastern Chinese population with tuberculosis. Int J Immunogenet 2010; 37: 135-138.