J Huazhong Univ Sci Technol [Med Sci]
DOI 10.1007/s11596-015-1405-6 35(2):157-168,2015

Toll-like Receptor Polymorphisms and Tuberculosis Susceptibility: A Comprehensive Meta-analysis

Qin SUN (孙 勤)[1, 2], Qing ZHANG (张 青)[2], He-ping XIAO (肖和平)[2], Chong BAI (白 冲)[1#]
[1]*Department of Respiratory Diseases, Changhai Hospital, the Second Military Medical University, Shanghai 200433, China*
[2]*Clinic and Research Center of Tuberculosis, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China*

Summary: The polymorphisms of toll-like receptor (TLR) have been hypothesized to affect the tuberculosis susceptibility. However, the direct evidence remains controversial. Here we performed a comprehensive meta-analysis to summarize the associations between TLR polymorphisms and tuberculosis susceptibility. We systematically searched the PubMed, Embase, Cochrane library, and Chinese National Knowledge Infrastructure up to April 25, 2014. Case-control studies investigating TLR polymorphisms and tuberculosis susceptibility were included in the meta-analysis. Pooled odds ratios and corresponding 95% confidence intervals were calculated for cases and controls. Stata 11.0 and Review Manager 5.1 were adopted to conduct statistical analysis. We included 29 studies, involving 17 804 individuals. The results revealed an obvious increase of tuberculosis risk in TLR2 2258AA, and decreased risk in TLR6 745TT and TLR8 rs3761624 GA genotypes. Meanwhile, different genetic models were performed. TLR8 rs3764879C, TLR8 rs3761624A and TLR8 rs3764880A alleles were associated with high susceptibility, while TLR6 745T and TLR8 rs3788935C alleles were protective. Other polymorphisms, including TLR9 1486C/T, did not show significant associations with tuberculosis infection. Finally, subgroup analysis in TLR8 rs3764880 according to gender found a slight elevated effect of A allele in males. The meta-analysis suggests significant associations between several TLR polymorphisms and tuberculosis, including TLR2 2258G/A, TLR6 745C/T, TLR8 rs3761624, TLR8 rs3764879, TLR8 rs3761624 and TLR8 rs3764880. This study serves as the framework for additional studies to determine further the role of TLRs in tuberculosis infection.
Key words: Toll-like receptor; polymorphism; tuberculosis; susceptibility; meta-analysis

Tuberculosis (TB) is a contagious and potentially fatal infection caused by various strains of mycobacterium. A significant human pathogen worldwide, TB causes clinical disease in some cases while remaining asymptomatic in others. Various factors contribute to this process, including environment, lifestyle and diet. Interestingly, genetics also plays a role, specifically polymorphisms of toll-like-receptor (TLR) family members, which have been hotspots in recent studies[1–3].

TLRs are a class of proteins that lie at the core of our microbe detection system, playing a key role in our innate immune response. There are 13 mammalian TLR receptors (TLR1 to TLR13). These receptors are the key first recognizers of foreign pathogens, with each TLR sensing a distinct repertoire of conserved microbial molecules. Collectively the TLR family members can detect most microbes. TLRs function as dimmers and interact with adaptor proteins (such as MyD88, MAL/TIRAP, TRAM and TRIF) to activate macrophages and dendritic cells during the immune response. Knowing this, it is hypothesized that polymorphisms of TLRs can affect TB susceptibility. Numerous studies have focused on this point, but the results remain controversial. Here, we performed a comprehensive meta-analysis to obtain a systematic summary on the associations between TLR polymorphisms and TB susceptibility[4, 5].

Qin SUN, E-mail: sunqinbonjour@163.com
#Corresponding author, E-mail: bc7878@sohu.com

1 MATERIALS AND METHODS

1.1 Study Selection

We conducted a systematic search of peer-reviewed journal including data about the association between TLR polymorphisms and TB susceptibility. Our search included PubMed, Embase, Cochrane Library and the Chinese National Knowledge Infrastructure (CNKI), and the search included all information until April 25, 2014. The following key words were included in the search: “tuberculosis” in combination with “polymorphism” or “variant” or “genotype” or “allele” or “mutation”; and in combination with “toll” or “TLR” or “toll-like receptor” or “toll like receptor”. Search results were limited to English and Chinese language articles. Studies were selected based on the following criteria: (1) case-control studies of unrelated individuals; (2) evaluation of TLR polymorphisms and TB susceptibility; (3) TB was confirmed by clinical, radiological, or bacteriological investigations; and (4) genotype distribution in both cases and controls were available. Studies were excluded based on the following criteria: (1) Study design based on family or sibling pairs; (2) genotype frequencies not reported; (3) data from reviews and abstracts. Additional studies were

also identified by hand searching reference lists of original studies and review articles including meta-analysis.

1.2 Data Extraction and Quality Assessment

The following information was extracted from each analyzed study: first author, the year of publication, age, ethnicity, genotyping method, total number of participants and genotype frequency in cases and controls. *P*-values for Hardy–Weinberg equilibrium (HWE) of the genotypes in the control groups were calculated and summarized in the tables. The quality of the selected studies was evaluated independently by two authors (Q SUN and Q ZHANG) according to the Newcastle-Ottawa Scale (NOS)[6]. The detail of NOS included patient selection, comparability of study groups, and ascertainment of outcome. NOS scores ranged from 0 to 9, with a score ≥5 considering of higher methodological quality.

1.3 Statistical Methods

HWE was examined in controls by the chi-square test for each polymorphism in each study. The association between TLR polymorphisms and TB susceptibility was estimated by means of odds ratios (OR) and corresponding 95% confidence intervals (CI) comparing experimental cases to controls. Heterogeneity was assessed by the Q test and I^2 test[7]. The fixed-effects model was used when effects were assumed to be homogeneous, while the random-effects model was used when they were known to be heterogeneous. Sensitivity analyses were performed by excluding the study with the widest CI and those studies not in HWE. The Begg's test[8] and Egger's test[9] were used to evaluate the publication bias only when the sample number was greater than five. Statistical analyses were carried out using the Stata 11.0 (College Station, USA) and Review Manager 5.1 software (Oxford, England). $P<0.05$ was considered statistically significant for all tests.

2 RESULTS

2.1 Study Characteristics

A total of 29 articles were included in the meta-analysis[10–38]. Forty were identified by our primary means and an additional two by hand searching. Thirteen were excluded using the following rationale: one was conducted only in healthy volunteers; three had overlapping data; two had a lack of concrete data; five reported only a single polymorphism which was not efficient for meta-analysis; and two focused exclusively on HIV-infected individuals (fig. 1). The following TLR polymorphisms were included in the meta-analysis (table 1): 5 studies[23, 26, 27, 35, 36] for TLR1 1805T/G (rs5743018), 9 studies[12, 21–23, 27, 32, 34, 35, 37] for TLR2 2258G/A (rs5743708), 9 studies[15, 17, 22, 24, 28, 29, 31, 35, 37] for TLR2 597T/C (rs3804099), 4 studies[10, 24, 32, 34] for TLR2 2029C/T (rs1695), 6 studies[15, 19, 22, 28, 29, 35] for TLR2 1350T/C (rs3804100), 8 studies[11, 14, 25, 27, 33, 35, 37, 38] for TLR4 896A/G (rs4986790), 6 studies[25, 27, 33, 35, 37, 38] for TLR4 1196C/T (rs4986791), 2 studies[27, 35] for TLR6 745C/T (rs5743810), 2 studies[18, 30] for TLR8 rs3788935, 2 studies[18, 30] for TLR8 rs3764879, 2 studies[18, 30] for TLR8 rs3761624, 3 studies[18, 20, 30] for TLR8 rs3764880, and 2 studies[27, 38] for TLR9 1486C/T (rs187084). The pooled sample size was 17 804 (8819 cases and 8985 controls). The genotype and allele distributions of all the polymorphisms are shown in table 2. In 5 studies from 4 papers[12, 20, 24, 25], the genotype distributions in controls were deviated from HWE. The detailed quality assessment of included studies is presented in table 3. Overall, the methodological quality of the included study was relatively high (NOS scores ranging from 5–9).

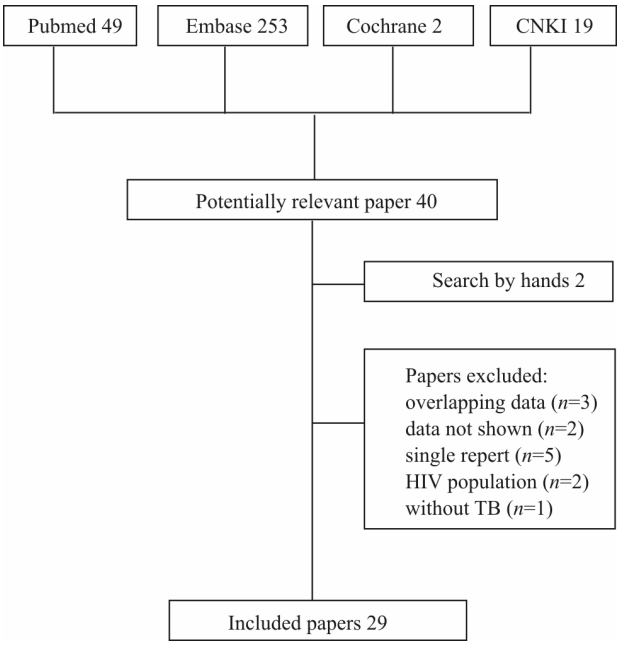


Fig. 1 Study selection procedure

Table 1 Characteristics of studies included in the meta-analysis

Authors	Year	Population	Age ($\bar{x}\pm s$ or range)		Sample (n)		Genotyping method
			Case	Control	Case	Control	
Ben-Ali[10]	2004	Tunisian	25–70	22–50	33	33	PCR-Sequencing
Castiblanco[16]	2008	Colombian	/	/	147	391	PCR-RFLP
Caws[17]	2008	Vietnamese	15–89	/	165	377	PCR-RFLP
Che[28]	2011	Chinese Han	/	/	115	156	PCR-Sequencing
Chen[19]	2010	Taiwanese	56.7±18.7	53.9±11.5	184	184	PCR-Sequencing
Dalgic[20]	2011	Turkish	8.80±4.71	8.62±4.78	124	150	PCR-RFLP
Dalgic[21]	2011	Turkish	8.11±4.89	8.52±4.55	124	200	PCR-RFLP
Davila[18]	2008	Indonesian & Russian	14–86	15–70	2212	2166	PCR-Sequencing

(To be continued on the next page)

（Continued from the front page）

Etokebe[22]	2010	Croatian	51.03±18.71	41.84±11.90	186	551	PCR-Sequencing
Jahantigh[38]	2013	Iranian	51.1±20	48.4±14.7	124	149	PCR-RFLP
Khor[13]	2007	West African	/	/	671	593	PCR-RFLP
Li[29]	2011	Chinese Han	46.7±20.4	27.7±11.2	300	215	PCR-RFLP
Li[30]	2013	Chinese Han	54±16	52±18	368	355	PCR-LDR
Ma[23]	2010	Chinese Han	34.75±16.67	38.17±17.39	543	544	PCR-RFLP
Ma-a[35]	2007	African American	/	/	339	194	PCR-Sequencing
Ma[35]	2007	European American	/	/	180	110	PCR-Sequencing
Ma-h[35]	2007	Hispanic American	/	/	375	114	PCR-Sequencing
Naderi[24]	2013	Iranian	/	/	174	177	PCR-RFLP
Najmi[25]	2010	Indian	27.2±11.4	/	95	206	PCR-RFLP
Newport[11]	2004	Gambian	19–58	18–50	320	320	PCR-ARMS
Ocejo-Vinyals[26]	2013	Cantabrian	/	/	190	192	PCR-RFLP
Ogus[12]	2004	Turkish	35.4±13.5	35.9±14.8	151	116	PCR-SSP
Rosas-Taraco[14]	2007	Mexican	/	/	104	114	PCR-RFLP
Sanchez[37]	2012	Colombian	39 (26–51)	42 (25–54)	499	320	PCR-MS
Selvaraj[27]	2010	Dravidian	34.92±11.42	32.33±9.75	206	212	PCR-RFLP
Shi[31]	2012	Chinese Han	38.3±14.8	25±2.4	20	20	PCR-RFLP
Thuong[15]	2007	Vietnamese	/	/	358	389	PCR-MS
Uciechowski[36]	2011	German	58.5±16.8	30.5±7.7	45	49	PCR-Sequencing
Xue[32]	2010	Chinese Han	39.5±17.9	26.3±8.5	205	203	PCR-Sequencing
Yang[33]	2009	Chinese Han	13–82	21–54	185	110	PCR-RFLP
Yu[34]	2008	Chinese Han	/	/	77	75	PCR-RFLP

PCR: polymerase chain reaction; SSP: sequence-specific primers; RFLP: restriction fragment length polymorphism; MS: mass spectroscopy. Ma-a, Ma-e and Ma-h: different ethnic populations in the study by Ma *et al* in 2007

Table 2 Genotype and allele distribution

SNP	Study		Case					Control					HWE	
	Authors	Year												
TLR1 1805T/G			GG	GT	TT	G	T	GG	GT	TT	G	T	χ^2	*P*
RS5743018	Ma-a[35]	2007	4	63	272	71	607	13	61	120	87	301	1.795	0.180
	Ma-e[35]	2007	107	61	12	275	85	63	33	14	159	61	6.956	0.008
	Ma-h[35]	2007	20	83	272	123	627	14	39	61	67	161	3.518	0.061
	Ma[23]	2010	510	32	1	1052	34	509	34	1	1052	36	0.294	0.588
	Selvaraj[27]	2010	1	9	192	11	393	0	16	189	16	394	0.338	0.561
	Uciechowski[36]	2011	36	5	4	77	13	24	19	6	67	31	0.525	0.469
	Ocejo-Vinyals[26]	2013	58	82	50	198	182	34	98	60	162	218	0.306	0.580
TLR2 2258G/A			GG	GA	AA	G	A	GG	GA	AA	G	A		
rs5743708	Ogus[12]	2004	124	13	14	261	41	107	7	2	221	11	12.783	0.000
	Ma-a[35]	2007	337	2	0	676	2	194	0	0	388	0	/	/
	Ma-e[35]	2007	171	9	0	351	9	105	5	0	215	5	0.059	0.807
	Ma-h[35]	2007	374	1	0	749	1	110	4	0	224	4	0.036	0.849
	Yu[34]	2008	76	1	0	153	1	75	0	0	150	0	/	/
	Etokebe[22]	2010	102	1	0	205	1	104	1	0	209	1	0.002	0.961
	Ma[23]	2010	543	0	0	1086	0	544	0	0	1088	0	/	/
	Selvaraj[27]	2010	192	1	0	385	1	198	1	0	397	1	0.001	0.972
	Xue[32]	2010	204	1	0	409	1	202	1	0	405	1	0.001	0.972
	Dalgic[21]	2011	93	31	0	217	31	186	14	0	386	14	0.263	0.608
	Sanchez[37]	2012	463	3	0	929	3	296	4	0	596	4	0.014	0.907
TLR2 597T/C			TT	TC	CC	T	C	TT	TC	CC	T	C		
rs3804099	Caws[17]	2008	87	67	11	241	89	153	122	31	428	184	0.825	0.364
	Che[28]	2011	52	54	9	158	72	68	68	20	204	108	0.214	0.644
	Etokebe[22]	2010	66	84	40	216	164	162	244	83	568	410	0.298	0.585

(To be continued on the next page)

（Continued from the front page）

	Li[29]	2011	53	57	12	163	81	120	110	32	350	174	0.751	0.386
	Ma-a[35]	2007	46	165	128	257	421	29	100	65	158	230	0.889	0.346
	Ma-e[35]	2007	55	90	35	200	160	41	47	22	129	91	1.562	0.211
	Ma-h[35]	2007	133	191	51	457	293	18	80	16	116	112	18.601	0.000
	Naderi[24]	2013	27	134	13	188	160	52	120	5	224	130	37.257	0.000
	Sanchez[37]	2012	173	220	72	566	364	95	153	52	343	257	0.514	0.473
	Shi[31]	2012	7	11	2	25	15	9	10	1	28	12	0.726	0.394
	Thuong[15]	2007	177	138	35	492	208	205	154	18	564	190	2.633	0.105
TLR2 2029C/T			TT	TC	CC	T	C	TT	TC	CC	T	C		
rs1695	Ben-Ali[10]	2004	0	31	2	31	35	0	10	23	10	56	1.052	0.305
	Naderi[24]	2013	0	40	134	40	308	0	29	148	29	325	1.409	0.235
	Xue[32]	2010	0	0	205	0	410	0	0	203	0	406	/	/
	Yu[34]	2008	0	0	77	0	154	0	0	75	0	150	/	/
TLR2 1350T/C			TT	TC	CC	T	C	TT	TC	CC	T	C		
rs3804100	Che[28]	2011	60	48	7	168	62	79	61	16	219	93	0.670	0.413
	Chen[19]	2010	131	45	8	307	61	121	55	8	297	71	0.297	0.586
	Etokebe[22]	2010	159	26	1	344	28	483	67	1	1033	69	0.709	0.400
	Li[29]	2011	59	53	10	171	73	136	104	22	376	148	0.112	0.738
	Ma-a[35]	2007	299	38	2	636	42	169	25	0	363	25	0.920	0.337
	Ma-e[35]	2007	151	24	5	326	34	101	9	0	211	9	0.200	0.655
	Ma-h[35]	2007	312	62	1	686	64	100	14	0	214	14	0.488	0.485
	Thuong[15]	2007	215	138	19	548	156	232	138	13	602	164	1.914	0.166
TLR4 896A/G			AA	AG	GG	A	G	AA	AG	GG	A	G		
rs4986790	Jahantigh[38]	2013	129	2	0	246	2	146	3	0	295	3	0.015	0.901
	Ma-a[35]	2007	281	57	1	619	59	235	58	5	528	68	0.489	0.484
	Ma-e[35]	2007	159	20	1	338	22	110	4	0	224	4	0.350	0.554
	Ma-h[35]	2007	353	22	0	728	22	206	44	0	456	44	0.151	0.698
	Najmi[25]	2010	95	34	6	224	46	54	8	0	116	8	2.328	0.127
	Newport[11]	2004	241	62	4	544	70	235	58	5	528	68	0.413	0.521
	Rosas-Taraco[14]	2007	94	10	0	198	10	151	53	3	355	59	0.036	0.849
	Sanchez[37]	2012	429	36	1	894	38	157	36	1	350	38	0.055	0.814
	Selvaraj[27]	2010	153	47	4	353	55	95	14	1	204	16	0.469	0.493
	Yang[33]	2009	85	0	0	170	0	270	29	1	569	31	0.055	0.814
TLR4 1196C/T			CC	CT	TT	C	T	CC	CT	TT	C	T		
rs4986791	Jahantigh[38]	2013	112	10	2	234	14	141	7	1	289	9	0.970	0.030
	Ma-a[35]	2007	325	14	0	664	14	178	16	0	372	16	0.359	0.549
	Ma-e[35]	2007	161	18	1	340	20	97	12	1	206	14	0.787	0.375
	Ma-h[35]	2007	357	18	0	732	18	108	6	0	222	6	0.083	0.773
	Najmi[25]	2010	105	26	4	236	34	206	43	1	455	45	0.627	0.429
	Sanchez[37]	2012	429	36	1	894	38	272	26	1	570	28	0.199	0.655
	Selvaraj[27]	2010	150	49	4	349	57	152	46	5	350	56	0.451	0.502
	Yang[33]	2009	85	0	0	170	0	110	0	0	220	0	/	/
TLR6 745C/T			CC	CT	TT	C	T	CC	CT	TT	C	T		
rs5743810	Ma-a[35]	2007	289	47	3	625	53	137	50	7	324	64	0.805	0.370
	Ma-e[35]	2007	61	88	31	210	150	38	46	26	122	98	2.594	0.107
	Ma-h[35]	2007	291	74	10	656	94	78	31	5	187	41	0.696	0.404
	Selvaraj[27]	2010	0	2	197	2	396	0	3	199	3	401	0.011	0.915
TLR8			GG	GC	CC	G	C	GG	GC	CC	G	C		
rs3788935	Davila[18]	2008	498	109	151	1105	411	1401	837	125	3639	1087	0.000	1.000
	Li[30]	2013	238	116	14	296	72	230	112	14	286	69	0.006	0.937
TLR8			GG	GC	CC	G	C	GG	GC	CC	G	C		
rs3764879	Davila[18]	2008	497	112	151	1106	414	1390	830	124	3610	1078	0.000	0.995
	Li[30]	2013	245	110	13	600	136	237	106	12	580	130	0.001	0.972
TLR8			GG	AG	AA	G	A	GG	AG	AA	G	A		
rs3761624	Davila[18]	2008	499	108	152	1106	412	1264	798	126	3326	1050	0.000	0.997
	Li[30]	2013	241	57	13	596	140	222	133	13	572	138	1.651	0.199

(To be continued on the next page)

Continued from the front page）

TLR8			GG	AG	AA	G	A	GG	AG	AA	G	A		
rs3764880	Dalgic[21]	2011	29	26	69	84	164	51	26	73	128	172	62.542	0.000
	Davila[18]	2008	499	108	152	1106	412	1264	798	126	3326	1050	0.000	0.997
	Li[30]	2013	238	116	14	592	144	230	112	14	572	138	0.006	0.937
TLR9			TT	TC	CC	T	C	TT	TC	CC	T	C		
1486C/T	Jahantigh[38]	2013	63	51	10	177	71	82	59	8	223	75	0.391	0.532
rs187084	Selvaraj[27]	2010	75	91	27	241	145	84	92	32	260	156	0.662	0.416

HWE: Hardy–Weinberg equilibrium; Ma-a, Ma-e and Ma-h: different ethnic populations in the study by Ma *et al* in 2007

Table 3 Quality assessment of studies included in the meta-analysis

Study/Year	Patient selection	Comparability of study groups	Ascertainment of outcome	Overall NOS scores
Ben-Ali 2004[10]	3	1	1	5
Castiblanco 2008[16]	3	2	2	7
Caws 2008[17]	3	0	2	5
Che 2011[28]	4	1	2	7
Chen 2010[19]	4	2	2	8
Dalgic 2011[20]	4	2	2	8
Dalgic 2011[21]	4	2	2	8
Davila 2008[18]	4	2	3	9
Etokebe 20110[22]	3	1	1	5
Jahantigh 2013[38]	4	1	2	7
Khor 2007[13]	3	1	1	5
Li 2011[29]	2	1	2	5
Li 2013[30]	2	1	2	5
Ma 2010[23]	4	2	2	8
Ma 2007[35]	4	2	2	8
Naderi 2013[24]	3	2	2	7
Najmi 2010[25]	4	2	2	8
Newport 2004[11]	4	2	2	8
Ocejo-Vinyals 2013[26]	3	2	2	7
Ogus 2004[12]	3	2	2	7
Rosas-Taraco 2007[14]	4	2	2	8
Sanchez 2012[37]	4	2	2	8
Selvaraj 2010[27]	4	2	2	8
Shi 2012[31]	4	1	2	7
Thuong 2007[15]	3	0	2	5
Uciechowski 2011[36]	4	1	2	7
Xue 2010[32]	4	2	3	7
Yang 2009[33]	4	0	2	6
Yu 2008[34]	4	2	2	8

Patient selection including: (1) Is the case definition adequate? (2) representativeness of the cases; (3) selection of controls; (4) definition of controls. ascertainment of outcome including: (1) ascertainment of exposure; (2) same method of ascertainment for both groups; (3) non-response rate

2.2 Quantitative Data Synthesis

As a general rule, anytime the high heterogeneities were suggested by the $P_{\text{heterogeneity}}$ and I^2, we chose a random-effect model to analyze the data. Conversely, anytime low heterogeneities were suggested, we chose a fixed-effect model. All $P_{\text{heterogeneity}}$ and I^2 findings are shown in table 4. In all polymorphisms where we analyzed greater than 5 articles, no publication bias was observed following analysis by the Begg's and Egger's tests. In all cases where we did not observe an association between the given polymorphism and TB infection, we performed sensitivity analysis by deleting one study each time, but obtained no significant results in any cases.

Table 4 Comparative results

Polymorphisms	Genotype/Allele	OR	95% CI	I^2%	$P_{\text{heterogeneity}}$	Effect model	P_{meta}	P_{Egger}	P_{Begg}
TLR1	T *vs.* G	1.08	0.66–1.76	90	<0.00001	R	0.77	0.724	1
1805T/G	TT+GT *vs.* GG	0.97	0.51–1.84	82	<0.0001	R	0.93	0.466	0.452
RS5743018	TT *vs.* GT+GG	1.25	0.73–2.16	78	0.0001	R	0.41	0.37	0.548
	GT *vs.* GG	0.83	0.48–1.45	72	0.002	R	0.52	0.869	0.452
	TT *vs.* GG	1.09	0.42–2.80	81	<0.0001	R	0.86	0.66	0.452
TLR2	G *vs.* A	0.72	0.35–1.48	54	0.02	R	0.37	0.03	0.536
2258G/A	AA+GA *vs.* GG	1.27	0.57–2.83	59	0.01	R	0.56	0.038	0.536
rs5743708	AA *vs.* GA+GG	1.74	0.15–19.90	79	0.03	R	0.65	/	/

(To be continued on the next page)

Continued from the front page）

	GA *vs.* GG	1.21	0.56–2.63	53	0.02	R	0.62	0.047	0.536
	AA *vs.* GG	6.04	1.34–27.18	/	/	R	0.02	/	/
TLR2 597T/C rs3804099	C *vs.* T	1.01	0.89–1.16	56	0.01	R	0.84	0.82	0.755
	CC+TC *vs.* TT	1	0.79–1.27	67	0.0007	R	0.98	0.29	0.276
	CC *vs.* CT+TT	1.03	0.85–1.25	34	0.16	F	0.76	0.338	0.276
	CT *vs.* TT	0.99	0.78–1.26	66	0.001	R	0.94	0.66	0.436
	CC *vs.* TT	1.05	0.74–1.47	62	0.004	R	0.79	0.605	0.876
TLR2 2029C/T rs1695	T *vs.* C	2.57	0.77–8.51	84	0.01	R	0.12		
	TC+TT *vs.* CC	6.72	0.29–153.27	93	0.0002	R	0.23		
	TT *vs.* TC+CC	/	/	/	/	/	/		
	TC *vs.* CC	6.72	0.29–153.27	93	0.0002	R	0.23		
	TT *vs.* CC	/	/	/	/	/	/		
TLR2 1350T/C rs3804100	T *vs.* C	0.95	0.83–1.09	21	0.27	F	0.43	0.144	0.108
	CC+TC *vs*. TT	1.09	0.93–1.28	0	0.43	F	0.28	0.364	0.266
	CC *vs*. TC+TT	1.13	0.77–1.67	0	0.61	F	0.53	0.79	1
	TC *vs*. TT	1.07	0.91–1.27	0	0.6	F	0.4	0.404	0.386
	CC *vs*. TT	1.17	0.79–1.73	0	0.61	F	0.45	0.847	0.806
TLR4 896A/G rs4986790	G *vs*. A	0.81	0.48–1.36	85	<0.00001	R	0.43	0.554	0.602
	GG+GA *vs*. AA	0.79	0.46–1.37	85	<0.00001	R	0.4	0.545	0.917
	GG *vs*. GA+AA	0.86	0.43–1.72	0	0.57	F	0.67	0.781	1
	GA *vs*. AA	0.79	0.46–1.35	84	<0.00001	R	0.38	0.561	0.917
	GG *vs*. AA	0.88	0.44–1.73	0	0.46	F	0.7	0.776	1
TLR4 1196C/T rs4986791	T *vs*. C	1.62	0.87–3.01	2	0.39	F	0.13	0.748	0.764
	TT+TC *vs*. CC	0.99	0.79–1.26	18	0.3	F	0.97	0.824	0.764
	TT *vs*. TC+CC	1.43	0.61–3.35	0	0.43	F	0.41	0.703	0.806
	TC *vs*. CC	0.97	0.76–1.23	0	0.44	F	0.81	0.876	0.548
	TT *vs*. CC	1.46	0.62–3.42	0	0.42	F	0.39	0.716	0.806
TLR6 745C/T rs5743810	T *vs*. C	0.66	0.44–0.90	65	0.04	R	0.04		
	TT+TC *vs*. CC	0.64	0.38–1.06	72	0.03	R	0.08		
	TT *vs*. TC+CC	0.61	0.39–0.97	0	0.41	F	0.04		
	TC *vs*. CC	0.69	0.40–1.19	74	0.02	R	0.18		
	TT *vs*. CC	0.57	0.34–0.95	29	0.24	F	0.03		
TLR8 rs3788935	C *vs*. G	1.21	1.07–1.38	11	0.29	F	0.002		
	CG+CC *vs*. GG	0.84	0.65–1.09	57	0.13	R	0.2		
	CC *vs*. CG+GG	2.17	0.48–9.70	93	0.0002	R	0.31		
	CG *vs*. GG	0.6	0.22–1.61	96	<0.00001	R	0.31		
	CC *vs*. GG	1.91	0.56–6.53	89	0.002	R	0.3		
TLR8 rs3764879	C *vs*. G	1.16	0.95–1.24	50	0.16	R	0.14		
	CC+CG *vs*. GG	0.85	0.66–1.10	55	0.14	R	0.22		
	CC *vs*. CG+GG	2.27	0.55–9.35	91	0.0007	R	0.26		
	CG *vs*. GG	0.61	0.23-1.60	96	<0.00001	R	0.31		
	CC *vs*. GG	2.01	0.64–6.36	87	0.006	R	0.23		
TLR8 rs3761624	A *vs*. G	1.13	1.01–1.28	39	0.2	F	0.04		
	AA+GA *vs*. GG	0.57	0.36–0.92	84	0.01	R	0.02		
	AA *vs*. GA+GG	2.34	0.70–7.83	88	0.003	R	0.17		
	GA *vs*. GG	0.36	0.29–0.43	0	0.51	F	<0.00001		
	AA *vs*. GG	1.78	0.55–5.74	88	0.005	R	0.33		
TLR8 rs3764880	A *vs*. G	1.17	1.05–1.31	27	0.25	F	0.006		
	AA+GA *vs*. GG	1	0.65–1.52	82	0.004	R	0.99		
	AA *vs*. GA+GG	1.81	0.69–4.73	92	<0.00001	R	0.23		
	GA *vs*. GG	0.81	0.32–2.06	95	<0.00001	R	0.66		
	AA *vs*. GG	1.83	0.94–3.57	81	0.006	R	0.08		
TLR9 1486C/T rs187084	C *vs*. T	1.07	0.85–1.34	0	0.47	F	0.57		
	CC+TC *vs*. TT	1.11	0.82–1.51	0	0.74	F	0.49		
	CC *vs*. TC+TT	1.03	0.64–1.65	0	0.33	F	0.92		
	TC *vs*. TT	1.12	0.81–1.54	0	0.96	F	0.51		
	CC *vs*. TT	1.09	0.66–1.82	0	0.36	F	0.73		

R: random-effect model; F: fixed-effect model; OR: odds ratio; CI: confidence interval

2.2.1 TLR1 1805T/G Polymorphism Five case-control studies (1847 cases and 1408 controls) were included for this polymorphism[23, 26, 27, 35, 36]. When all the eligible studies were pooled, no significant associations between TLR1 1805T/G polymorphism and TB risk were found in the co-dominant models (TT *vs.* GG: OR=1.09, 95% CI=0.42–2.80, *P*=0.86; GT *vs.* GG: OR=0.83, 95% CI=0.48–1.45, *P*=0.52), the dominant model (TT+GT *vs.* GG: OR=0.97, 95% CI=0.51–1.84), the recessive model (TT *vs.* GT+GG: OR=1.25, 95% CI=0.73–2.16, *P*=0.41) and the allele model (T *vs.* G: OR=1.08, 95% CI=0.66–1.76, *P*=0.77). All studies, except for one, in control groups conformed to the HWE (*P*>0.05).

2.2.2 TLR2 2258G/A Polymorphism Nine case-control studies (2756 cases and 2160 controls) were included[12, 21–23, 27, 32, 34, 35, 37]. All studies, except for one, in control groups conformed to the HWE (*P*>0.05). The publication bias by Begg's test showed no significant bias in any groups. However, the Egger's test identified 3 comparisons (G *vs.* A: $P_{\text{Egger's}}$=0.03; AA+GA *vs.* GG: $P_{\text{Egger's}}$=0.038; GA *vs.* GG: $P_{\text{Egger's}}$=0.047). In co-dominant model analysis, the overall OR for the AA *vs.* GG was 6.04 (95% CI 1.34–27.18, *P*=0.02) in the random-effect model, indicating an association of the AA genotype with risk of TB infection.

2.2.3 TLR2 597T/C Polymorphism Nine case-control studies (2495 cases and 2505 controls) were included[15, 17, 22, 24, 28, 29, 31, 35, 37]. No significant associations were found in different models. Two control groups did not meet the HWE (*P*=0.000).

2.2.4 TLR2 2029C/T Polymorphism Four case-control studies (489 cases and 488 controls) were included[10, 24, 32, 34]. No significant associations between TLR2 2029C/T polymorphism and TB risk were found in different models. All studies in control groups conformed to the HWE (*P*>0.05).

2.2.5 TLR2 1350T/C Polymorphism Six case-control studies (1873 cases and 1954 controls) were included[15, 19, 22, 28, 29, 35]. No significant associations between TLR2 1350T/C polymorphism and TB risk were found in different models. All studies in control groups conformed to the HWE (*P*>0.05).

2.2.6 TLR4 896A/G Polymorphism Eight case-control studies (2326 cases and 1982 controls) were included[11, 14, 25, 27, 33, 35, 37, 38]. There were no significantly statistical results in different models linking the TLR4 896A/G polymorphism to the risk of AB infection. All studies in control groups conformed to the HWE (*P*>0.05).

2.2.7 TLR4 1196C/T Polymorphism Six case-control studies (1907 cases and 1429 controls) were included[25, 27, 33, 35, 37, 38]. We did not find any significant associations between TLR4 1196C/T polymorphism and the risk of TB in different models. All studies except for one conformed to the HWE (*P*>0.05).

2.2.8 TLR6745C/T Polymorphism Two case-control studies (1093 cases and 620 controls) were included[27, 35]. All studies in control groups conformed to the HWE (*P*>0.05). The pooled OR for T *vs.* C was 0.66 (95% CI 0.44–0.90, *P*=0.04), suggesting a protective role of T allele in TB. In addition, significant associations were also found in the recessive model (TT *vs.* TC+CC: OR=0.61, 95% CI=0.39–0.97, *P*=0.04) and the co-dominant model (TT *vs.* CC: OR=0.57, 95% CI=0.34–0.95, *P*=0.03). Both proved the decreased susceptibility to TB in TT genotype. In TC *vs.* CC, the result was not statistically significant (OR=0.69, 95% CI=0.40–1.19, *P*=0.18). Besides, in the dominant model (TT+TC *vs.* CC), OR=0.64, 95% CI=0.38–1.60 and *P* =0.08. Both indicated no association between TC genotype and TB.

2.2.9 TLR8 rs3788935 Polymorphism Two case-control studies (1126 cases and 2719 controls) were included[18, 30]. We found a significant increased risk of TB infection in C allele (OR=1.21, 95% CI=1.07–1.38, *P*=0.002). No obvious associations were shown in other comparisons (CG+CC *vs.* GG: OR=0.84, 95% CI=0.65–1.09, *P* =0.2; CC *vs.* CG+GG: OR=2.17, 95% CI=0.48–9.70, *P*=0.31; CG *vs.* GG: OR=0.6, 95% CI=0.22–1.61, *P*=0.31; CC *vs.* GG: OR=1.91, 95% CI=0.56–6.53, *P*=0.30). All studies in control groups conformed to the HWE (*P*>0.05).

2.2.10 TLR8 rs3764879 Polymorphism Two case-control studies (1128 cases and 2699 controls) were included[18, 30]. When the fixed-effect model was calculated, the OR=1.20 (95% CI=1.07–1.35, *P*=0.002), indicating increased susceptibility to TB in the C allele. No statistically significant results were found in other groups. All studies in control groups conformed to the HWE (*P*>0.05).

2.2.11 TLR8 rs3761624 Polymorphism Two case-control studies (1070 cases and 2556 controls) were included[18, 30]. We found significant differences in the allele model (A *vs.* G: OR=1.13, 95% CI=1.01–1.28, *P*=0.04), the dominant model (AA+GA *vs.* GG: OR=0.57, 95% CI=0.36–0.92, *P*=0.02) and the co-dominant model (GA *vs.* GG: OR=0.36, 95% CI=0.29–0.43, *P*<0.00001). The data suggested increased risk in A allele and decreased risk in AA+GA and GA group. All studies in control groups conformed to the HWE (*P*>0.05).

2.2.12 TLR8 rs3764880 Polymorphism Three case-control studies (1251 cases and 2694 controls) were included[18, 20, 30]. In A *vs.* G, the OR=1.17, 95% CI=1.05–1.31 and *P*=0.006, suggesting increased risk in A allele. Furthermore, we conducted analyses according to gender, and found a slight elevated effect of A allele in male *vs.* female (A *vs.* G: OR_{male}=1.34, 95% CI=0.77–2.33, P_{male}=0.30; OR_{female}=1.15, 95% CI=0.73–1.80, P_{female}=0.55). In addition, the OR for AA *vs.* GG was 1.83 (0.94–3.57, *P*=0.08), which may be significant with more available studies in the future. One of the studies in control groups did not meet the HWE.

2.2.13 TLR9 1486C/T Polymorphism Two case-control studies (317 cases and 357 controls) were included[27, 38]. We found no statistically significant results, indicating no associations between TLR9 1486C/T polymorphism and TB risk. All studies in control groups conformed to the HWE (*P*>0.05).

3 DISCUSSION

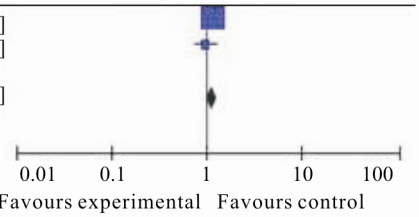
A large number of studies have investigated the relationship between TLR polymorphisms and suscep-

tibility to TB infection. However, the results are inconsistent and inconclusive. This is the most comprehensive meta-analysis summarizing the associations between TLR family polymorphisms and the risk of TB performed to date. We found an increased risk of TB infection in the TLR2 2258AA genotype, and a decreased risk in the TLR6 745TT and TLR8 rs3761624 GA genotypes. Using different genetic models, TLR8 rs3764879C, TLR8 rs3761624A and TLR8 rs3764880A alleles were also associated with high TB susceptibility, while TLR6 745T and TLR8 rs3788935C alleles were protective as proven (fig. 2).

TLR8 rs3761624 A *vs.* G

Study or subgroup	A Events	A Total	G Events	G Total	Weight	Odds Ratio M-H,Fixed,95% CI
Davila 2008	412	1462	1106	4432	77.6%	1.18 [1.03,1.35]
Li 2012	140	278	596	1168	22.4%	0.97 [0.75,1.26]
Total (95% CI)		1740		5600	100.0%	1.13 [1.01,1.28]
Total events	552		1702			

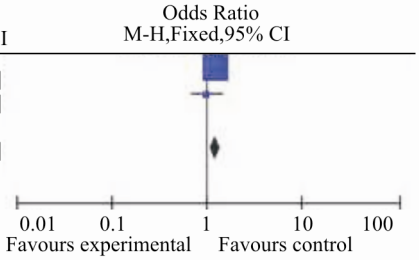
Heterogeneity: Chi^2=1.65, df=1 (*P*=0.20); I^2=39%
Test for overall effect: *Z*=2.08 (*P*=0.04)



TLR8 rs 3788935 G *vs.* G

Study or subgroup	C Events	C Total	G Events	G Total	Weight	Odds Ratio M-H,Fixed,95% CI
Davila 2008	411	1498	1105	4744	87.2%	1.25 [1.09,1.42]
Li 2012	72	141	296	582	12.8%	0.97 [0.70,1.46]
Total (95%CI)		1639		5326	100.0%	1.21 [1.07,1.38]
Total events	483		1401			

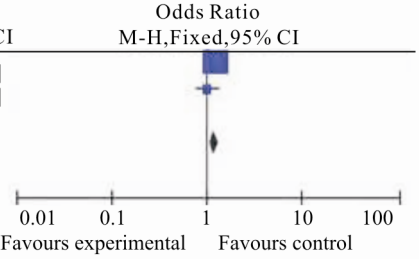
Heterogeneity: Chi^2=1.12, df=1 (*P*=0.29); I^2=11%
Test for overall effect: *Z*=3.07 (*P*=0.04)



TLR8 rs3764879 G *vs.* G

Study or subgroup	C Events	C Total	G Events	G Total	Weight	Odds Ratio M-H,Fixed,95% CI
Davila 2008	414	1492	1106	4716	78.1%	1.25 [1.10,1.43]
Li 2012	136	266	600	1180	21.9%	0.97 [0.77,1.32]
Total (95%CI)		1758		5896	100.0%	1.20 [1.07,1.35
Total events	550		1706			

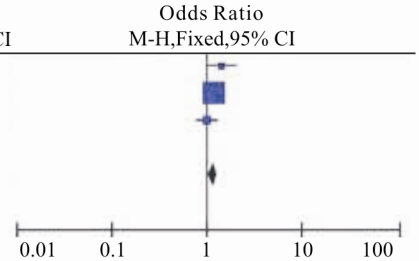
Heterogeneity: Chi^2=2.01, df=1 (*P*=0.16); I^2=50%
Test for overall effect: *Z*=3.03 (*P*=0.002)



TLR8 rs3764880 A *vs.* G

Study or subgroup	C Events	C Total	G Events	G Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davila 2011	164	336	84	212		1.45 [1.03,2.06]
Davila 2008	412	1462	1106	4432		1.18 [1.03,1.35]
Li 2012	144	282	592	1164		1.01 [0.78,1.31]
Total (95% CI)		2080		5808		1.17 [1.05,1.31]
Total events			1782			

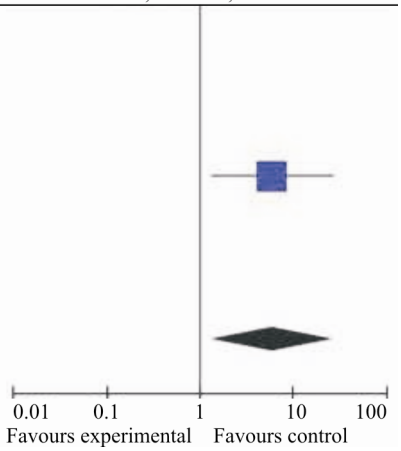
Heterogeneity: Chi^2=2.75, df=2 (*P*=0.16); I^2=27%
Test for overall effect: *Z*=2.76 (*P*=0.002)



TLR2 2258 AA *vs.* GG

Study or subgroup	AA Events	AA Total	GG Events	GG Total	Weight	Odds Ratio M-H, Random, 95% CI
Daigic 2011	0	0	93	279		Not estimable
Etokebe 2010	0	0	543	1087		Not estimable
Ma 2010	0	0	102	206		Not estimable
M-a 2007	0	0	171	276		Not estimable
M-a 2007	0	0	337	531		Not estimable
M-h 2007	0	0	374	484		Not estimable
Ogus 2004	14	16	124	231	100.0%	6.04 [1.34, 27.18]
Sanchez 2012	0	0	463	759		Not estimable
Selvaraj 2010	0	0	192	390		Not estimable
Xue 2010	0	0	204	406		Not estimable
Yu 2008	0	0	76	151		Not estimable
Total (95% CI)		16		4800	100.0%	6.04 [1.34,27.18]
Total events	14		2679			

Heterogeneity. not applicable
Test for overall effect: *Z*=2.34 (*P*=0.02)



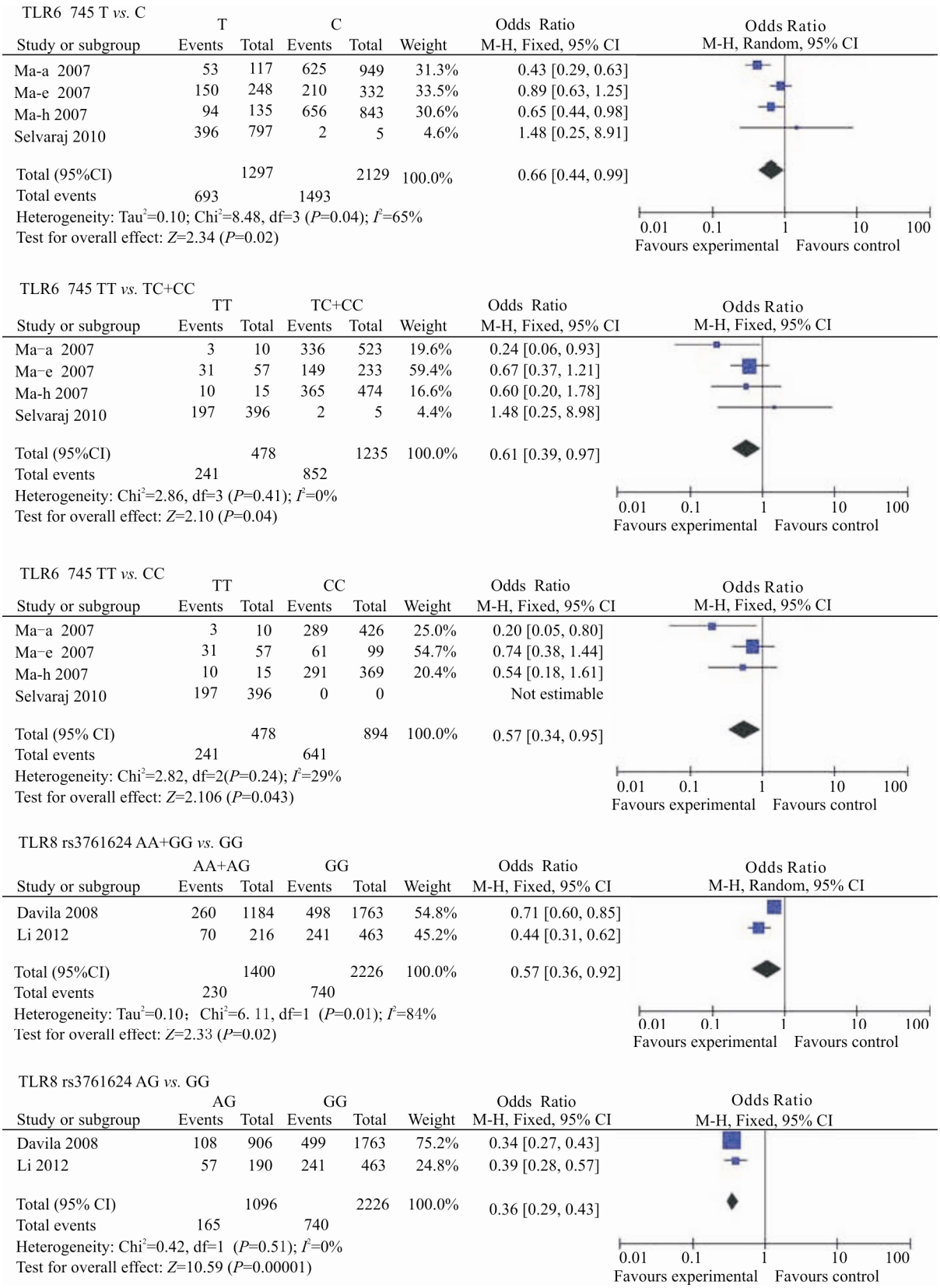


Fig. 2 Forest plot figures of significant comparisons

TLR1, TLR2, TLR4, TLR6 and TLR9 have all been implicated in the host immune response against TB infection. TLR2, abundant in respiratory epithelial cells lining the lung, plays a critical role in this response by mediating the response to infection through multiple pathways including macrophage activation, dentritic

cells maturation, the Th1, Th2, Th17 type response and antigen processing suppressing[39]. In addition, TLR2 could cooperate with other TLRs, such as TLR1/6/9[40–43]. Among various TLR2 polymorphisms, 2258G/A, 597T/C, 2029C/T and 1350T/T are the most widely researched. However, we only found TLR2 2258AA genotype related to high TB risk in this meta-analysis.

We found the TLR6 745TT genotype and TLR6 745T allele were protective factors. In response to and defense against TB infection, TLR6 forms a critical heterodimeric complex with TLR2 to activate macrophages[42]. Further, a dominant-negative mutant of mouse TLR6 suppresses the ability of transfected cells to respond to soluble TB factor[44]. It is still controversial whether TLR6 polymorphism has important roles in TB susceptibility. Our data confirmed that TLR6 745C/T polymorphism has altered the risk of TB.

A number of previous studies have explored the occurrence of TLR8 variants in different diseases, such as enterovirus-associated dilated cardiomyopathy and coronary artery disease[45, 46]. TLR8 is a recently described TLR member in responding to microbes' stimulation. Our results provide analysis, for the first time, of roles for the TLR8 gene in susceptibility to pulmonary TB. Several TLR8 polymorphisms exhibited considerable potential in altering TB susceptibility.

TLR8 resides on the X chromosome, which can be influenced by X-inactivation in females. Thus, it is reasonable to hypothesize that gender may be one of the stratified factors in TLR8-mediated TB infection. Although still controversial, we conducted subgroup analyses according to gender. We indeed found an elevation of A allele effect in male as compared with that in female. However, the results were not statistically significant (P>0.05). In addition to above mentioned TLR polymorphism, TLR9 rs352139 polymorphism might have an important role in the susceptibility to M. TB[47].

Several meta-analyses have addressed the Toll-like receptor polymorphism and risk of pulmonary TB; however, most were focused on a few polymorphism or in special population. For example, Zhang *et al*' report[48] focused on the TLR-1, -2, and -6 gene polymorphism; Wang *et al*' study[49] limited the studied population only in Asian population. TLR-8, and -9 have not been reported in previous meta-analysis. Here, we conducted a more comprehensive study to serve as the framework for further studies. To achieve this aim, we took an unbiased approach and included all variants found in greater than one report, not simply the ones of our choosing (fig. 1). Our study is the most comprehensive meta-analysis summarizing the associations between all the TLR gene polymorphisms and risk of TB.

In addition, some studies were limited with controversial results, including TLR8 and TLR9. We conducted the preliminary analysis to offer clues for larger-scale studies worldwide. Also, the heterogeneities are relatively obvious, which may be due to different population, genotyping method and studies' quality. We conducted meta-recession and sensitivity analysis, but did not confirm the main source (data not shown). Finally, publication biases were detected in TLR2 2258G/A by Egger's test, but not Begg's test. We broadened our searching method and found no more available publications (data not shown). The sample number (n=11) also limited the efficiency of these two tests.

Some limitations should be addressed in our study. First, this study was based on the unadjusted or crude estimates due to lack of sufficient data in the studies. A precise analysis would be more appropriate considering individual information on covariates. Second, significant heterogeneity was observed in the analysis, and some confounders such as age, gender and other environmental factors might be the source of heterogeneity. Finally, we did not perform subgroup analysis vs subgroup analysis had a relatively lower power based on a small number of studies, particularly in some subtypes of Toll-like receptor.

In conclusion, we summarized the association of TLR family polymorphisms and TB susceptibility. Overall, we revealed significant associations between several TLR polymorphisms and TB, including TLR2 2258G/A, TLR6 745C/T, TLR8 rs3761624, TLR8 rs3764879, TLR8 rs3761624 and TLR8 rs3764880. More high quality case-control studies are necessary, especially in the very potential TLR8 polymorphisms.

Conflict of Interest Statement

The authors declare that they have no competing interests.

REFERENCES

1 Davies PD, Grange JM. Factors affecting susceptibility and resistance to tuberculosis. Thorax, 2001, 56(Suppl 2):ii23-29
2 Maliarik MJ, Iannuzzi MC. Host genetic factors in resistance and susceptibility to tuberculosis infection and disease. Semin Respir Crit Care Med, 2003, 24(2):223-228
3 Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiol Rev, 2001, 23(2):288-301
4 Basu S, Fenton MJ. Toll-like receptors: function and roles in lung disease. Am J Physiol Lung Cell Mol Physiol, 2004,286(5):L887-892
5 Beutler B. Inferences, questions and possibilities in Toll-like receptor signalling. Nature, 2004,430(6996):257-263
6 Wells G, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
7 Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. BMJ, 2003,327(7414): 557-560
8 Begg CB, Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst, 1989,81(2):107-115
9 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997,315(7109):629-634
10 Ben-Ali M, Barbouche MR, Bousnina S, *et al*. Toll-like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients. Clin Diagn Lab Immunol, 2004,11(3):625-626
11 Newport MJ, Allen A, Awomoyi AA, *et al*. The toll-like receptor 4 Asp299Gly variant: no influence on LPS responsiveness or susceptibility to pulmonary

tuberculosis in The Gambia. Tuberculosis (Edinb), 2004,84(6):347-352
12 Ogus AC, Yoldas B, Ozdemir T, *et al*. The Arg753GLn polymorphism of the human toll-like receptor 2 gene in tuberculosis disease. Eur Respir J, 2004,23(2):219-223
13 Khor CC, Chapman SJ, Vannberg FO, *et al*. A Mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. Nat Genet, 2007,39(4):523-528
14 Rosas-Taraco AG, Revol A, Salinas-Carmona MC, *et al*. CD14 C(-159)T polymorphism is a risk factor for development of pulmonary tuberculosis. J Infect Dis, 2007,196(11):1698-1706
15 Thuong NT, Hawn TR, Thwaites GE, *et al*. A polymorphism in human TLR2 is associated with increased susceptibility to tuberculous meningitis. Genes Immun, 2007,8(5):422-428
16 Castiblanco J, Varela DC, Castano-Rodriguez N, *et al*. TIRAP (MAL) S180L polymorphism is a common protective factor against developing tuberculosis and systemic lupus erythematosus. Infect Genet Evol, 2008,8(5):541-544
17 Caws M, Thwaites G, Dunstan S, *et al*. The influence of host and bacterial genotype on the development of disseminated disease with *Mycobacterium tuberculosis*. PLoS Pathog, 2008,4(3):e1000034
18 Davila S, Hibberd ML, Hari Dass R, *et al*. Genetic association and expression studies indicate a role of toll-like receptor 8 in pulmonary tuberculosis. PLoS Genet, 2008,4(10):e1000218
19 Chen YC, Hsiao CC, Chen CJ, *et al*. Toll-like receptor 2 gene polymorphisms, pulmonary tuberculosis, and natural killer cell counts. BMC Med Genet, 2010,11:17
20 Dalgic N, Tekin D, Kayaalti Z, *et al*. Relationship between toll-like receptor 8 gene polymorphisms and pediatric pulmonary tuberculosis. Dis Markers, 2011,31(1):33-38
21 Dalgic N, Tekin D, Kayaalti Z, *et al*. Arg753Gln polymorphism of the human Toll-like receptor 2 gene from infection to disease in pediatric tuberculosis. Hum Immunol, 2011,72(5):440-445
22 Etokebe GE, Skjeldal F, Nilsen N, *et al*. Toll-like receptor 2 (P631H) mutant impairs membrane internalization and is a dominant negative allele. Scand J Immunol, 2010,71(5):369-381
23 Ma MJ, Xie LP, Wu SC, *et al*. Toll-like receptors, tumor necrosis factor-alpha, and interleukin-10 gene polymorphisms in risk of pulmonary tuberculosis and disease severity. Hum Immunol, 2010,71(10):1005-1010
24 Naderi M, Hashemi M, Hazire-Yazdi L, *et al*. Association between toll-like receptor2 Arg677Trp and 597T/C gene polymorphisms and pulmonary tuberculosis in Zahedan, Southeast Iran. Braz J Infect Dis, 2013,17(5):516-520
25 Najmi N, Kaur G, Sharma SK, *et al*. Human Toll-like receptor 4 polymorphisms TLR4 Asp299Gly and Thr399Ile influence susceptibility and severity of pulmonary tuberculosis in the Asian Indian population. Tissue Antigens, 2010,76(2):102-109
26 Ocejo-Vinyals JG, Puente de Mateo E, Ausin F, *et al*. Human toll-like receptor 1 T1805G polymorphism and susceptibility to pulmonary tuberculosis in northern Spain. Int J Tuberc Lung Dis, 2013,17(5):652-654
27 Selvaraj P, Harishankar M, Singh B, *et al*. Toll-like receptor and TIRAP gene polymorphisms in pulmonary tuberculosis patients of South India. Tuberculosis (Edinb), 2010,90(5):306-310
28 Che NY, Jiang SW, Gao TJ, *et al*. Relationship between toll-like receptor 2 gene polymorphism and pulmonary tuberculosis in Chinese Han population. J Chin Antituberc Assoc (Chinese), 2011,33(4):204-208
29 Li S. Association analysis between polymorphism of TLR2 and TIRAP gene and tuberculosis in Han population. Jilin Agricultural University Master degree thesis (Chinese), 2011.
30 Li T, Zhang J, Zhang GZ, *et al*. Association analysis between polymorphism of TLR8 gene and tuberculosis in Han population from Northeast China. J Jilin Univ (Medicine Edition, Chinese), 2013,39(3):584-587
31 Shi YJ, Wang Q, Guan YQ, *et al*. Associativity of T597C polymorphisms of Toll- like receptors 2 gene with susceptibility to tuberculous meningitis in Han population of southern China. J Xinxiang Med Coll (Chinese), 2012,29(4):253-256
32 Xue Y. The association analysis of CD14 and TLR2 genes with tuberculosis in the Han Chinese population. Zhejiang University PhD thesis (Chinese), 2010.
33 Yang HB. Association analysis between Toll-like receptor and pleural effusions. Guangxi Med Univ PhD thesis, 2009.
34 Yu SL. A preliminary study on the role of TLR-2 in tuberculosis infection in macrophages and its susceptibility to tuberculosis. Fudan Univ Master degree thesis, 2008.
35 Ma X, Liu Y, Gowen BB, *et al*. Full-exon resequencing reveals toll-like receptor variants contribute to human susceptibility to tuberculosis disease. PLoS One, 2007,2(12):e1318
36 Uciechowski P, Imhoff H, Lange C, *et al*. Susceptibility to tuberculosis is associated with TLR1 polymorphisms resulting in a lack of TLR1 cell surface expression. J Leukoc Biol, 2011,90(2):377-388
37 Sanchez D, Lefebvre C, Rioux J, *et al*. Evaluation of Toll-like receptor and adaptor molecule polymorphisms for susceptibility to tuberculosis in a Colombian population. Int J Immunogenet, 2012,39(3):216-223
38 Jahantigh D, Salimi S, Alavi-Naini R, *et al*. Association between TLR4 and TLR9 gene polymorphisms with development of pulmonary tuberculosis in Zahedan, southeastern Iran. Sci World J, 2013,2013:534053
39 Yu X, Zeng J, Xie J. Navigating through the maze of TLR2 mediated signaling network for better mycobacterium infection control. Biochimie, 2014,102c:1-8
40 Erridge C. Endogenous ligands of TLR2 and TLR4: agonists or assistants? J Leukoc Biol, 2010,87(6):989-999
41 Oosting M, Ter Hofstede H, Sturm P, *et al*. TLR1/TLR2 heterodimers play an important role in the recognition of Borrelia spirochetes. PLoS One, 2011,6(10):e25998
42 Farhat K, Riekenberg S, Heine H, *et al*. Heterodimerization of TLR2 with TLR1 or TLR6 expands the ligand spectrum but does not lead to differential signaling. J Leukoc Biol, 2008,83(3):692-701
43 Zhang CY, Bai N, Zhang ZH, *et al*. TLR2 signaling subpathways regulate TLR9 signaling for the effective induction of IL-12 upon stimulation by heat-killed Brucella abortus. Cell Mol Immunol, 2012,9(4):324-333
44 Bulut Y, Faure E, Thomas L, *et al*. Cooperation of

Toll-like receptor 2 and 6 for cellular activation by soluble tuberculosis factor and Borrelia burgdorferi outer surface protein A lipoprotein: role of Toll-interacting protein and IL-1 receptor signaling molecules in Toll-like receptor 2 signaling. J Immunol, 2001,167(2): 987-994

45 Chen Z, Ma G, Qian Q, *et al*. Toll-like receptor 8 polymorphism and coronary artery disease. Mol Biol Rep, 2009,36(7):1897-1901

46 Satoh M, Akatsu T, Ishikawa Y, *et al*. Association between toll-like receptor 8 expression and adverse clinical outcomes in patients with enterovirus-associated dilated cardiomyopathy. Am Heart J, 2007,154(3):581-588

47 Kobayashi K, Yuliwulandari R, Yanai H, *et al*. Association of TLR polymorphisms with development of tuberculosis in Indonesian females. Tissue Antigens, 2012,79(3):190-197

48 Zhang Y, Jiang T, Yang X, *et al*. Toll-like receptor -1, -2, and -6 polymorphisms and pulmonary tuberculosis susceptibility: a systematic review and meta-analysis. PLoS One, 2013,8(5):e63357

49 Wang JJ, Xia X, Tang SD, *et al*. Meta-analysis on the associations of TLR2 gene polymorphisms with pulmonary tuberculosis susceptibility among Asian populations. PLoS One, 2013,8(10):e75090

(Received Sep. 30, 2014; revised Mar. 2, 2015)