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The role of Toll-like receptor gene polymorphisms in tuberculosis susceptibility: a systematic review and meta-analysis

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ABSTRACT

Introduction: Susceptibility to tuberculosis (TB) infection varies in individuals and is linked to genetic variations in the toll-like receptors (TLRs) genes. The current study employed a systematic literature review and meta-analysis to describe the most prevalent single nucleotide polymorphisms (SNPs) from various TLRs and to assess the association between these polymorphisms and tuberculosis susceptibility.
Methods: The PubMed, Google Scholar, Scopus, and ISI Web of Knowledge databases were searched for all articles published before May 25, 2015, that contained the target keywords. Following the application of the inclusion and exclusion criteria, a total of 37 relevant articles were identified that examined the association between the TLRs gene polymorphism and susceptibility to tuberculosis.
Result: A meta-analyses approach to the research determined that there is a statistically significant association between TLR1 rs4833095, TLR6 rs5743810, and TLR8 rs3788935 in the allelic model and also TLR1 rs4833095, TLR1 rs5743018, TLR2 rs5743708, TLR6 rs5743810, and TLR8 rs3761624 in the co-dominant model with increased or decreased susceptibility to tuberculosis. No associations were observed between the other TLRs polymorphisms and tuberculosis risk.
Discussion: Several studies have found that host genetic factors, such as SNPs in TLRs gene, may increase an individual's susceptibility to tuberculosis. Therefore, the identification of these SNPs is important to investigate immune responses to TB.
Conclusion: The present study concluded that there is an association between some polymorphisms of TLRs and tuberculosis risk. Thus, for a better understanding about the role of SNPs to TB susceptibility, additional studies on alternative TLRs SNPs are needed.

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Introduction

Tuberculosis (TB) asymptomatically (latently) infects one-third of the global population and remains a major concern to global public health (1). However, due to factors that influence how the host and pathogen interact, including the pathogenic characteristics of the *Mycobacterium tuberculosis (M. tuberculosis*), environmental factors, individual lifestyle and diet, host genetics, and immunological factors, only 10% of latently infected subjects progress to develop the active form of the disease (2-4). In the early phase of TB infection, the host's innate immune system responds, and toll-like receptors (TLRs) play a significant role in this process (3). TLRs are a family of receptors that are expressed

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on the surface of the cell membrane or on the membrane of the endocytic vesicles of the macrophages and dendritic cells (DCs) of the mammalian innate immune system that are capable of recognizing the conserved structures of microorganisms designed as pathogen-associated molecular patterns (PAMPs). TLRs lead to phagocyte activation by enabling the nuclear transcription factor (NFκB), and they trigger an inflammatory response and the production of proinflammatory cytokines, chemokines, and nitric oxide through innate immune cells (5). To date, among the 11 mammalian TLRs that have been identified, TLR1, TLR2, TLR4, TLR6, TLR8, and TLR9 are functional in humans and are involved in the recognition of mycobacteria-associated products (3). In recent years, a multitude of investigations have described the role genetic variations in the host play in the process by which tuberculosis progresses from latent to active forms. Single nucleotide polymorphisms (SNPs) in TLRs genes play an important role in disease susceptibility, especially susceptibility to TB (6). This DNA variation alters TLRs' ability to bind its cell-surface ligands in M. tuberculosis. This allows the bacterium to evade elimination by the immune system and the disease subsequently progresses (3). As such, the identification of the host genetic factors that impact on individual's susceptibility to tuberculosis, such as SNPs at TLRs genes, is important to facilitating the development of new therapy methods and vaccines.

The purpose of this paper was to conduct a systematic review and meta-analysis to evaluate the most prevalent single nucleotide polymorphisms from various TLRs and to understand the association between these polymorphisms and tuberculosis susceptibility.

Methods

Search strategy and evaluation criteria

A computer-assisted search was conducted using the PubMed, Scopus, Google Scholar, and ISI web of knowledge databases to identify English-language articles that were published before May 25, 2015, that examined the association between TLR gene polymorphisms and TB susceptibility. The medical terms ["toll-like receptors" OR "TLRs" AND "M. tuberculosis"] and ["tuberculosis" AND"polymorphism" OR "mutation" OR "variant"] were used to identify relevant case-control articles. Hand screening of the reference lists of any articles that were found was also performed to detect any additional studies that were of relevance to the systematic review that may have been missed during the initial database search. The title, abstract, and full text of the articles were screened against the inclusion and exclusion criteria. The inclusion criteria were as follows: 1) case-control articles published in the English language, 2) articles that assessed TLR polymorphisms and TB susceptibility, and 3) articles that contained data for both case and control groups. The exclusion criteria was as follows: 1) in a language other than English, 2) article abstract only, 3) review articles, 4) papers that assessed polymorphisms in NTMs, 5) studies that evaluated polymorphisms and susceptibility to other infectious diseases, and 6) articles that did not report data for the polymorphism frequencies.

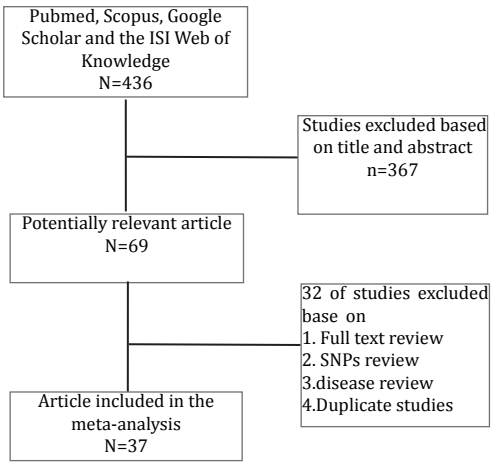

Figure 1. Flow chart of search strategy and evaluation criteria

Statistical analysis

The association between the TLRs gene polymorphism and TB susceptibility were expressed as odds ratio (ORs) and 95% confidence intervals (95% CIs). This association was considered statistically significant if the p value was less than 0.05. We pooled data from studies using random effects model (der-Simoniam and Laird method) for high heterogeneity studies and the fixed-effect model (Mantel-Haenszel method) for the low heterogeneity studies. Heterogeneity was assessed by Cochrane Q test ($p<0.05$ was considered statistically significant) and I2 index. Allelic and co-dominant models were conducted to investigate the significance of the association between the polymorphisms and TB risk in populations. All statistical analyses were performed using CMA version 2.

Results

A total of 436 case-control studies on the TLRs gene polymorphism published before May 25, 2015, were collected in this systematic review and meta-analysis. On the basis of the title, abstract and full article screening, a meta-analysis was performed on 37 of these articles (Figure 1). A total of six studies examined toll-like receptor 1 gene polymorphism, 17 studies considered toll-like receptor 2 gene polymorphism, 11 studies assessed toll-like receptor 4 gene poly-

Table 1. Characteristics of the 37 studies included in the meta-analysis

Author Reference	Year	Method(s)	Area	Ethnicity	Case	Control	SNP
Jahantigh (7)	2013	PCR-RFLP	Iran	Asian	124	149	TLR4 rs4986790 TLR4rs4986791 TLR9rs187084
Naderi (8)	2013	ARMS-PCR	Iran	Asian	174	177	TLR2 rs1695 TLR2 rs3804099
Bukhari (9)	2014	PCR-RFLP	Pakistan	Asian	103	87	TLR8 rs3764880
Najmi (10)	2010	PCR-RFLP	India	Asian	95	206	TLR4rs4986790 TLR4rs4986791
Dittrich (11)		PCR-Sequencing	India	Asian	206	239	TLR1 rs4833095
Selvaraj (12)	2010	PCR-RFLP	India	Asian	206	212	TLR1rs5743018 TLR2rs5743708 TLR4rs4986790 TLR4rs4986791 TLR6rs5743810 TLR9 rs187084 TLR9 rs5743836
Davila (13)	2008	PCR-Sequencing	Indonesia & Russia	Asian	2212	2166	TLR8rs3788935 TLR8rs3764879 TLR8rs3761624 TLR8 rs3764880
Caws (14)	2008	PCR-RFLP	Vietnam	Asian	165	377	TLR2 rs3804099
Thuong (15)	2007	PCR-MS	Vietnam	Asian	358	389	TLR2rs3804099 TLR2rs3804100
Graustein (16)	2015	PCR-Sequencing	Vietnam	Asian	352	382	TLR9 rs352142 TLR9 rs352143
Kobayashi (17)	2011	DigiTag2 assay	Indonesia & Vietnam	Asian	815	1018	TLR9 rs352139
Yu (18)	2008	PCR-RFLP	China	Asian	77	75	TLR2rs5743708 TLR2rs1695
Yang (19)	2009	PCR-RFLP	China	Asian	185	110	TLR4rs4986790 TLR4rs4986791
Yang (20)	2013	Illumina Golden-Gate Genotyping Assay	China	Asian	200	200	TLR9 rs352139
Xue (21)	2010	PCR-Sequencing	China	Asian	205	203	TLR2rs5743708 TLR2rs1695
Shi (22)	2012	PCR-RFLP	China	Asian	20	20	TLR2 rs3804099
Ma (23)	2010	PCR-RFLP	China	Asian	543	544	TLR1rs5743018 TLR2rs5743708
Li (24)	2011	PCR-RFLP	China	Asian	300	215	TLR2rs3804099 TLR2rs3804100
Li (25)	2013	PCR-LDR	China	Asian	368	355	TLR8rs3788935 TLR8rs3764879 TLR8rs3761624 TLR8 rs3764880
Che (26)	2011	PCR-Sequencing	China	Asian	115	156	TLR2rs3804099 TLR2rs3804100
Jin (27)	2007	PCR-SSP	China	Asian	170	199	TLR2 rs5743708
Chen (28)	2010	PCR-Sequencing	Taiwan	Asian	184	184	TLR2 rs3804100
Newport (29)	2004	ARMS-PCR	Gambia	African	320	320	TLR4 rs4986790
Fitness (30)	2004	PCR-LDR	Malawi	African	133	298	TLR4 rs4986790
Olesen (31)	2007	TaqMan	Guinea Bissau	African	321	347	TLR4rs4986790 TLR4rs4986791 TLR9rs187084 TLR9 rs5743836
Ben-Ali (32)	2004	PCR-Sequencing	Tunisia	African	33	33	TLR2 rs1695
Sanchez (33)	2012	PCR-MS	Colombia	American	499	320	TLR2rs5743708 TLR2rs3804099 TLR4rs4986790 TLR4rs4986791

Author Reference	Year	Method(s)	Area	Ethnicity	Case	Control	SNP
Rosas-Taraco (34)	2007	PCR-RFLP	Mexico	American	104	114	TLR4 rs4986790
Ma (35)	2007	PCR-Sequencing	USA	American	894	418	TLR1 rs5743018 TLR2 rs5743708 TLR2 rs3804099 TLR2 rs3804100 TLR4 rs4986790 TLR4 rs4986791 TLR6 rs5743810
Torres-garcia (4)	2013	TaqMan	Mexico	American	90	90	TLR4rs4986790 TLR9rs352139 TLR9 rs5743836
Uciechowski (36)	2011	PCR-Sequencing	German	European	45	49	TLR1 rs5743018
Dalgic (37)	2011	PCR-RFLP	Turkey	European	124	150	TLR8 rs3764880
Dalgic (38)	2011	PCR-RFLP	Turkey	European	198	200	TLR2 rs5743708
Ogus (39)	2004	PCR-SSP	Turkey	European	151	116	TLR2 rs5743708
Etokebe (40)	2010	PCR-Sequencing	Croatia	European	186	551	TLR2rs5743708 TLR2rs3804099 TLR2rs3804100
Bulat-Kardum (41)		TaqMan	Croatia	European	244	597	TLR10rs11096957
Ocejo-Vinyals (42)	2013	PCR-RFLP	Spain	European	190	192	TLR1 rs5743018

PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; ARMS: amplification-refractory mutation system; LDR: ligase detection reaction; SSP: sequence-specific primers; MS: mass spectroscopy.

Table 2. Comparative results of genotype and allele in the meta-analysis.

SNP	Genotype/ Allele	Odds Ratio	95% CI	I2%	Z value	P value	Effect
TLR1 rs4833095	A vs. G	0.693	(0.532-0.903)	0	-2.715	0.007	F
	AA vs. GG	2.009	(1.195-3.378)	0	2.632	0.008	F
	AA vs. GA	1.244	(0.795-1.947)	0	0.955	0.340	F
TLR1 rs5743018	T vs. G	0.917	(0.529-1.590)	90.1	-0.308	0.758	R
	TT vs. GG	0.784	(0.293-2.094)	81	-0.486	0.627	R
	TT vs. GT	1.603	(1.281-2.006)	23.5	4.120	0.000	F
TLR2 rs1695	C vs. T	0.39	(0.118-1.292)	83.7	-1.541	0.123	R
	CC vs. TT	/	/	/	/	/	/
	CC vs. CT	0.149	(0.007-3.261)	92.4	-1.209	0.227	R
TLR2 rs3804099	C vs. T	1.012	(0.889-1.153)	50.5	0.185	0.853	R
	CC vs. TT	1.053	(0.734-1.512)	64.1	0.281	0.779	R
	CC vs. CT	1.096	(0.918-1. 308)	41.9	1.013	0.311	F
TLR2 rs3804100	C vs. T	1.059	(0.923-1.215)	10	0.816	0.415	F
	CC vs. TT	1.118	(0.737-1.696)	5.1	0.524	0.600	F
	CC vs. CT	1.078	(0.704-1.650)	0	0.345	0.73	F
TLR2 rs5743708	A vs. G	1.95	(1.055-3.605)	62.7	2.131	0.033	R
	AA vs. GG	5.354	(1.372-20.894)	0	2.415	0.016	F
	AA vs. GA	3.769	(0.659-21.547)	0	1.492	0.136	F
TLR4 rs4986790	A vs. G	0.808	(0.485-1.346)	82	-0.819	0.413	R

SNP	Genotype/ Allele	Odds Ratio	95% CI	I2%	Z value	P value	Effect
	AA vs. GG	0.614	(0.303-1.244)	0	-1.354	0.174	F
	AA vs. GA	0.674	(0.322-1.413)	0	-1.044	0.297	F
TLR4 rs4986791	C vs. T	1.031	(0.746-1.425)	52.3	0.187	0.852	R
	CC vs. TT	0.942	(0.362-2.452)	25.4	-0.122	0.903	F
	CC vs. CT	0.874	(0.388-1.970)	0	-0.325	0.745	F
TLR6 rs5743810	C vs. T	0.628	(0.514-0.767)	0	-4.561	0.00	F
	CC vs. TT	0.457	(0.289-0.722)	0	-3.352	0.001	F
	CC vs. CT	0.740	(0.463-1.185)	0	-1.254	0.21	F
TLR8 rs3761624	A vs. G	1.134	(1.008-1.277)	39.3	2.089	0.037	F
	AA vs. GG	1.782	(0.554-5.738)	87.4	0.969	0.333	R
	AA vs. GA	4.830	(1.305-17.876)	88.6	2.359	0.018	R
TLR8 rs3764879	C vs. G	1.163	(0.952-1.421)	50.2	1.475	0.14	R
	CC vs. GG	2.014	(0.639-6.350)	86.6	1.195	0.232	R
	CC vs. GC	3.181	(0.385-26.305)	95.6	1.074	0.283	R
TLR8 rs3764880	A vs. G	0.845	(0.503-1.420)	93.4	-0.635	0.525	R
	AA vs. GG	1.041	(0.380-2.850)	89.1	0.078	0.938	R
	AA vs. GA	1.537	(0.337-7.008)	96.3	0.555	0.579	R
TLR8 rs3788935	C vs. G	1.216	(1.074-1.376)	10.7	3.081	0.002	F
	CC vs. GG	1.911	(0.560-6.526)	89.3	1.034	0.301	R
	CC vs. GC	3.084	(0.336-28.292)	96.3	0.996	0.319	R
TLR9 rs187084	C vs. T	1.068	(0.850-1.342)	0	0.562	0.574	F
	CC vs. TT	2.139	(0.412-11.113)	92.8	0.905	0.366	R
	CC vs. CT	1.089	(0.733-1.617)	0	0.423	0.673	F
TLR9 rs352139	A vs. G	0.856	(0.406-1.804)	91.2	-0.41	0.682	R
	AA vs. GG	0.881	(0.466-1.667)	74.8	-0.389	0.697	R
	AA vs. GA	0.832	(0.514-1.347)	63.7	-0.749	0.454	R
TLR9 rs352142	G vs. T	NA	NA	NA	NA	NA	NA
	GG vs. TT	2.422	(0.219-26.844)	0	0.721	0.471	F
	GG vs. GT	1.533	(0.131-17.968)	0	0.34	0.734	F
TLR9 rs352143	A vs. G	NA	NA	NA	NA	NA	NA
	AA vs. GG	4.686	(0.988-22.236)	0	1.944	0.052	F
	AA vs. GA	5.4	(1.033-28.227)	0	1.999	0.046	F
TLR9 rs5743836	T vs. C	1.236	(0.795-1.919)	0	0.941	0.346	F
	TT vs. CC	1.118	(0.724-1.726)	0	0.503	0.615	F
	TT vs. CT	1.185	(0.895-1.569)	0	1.182	0.237	F
TLR10 rs11096957	C vs. A	0.892	(0.721-1.103)	0	-1.056	0.291	F
	CC vs. AA	0.83	(0.547-1.259)	0	-0.877	0.381	F
	CC vs. AC	1.29	(0.877-1.897)	0	1.292	0.196	F

R: random-effect model; F: fixed-effect model; CI: confidence Interval; NA: not available.

morphism, 2 studies addressed toll-like receptor 6 gene polymorphism, 4 studies covered toll-like receptor 8 gene polymorphism, 7 studies investigated toll-like receptor 9 gene polymorphism, and 1 study examined toll-like receptor 10 gene polymorphism. As can be seen in the data presented in Table 1, PCR-RFLP, ARMS-PCR, PCR-Sequencing, PCR-MS, PCR-SSP, DigiTag2, TaqMan, and Illumina Golden-Gate Genotyping Assay were the methods that were most commonly used to determine TLRs gene polymorphism. Among TLRs, there was a significant association between TB risk and TLRs gene polymorphism: 1) allelic model: TLR1 rs4833095 (A vs. G, OR: 0.693, 95% CI: 0.532-0.903, Z: -2.715, P: 0.007), TLR6 rs5743810 (C vs. T, OR: 0.628, 95% CI: 0.514-0.767, Z: -4.561, P: 0.0) and TLR8 rs3788935 (C vs. G, OR: 1.216, 95% CI: 1.074-1.376, Z: 3.081, P: 0.002) and also 2) co-dominant model: TLR1 rs4833095 genotype (AA vs. GG, OR: 2.009, 95% CI: 1.195-3.378, Z: 2.632, P: 0.008), TLR1 rs5743018 genotype (TT vs. GT, OR: 1.603, 95% CI: 1.281-2.006, Z: 4.120, P: 0.0), TLR2 rs5743708 genotype (AA vs. GG, OR: 5.354, 95% CI: 1.372-20.894, Z: 2.415, P: 0.016), TLR6 rs5743810 genotype (CC vs. TT, OR: 0.457, 95% CI: 0.289-0.722, Z: -3.352, P: 0.001), TLR8 rs3761624 genotype (AA vs. GA, OR: 4.830, 95% CI: 1.305-17.876, Z: 2.359, P: 0.018) (Table 2).

Discussion

Several studies have found that host genetic factors may increase an individual's susceptibility to the development of various diseases (39). In the case of tuberculosis, single nucleotide polymorphisms (SNPs) within the TLR genes can cause defects in intracellular signaling in the host defense system, and this makes the host susceptible to TB disease (38). Some SNPs, which cause nucleotide sequence variations in the organism DNA, alter the function of the gene and make humans susceptible to TB infection (39). A large number of studies have found that polymorphisms in TLR1, TLR2, TLR4, TLR6, TLR8, and TLR9 are associated with TB susceptibility. However, one study recently showed that there is a significant association between TB risk and TLR10 rs11096957 gene polymorphism according to the dominant model (42). However, in other genetic models, allelic and co-dominant, there was no association between the TLR10 rs11096957 polymorphism and tuberculosis risk (C vs. A, OR: 0.892, P: 0.291 and CC vs. AA, OR: 0.83, P: 0.381). The TLR10 is usually associated with the TLR2 and assumed to be the only anti-inflammatory factor among TLRs (42).

This systematic review and meta-analysis employed allelic and co-dominant models and found that there is an association between a high susceptibility to the tuberculosis infection and the TLR1 rs4833095, TLR1 rs5743018, TLR2 rs5743708, and TLR8 rs3761624 genotypes, and a decreased susceptibility to the tuberculosis infection and the TLR6 rs5743810 genotype. Also, we found that TLR6 rs5743810 and TLR8 rs3788935 alleles may also be associated with a TB risk. The TLR1 plays a key role in the immune system's recognition of the *M. Tuberculosis* component (3). Therefore, SNPs may alter the TLR1 function. The findings of the present meta-analysis indicated that some of the TLR1 SNPs are associated with a susceptibility to tuberculosis (Table 2). A recent study by Dietrich et al. explored the association between TLR1 rs4833095 SNPs and host susceptibility to TB (A vs. G, OR: 0.693, P: 0.007 and AA vs. GG, OR: 2.009, P: 0.008) (11). In order to macrophage activation and due to the production of inflammatory cytokines in response to TB infection, the TLR2 plays an important role (3). Among the various TLR2 SNPs that were investigated as part of the current study, only TLR2 rs5743708 polymorphism had an impact on susceptibility to TB. TLRs which are implicate in the initial identification of mycobacterial CpG DNA, and also mycobacterial cell wall components and heat-labile soluble mycobacterial factor to initiate the innate responses against tuberculosis are TLR9 and TLR4 respectively (44). As shown in Table 2, we found no significant association between each of the TLR4 and TLR9 polymorphisms in both allelic and co-dominant models. Research by Graustein et al. was the first to report a correlation between TLR9 rs352142 and TLR9 rs352143 SNPs and tuberculosis (16). However, on the basis of allelic and co-dominant models, no significant association was observed in our analysis (Table 2). In our analysis, the TLR6 rs5743810 allele and TLR6 rs5743810 genotype were associated with a decreased susceptibility to TB (C vs. T, OR: 0.62 8, P: 0.0, and CC vs. TT, OR: 0.457, P: 0.001). Most TLRs form homodimers, while TLR6 can form heterodimers with TLR2 and are involved in the response to mycobacterial antigens. Finally, many case-control reports have confirmed the association of SNPs within TLR8 with a risk of TB susceptibility in diverse populations (9). In our study, the relationship between TLR8 and susceptibility to tuberculosis was observed (Table 2).

Conclusion

The present study indicates that there is an association between some TLRs polymorphism (TLR1, TLR2, TLR6, and TLR8) and tuberculosis risk in allelic and co-dominant models. Thus, additional studies on TLRs and SNPs are required to develop a better understanding of the role host genetic factors, such as SNPs, in susceptibility to tuberculosis.

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Conflict of Interest

The authors declare no conflict of interest.

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