The association of interleukin-10 -1082, -819, -592 polymorphisms and tuberculosis risk

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ABSTRACT

الأهداف : دراسة العلاقة بين التعدد الشكلي للإنترلوكين 10- 1082، -819، -592 وخطر الإصابة بالتدرن الرئوي.

الطريقة : اُجريت هذه الدراسة في مستشفى الصين الغربي، شينغ دو، الصين وذلك خلال الفترة من يوليو إلى أكتوبر 2014م. لقد قمنا بالبحث في قاعدات البيانات عن الدراسات المنشورة عن هذا الموضوع حتى شهر أكتوبر 2014م، وقد شملت هذه القاعدات كلاً من: PubMed، وEMBASE، وWeb of Science، وChina National Knowledge Infrastructure، VIP، وWANGFANG.

النتائج : شملت الدراسة ما مجموعة 37 دراسة تضمنتها 8625 حالة مصابة بالتدرن الرئوي، و9928 من المشاركين في مجموعة الشاهد. لقد وجدنا علاقة بين التعدد الشكلي للإنترلوكين 10 1082— والاستعداد المناعي للتدرن الرئوي بين القوقازيين (95% ،OR– 1.83، GG versus GA+AA، CI– 1.03–3.24). وكان هناك علاقة بين التعدد الشكلي للإنترلوكين 10–819 والاستعداد المناعي للتدرن الرئوي بين الآسيويون (C versus T, OR- 0.88, 95% CI- 0.81-0.97; CC versus TT، OR– 0.79، 95% CI– 0.64–0.97؛ CC+CT versus TT، OR– 0.87، 95% CI– 0.77–0.98؛ CC versus CT+TT، (OR: 0.82، 98% CI– 0.98–0.98). ولقد كان هنالك علاقة بين التعدد الشكلي للإنترلوكين 592–10 والاستعداد المناعي للتدرن الرئوي بين الأسيوين (C versus A، OR– 0.74، 95% CI– 0.65–0.85؛ CC versus AA، OR– 0.55، 95% CI– 0.41–0.75؛ CA versus AA، OR– 0.73، 95% CI– 0.60–0.89 ؛CC+CA versus AA، OR– 0.69، 95% CI– 0.58–0.83؛ CA versus AA، OR– 0.66، 95% CI– 0.51–0.86). أما بالنسبة للقوقازيين فقد كانت النتائج (C versus A، OR– 1.25، 95% CI– 1.08–1.45؛ CC versus CA+AA، OR– 1.48، 95% CI– 1.16–1.89؛). وأخيراً فقد كانت نتائج الأوروبيين كالآتي (C versus A، OR– 1.31، 95% CI– 1.02–1.67؛ CC versus AA، OR– 1.88، 95% CI– 1.05–3.37).

الخاتمة : أظهر هذا التحليل البعدي بأنه يمكن أن يكون هنالك علاقة بين التعدد الشكلي للإنترلوكين 10 1082، 819—، 592—، وخطر الإصابة بالتدرن الرئوي في أعراق معينة تناولتها الدراسة.

Objectives: To assess the association between interleukin (IL)-10 -1082, -819, -592 polymorphisms and tuberculosis (TB) risk.

Methods: This study was conducted between July and October 2014 in West China Hospital, Chengdu,

Sichuan, China. We searched and collected data from PUBMED, EMBASE, Web of Science, China National Knowledge Infrastructure, VIP, and WANGFANG up to October 2014.

Results: A total of 37 studies were enrolled, including 8625 TB cases, and 9928 healthy controls. The IL-10-1082G/A polymorphism was found to be associated with TB susceptibility in Caucasian (GG versus GA+AA, odds ratio [OR] - 1.83, 95% confidence interval [CI] - 1.03-3.24). The IL-10-819C/T polymorphism was related to TB susceptibility among Asians (C versus T, OR - 0.88, 95% CI - 0.81-0.97; CC versus TT: OR - 0.79, 95% CI - 0.64-0.97; CC+CT versus TT: OR - 0.87, 95% CI - 0.77-0.98; CC versus CT+TT: OR - 0.82, 95% CI - 0.68-0.98). The IL-10-592C/A polymorphism was in association with TB susceptibility in Asians (C versus A: OR - 0.74, 95% CI - 0.65-0.85; CC versus AA: OR - 0.55, 95% CI - 0.41-0.75; CA versus AA: OR - 0.73, 95% CI - 0.60-0.89; CC+CA versus AA: OR - 0.69, 95% CI 0.58-0.83; CA versus AA: OR - 0.66, 95% CI 0.51-0.86), Caucasian (C versus A: OR - 1.25, 95% CI - 1.08-1.45; CC versus CA+AA: OR-1.48, 95% CI - 1.16-1.89), and Europeans (C versus A: OR - 1.31, 95% CI - 1.02-1.67; CC versus AA: OR - 1.88, 95% CI - 1.05-3.37).

Conclusion: This meta-analysis suggests that IL-10-1082G/A, IL-819C/T, and IL-592C/A polymorphisms might be associated with TB susceptibility in certain ethnicities.

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MT) has long plagued human beings, ranking as the second major cause of death from a single infectious agent following human immunodeficiency virus (HIV).[1] According to the World Health Organization in 2012,[1] there were approximately 8.6 million new TB cases, and 1.3 million deaths with the greatest burden of disease falling in developing countries. Nearly one-third of the world's population is infected with MT, but only a small fraction (5-15%) of the population develop clinical disease during their lifetime.[2] This clinical diversity on disease' susceptibility suggests both genetic predisposition, and environmental factors may contribute to the risk of infection by this pathogen following exposure and progression to TB disease.[3] Cytokines involved in the shifting of the T-helper (Th)1/Th2 balance are known to play crucial roles in the progression of MT infection.[4] Interleukin (IL)-10, as an immunoregulatory cytokine functions by down-regulating the Th1 driven pro-inflammatory response.[5] It can be utilized by certain intracellular pathogens, including MT, to debilitate the host immune response, which then leads to the failure of subsequent clearance from the host.[6] Studies[7] carried out in vivo reported that IL-10-deficient mice infected with MT exhibits enhanced anti-mycobacterial immunity, while over-expression of IL-10 reactivates chronic pulmonary TB, and reduces MT-induced apoptosis of murine macrophages.[8-11] The relationship between IL-10 and TB was also proven by several research conducted in humans.[12,13] For patients, especially those with anergic TB and have increased IL-10 production, it is reported that high level IL-10 plasma level was associated with shorter survival of TB patients.[12,13] Up until now, several studies have identified the association of IL-10 gene polymorphisms with altered IL-10 production, especially in 3 single nucleotide polymorphisms (SNPs) at positions -1082, -819, and -592 from the transcription start site.[14,15] Investigating the association of the IL-10 gene polymorphisms with TB susceptibility may promote our understanding of the pathogenesis

of TB, and explain individual differences in TB risk. What more, it is worth mentioning that Tobin et al[16] recently reported their success in optimizing the inflammatory response to mycobacterial infections through the host genotype-specific therapies, which may also add our attention to studies regarding the TB gene polymorphisms. Unfortunately, although in recent years, a number of molecular epidemiological studies have been conducted to evaluate the risk of TB associated with the polymorphisms of IL-10 gene, their findings are conflicting. Inconsistency of those results can be attributed to a small sample size, insufficient power, and ethnic diversity of the population. Hence, we undertook this meta-analysis to evaluate the association of IL-10 gene polymorphisms and TB risk. This report follows the PRISMA (Preferred Reporting Items For Systematic Reviews and Meta-Analyses) statement.[17]

Methods. *Search methods.* This study was conducted between July and October 2014 in West China Hospital, Chengdu, China. The following databases were searched without language restriction: PUBMED, EMBASE, Web of Science, VIP, China National Knowledge Infrastructure, and WANGFANG. The search strategies were as follows: 'TB' or 'tuberculosis' in combination with 'polymorphism' or 'variant' or 'genotype' or 'allele' or 'mutation', and in combination with "interleukin-10," or "IL-10". Furthermore, the reference lists of reports identified by this search strategy were also searched to select relevant articles. The last search was conducted in October 2014. The inclusion criteria were as follows: 1) case-control study; 2) genotype distribution in both cases and controls were available; and 3) evaluation of IL-10- 1082, -819, -592 polymorphisms and TB risk. Exclusion criteria were: 1) duplicate of previous publications; and 2) study design based on family, or sibling pairs.

Data extraction. Two investigators independently screened records initially identified by the title or abstract, and then independently reviewed these records for eligibility. Discrepancies were resolved by discussion and simultaneous reference to the relevant literature. The following variables were collected from studies: title, first author's name, year and source of publication, country of origin, ethnic descent of the study population, numbers of eligible cases and controls, and genotype distributions in cases and controls, definition of cases, HIV status, and genotyping method. If data concerning the genotype distributions were not displayed in the article, the investigators would contact the primary author in an attempt to obtain the missing data.

Statistical analysis. Hardy-Weinberg Equilibrium (HWE) was tested in the controls via the Chi-square test, and it was considered statistically significant when $p<0.05$. Heterogeneity was assessed by the I^2 based Q statistics, and I^2 test. Fixed effect model was adopted if the result of the heterogeneity test was $p>0.10$. Otherwise the random effect model was used.[18,19] Odds ratio (OR) and 95% confidence interval (CI) were used to assess the strength of association between IL-10 polymorphisms, and the risk of TB under allelic model, homozygote comparison, heterozygote comparison, dominant, and recessive genetic model. Stratified analyses were performed by ethnicity. Sensitivity analyses were also performed to assess the stability of the results by excluding studies deviating from HWE. Begg's and Egger's tests were used to test the possible publication bias each time, when more than 5 studies were pooled.[20] All statistical analyses were carried out using STATA version 12.0 (Stata Corp, College Station, Texas, USA) using 2-sided *p* values.

Results. *Study characteristics.* A total of 744 articles were initially identified. After excluding those that overlapped between the databases, 395 abstracts were retrieved for further evaluation. Then, 49 articles with full texts that met the inclusion criteria were assessed. Twelve articles were excluded for being reviews. Finally, a total of 37 studies, 31 in English, 5 in Chinese, and 1 in Turkish were included in this meta-analysis.[21-57] **Figure 1** provides a PRISMA flow diagram of the search. The characteristics of these 37 included studies are summarized in **Table 1**. They included 8625 cases and 9928 controls. Among them, there were 33 studies for the -1082G/A, 21 studies for the -819C/T, and 18 studies for the -592C/A. All the studies selected healthy people as controls. The study participants were diverse in ethnicity including African, Asian, European and Caucasian. The genotype distributions among the controls of all studies were consistent with HWE except for 11 studies for the -1082G/A, 4 studies for the -819C/T, and 4 studies for the -592C/A.

Quantitative synthesis of IL-10-1082G/A. The evaluation of association between IL-10-1082G/A polymorphism and TB risk are listed in **Table 2**. Overall, the results of pooling all studies showed no significant associations between the IL-10-1082 G/A polymorphism and TB risk under any of 5 genetic models (G versus A: OR - 1.04, 95% CI - 0.93-1.17; GG versus AA: OR - 1.27, 95% CI - 0.96-1.68; GA versus AA: OR - 1.02, 95% CI - 0.86-1.21; GG+GA

versus AA: OR - 1.05, 95% CI - 0.88-1.25; GG versus GA+AA: OR - 1.22, 95% CI - 0.96-1.56). Excluding studies deviating from HWE did not change the results (G versus A: OR - 0.97, 95% CI - 0.84-1.13; GG versus AA: OR - 1.08, 95% CI - 0.75-1.55; GA versus AA: OR - 0.94, 95% CI - 0.78-1.14; GG+GA versus AA: OR - 0.97, 95% CI - 0.80-1.17; GG versus GA+AA: OR - 1.05, 95% CI - 0.77-1.44). We further performed subgroup analyses in IL-10-1082 G/A polymorphism by ethnicity, and no association of IL-10-1082G/A polymorphism and TB risk was observed in Asian and African descendants. While statistically significant associations were found in European descendants under 3 genetic models (G versus A: OR - 1.38, 95% CI - 1.04-1.82; GG versus AA: OR - 2.08, 95% CI 1.02-4.25; GG versus GA+AA: OR - 1.80, 95% CI - 1.28-2.54), and in Caucasian descendants under one genetic models (GG versus GA+AA: OR - 1.83, 95% CI 1.03-3.24). However, after excluding studies deviating from HWE, we found the association disappeared among European descendants (G versus A: OR - 1.61, 95% CI- 0.94-2.75; GG versus AA: OR - 2.39, 95% CI - 0.73-7.79; GG versus GA+AA: OR - 1.80, 95% CI - 0.80-4.08). Significant heterogeneity was found in the overall analyses even after removing studies deviating
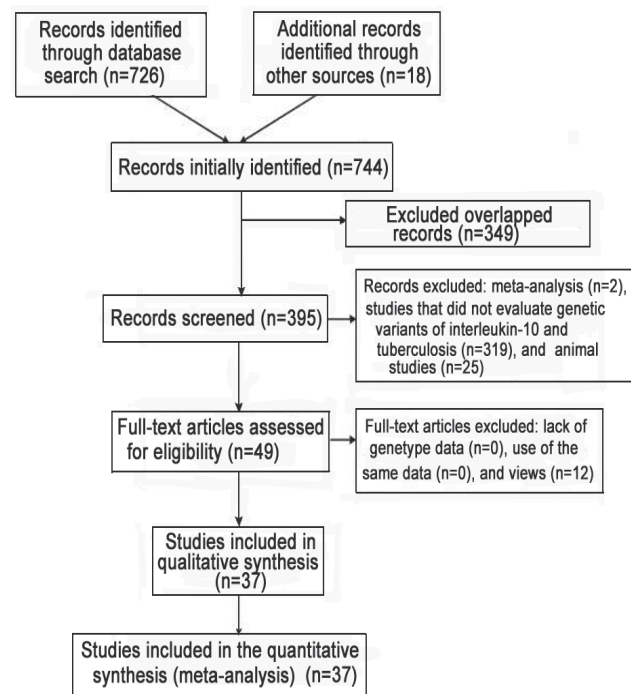

Figure 1 - Flow diagram of studies included in a meta-analysis from China.

Table 1 - Characteristics of literature included in the meta-analysis on interleukin polymorphisms and tuberculosis risk study from China.

Author	Year	Country	Language	Ethnicity	Diagnosis	HIV status	n, cases	n, controls	Genotyping method	SNPs
Bellamy et al[21]	1998	Gambia	English	African	PTB	Negative	401	408	Slot-blotting method	-1082, -819, -592
Trajkov et al[22]	2009	Republic of Macedonia	English	European	PTB	NA	75	301	PCR-SSP	-1082, -819, -592
Shin et al[23]	2005	Korea	English	Asian	PTB	Negative	459	871	MAPA	-1082, -819, -592
Ansari et al[24]	2009	Pakistan	English	Asian	PTB and EPTB	NA	188	188	PCR-ARMS	-1082
Selvaraj et al[25]	2008	India	English	Asian	PTB	Negative	166	188	PCR-SSP	-1082, -819
Amirzargar et al[26]	2006	Iran	English	Asian	PTB	NA	41	123	PCR-SSP	-1082, -819, -592
Delgado et al[27]	2002	Cambodia	English	Asian	PTB	Negative	358	106	PCR-SSP	-1082
Taype et al[28]	2010	Peru	English	Caucasian	PTB and EPTB	NA	626	513	PCR-RFLP	-1082, -592
Scola et al[29]	2003	Italy	English	European	PTB	NA	45	114	PCR-ARMS	-1082
Thye et al[30]	2009	Ghana	English	African	PTB	Negative	2010	2346	DASH	-1082, -819, -592
Lopez-Maderuelo et al[31]	2003	Spain	English	European	PTB	Negative	113	100	PCR-ARMS	-1082
Oral et al[32]	2006	Turkey	English	European	PTB and EPTB	NA	81	50	PCR-SSP	-1082, -819, -592
Ates et al[33]	2008	Turkey	English	European	PTB and EPTB	NA	128	80	PCR-ARMS	-1082, -819, -592
Prabhu Anand et al[34]	2007	India	English	Asian	PTB	NA	132	143	PCR-ARMS	-1082
Wu et al[35]	2008	China	English	Asian	PTB	NA	61	122	PCR-RFLP	-1082, -819, -592
Fitness et al[36]	2004	Malawi	English	African	PTB and EPTB	Negative	250	913	LDR	-1082, -819, -592
Oh et al[37]	2007	Korea	English	Asian	PTB	Negative	145	117	PCR-ARMS	-1082
Ma et al[38]	2007	China	Chinese	Asian	PTB	NA	40	40	PCR-SSP	-1082
García-Elorriaga et al[39]	2013	Mexico	English	Caucasian	PTB	Negative	40	47	Taqman	-1082, -592
Meenakshi et al[40]	2013	India	English	Asian	PTB	NA	100	100	PCR-ARMS	-1082
Mhmoud et al[41]	2013	Sudan	English	African	PTB	Negative	191	206	PCR-RFLP	-819, -592
Ben-Selma et al[42]	2011	Tunisia	English	African	PTB and EPTB	NA	131	95	PCR-RFLP	-1082, -819, -592
Ulger et al[43]	2013	Turkey	Turkish	European	PTB and EPTB	NA	84	110	PCR-ARMS	-1082
Ansari et al[44]	2011	Pakistan	English	Asian	PTB	Negative	102	166	PCR-ARMS	-1082
Akgunes et al[45]	2011	Turkey	English	European	PTB	NA	30	30	PCR-SSP	-1082, -819, -592
Ramaseri Sunder et al[46]	2012	India	English	Asian	PTB and EPTB	Negative	104	102	PCR-ARMS and PCR-RFLP	-1082
Mosaad et al[47]	2010	Egypt	English	African	PTB and EPTB	Negative	110	118	PCR-ARMS	-1082
Liang et al[48]	2011	China	English	Asian	PTB and EPTB	Negative	235	78	PCR-SNaPshot assay	-1082, -819, -592
Yang et al[49]	2013	China	English	Asian	PTB	NA	200	200	Illumina Golden-Gate Genotyping Assay	-1082, -819
Ma et al[50]	2010	China	English	Asian	PTB	Negative	543	544	PCR-ARMS	-819
Yang et al[51]	2010	China	Chinese	Asian	PTB	NA	200	200	PCR-SSP	-1082
Muhammad et al[52]	2011	Pakistan	English	Asian	PTB	NA	82	99	PCR-ARMS	-1082, -819, -592
Liu et al[53]	2009	China	Chinese	Asian	PTB	NA	141	135	PCR-RFLP	-1082, -819
Henao et al[54]	2006	Colombia	English	Caucasian	PTB and EPTB	Negative	190	135	PCR-SSP	-1082, -819, -592
Mei et al[55]	2012	China	Chinese	Asian	PTB	NA	169	156	PCR-RFLP	-592
Xin et al[56]	2012	China	Chinese	Asian	PTB	NA	308	310	PCR-ARMS	-1082, -819
Qi et al[57]	2014	China	English	Asian	PTB and EPTB	NA	346	374	Mass Array	-819

PTB - pulmonary tuberculosis, EPTB - extra pulmonary tuberculosis, HIV - human immunodeficiency virus, NA - not available, SNPs - single nucleotide polymorphisms, PCR - polymerase chain reaction, ARMS - amplification refractory mutation system, SSP - sequence specific primer, RFLP - restriction fragment length polymorphism, MAPA - multiplex automated primer extension analysis, DASH - dynamic allele-specific hybridization, LDR - ligase detection reaction

from HWE. However, some of the heterogeneity can be eliminated through ethnicity-specific analyses, which is observed in the studies conducted in Caucasian descendants. Among other subgroup analyses, only studies conducted in African descendants achieved improved heterogeneity after excluding studies deviating from HWE (**Table 2**). Results from Begg's and Egger's test suggested that publication bias may present in the studies investigating the association between the IL-10-1082G/A polymorphism and TB risk among Asian population (**Table 2**).

Quantitative synthesis of IL-10-819C/T. As shown in **Table 3**, the pooling analysis of total included studies indicated no association between IL-10-819C/T

Table 2 - Meta-analysis of interleukin (IL)-10-1082G/A polymorphism and tuberculosis risk according to a study from China.

Genetic model and population	Study	*P*-value	OR (95% CI)	Statistical model	I² (%)	*P*-value†	*P*-value‡
G versus A							
Overall	33	0.500	1.04 (0.93, 1.17)	Random	(68.8)	<0.001	0.549
	22*	0.731	0.97 (0.84, 1.13)	Random	(73.7)	<0.001	0.944
African	5	0.265	1.13 (0.91, 1.39)	Random	(74.4)	0.004	0.409
	3*	0.688	1.02 (0.93, 1.11)	Fixed	(0.0)	0.423	-
Asian	18	0.249	0.90 (0.75, 1.08)	Random	(68.1)	<0.001	0.86
	12*	0.098	0.81 (0.64, 1.04)	Random	(69.8)	<0.001	0.187
European	7	0.024	1.38 (1.04, 1.82)	Random	(60.0)	0.019	0.211
	4*	0.084	1.61 (0.94, 2.75)	Random	(77.2)	0.004	-
Caucasian	3	0.484	1.06 (0.89, 1.26)	Fixed	(32.3)	0.228	-
	3	0.484	1.06 (0.89, 1.26)	Fixed	(32.3)	0.228	-
GG versus AA							
Overall	30	0.090	1.27 (0.96, 1.68)	Random	(51.2)	0.001	0.145
	20*	0.680	1.08 (0.75, 1.55)	Random	(58.4)	0.001	0.449
African	5	0.347	1.20 (0.82, 1.77)	Random	(57.5)	0.051	0.196
	3*	0.883	0.98 (0.80, 1.21)	Fixed	(0.0)	0.431	0.967
Asian	17	0.866	0.96 (0.58, 1.58)	Random	(45.8)	0.021	0.349
	11*	0.488	0.77 (0.36, 1.63)	Random	(51.7)	0.023	0.007
European	6	0.044	2.08 (1.02, 4.25)	Random	(59.3)	0.031	0.178
	4*	0.150	2.39 (0.73, 7.79)	Random	(74.6)	0.008	-
Caucasian	2	0.075	1.89 (0.94, 3.80)	Fixed	(0.0)	0.873	-
	2	0.075	1.89 (0.94, 3.80)	Fixed	(0.0)	0.873	-
GA versus AA							
Overall	32	0.858	1.02 (0.86, 1.21)	Random	(68.0)	<0.001	0.697
	21	0.541	0.94 (0.78, 1.14)	Random	(69.7)	<0.001	0.856
African	5	0.115	1.32 (0.93, 1.87)	Random	(76.6)	0.002	0.225
	3	0.375	1.06 (0.94, 1.19)	Fixed	(0.0)	0.723	-
Asian	18	0.265	0.87 (0.68, 1.11)	Random	(65.0)	<0.001	0.41
	12	0.181	0.82 (0.61, 1.10)	Random	(68.7)	<0.001	0.164
European	7	0.446	1.26 (0.70, 2.27)	Random	(68.9)	0.004	0.805
	4	0.419	1.41 (0.61, 3.27)	Random	(78.9)	0.003	-
Caucasian	2	0.832	1.03 (0.80, 1.33)	Fixed	(0.0)	0.853	-
	2	0.832	1.03 (0.80, 1.33)	Fixed	(0.0)	0.853	-
GG+GA versus AA							
Overall	32	0.587	1.05 (0.88, 1.25)	Random	(71.30)	<0.001	0.505
	21	0.732	0.97 (0.80, 1.17)	Random	(73.90)	<0.001	0.97
African	5	0.119	1.32 (0.93, 1.88)	Random	(79.60)	0.001	0.245
	3	0.466	1.04 (0.93, 1.17)	Fixed	(0.00)	0.560	0.704
Asian	18	0.289	0.88 (0.68, 1.12)	Random	(68.1)	<0.001	0.33
	12	0.179	0.82 (0.61, 1.10)	Random	(71.8)	<0.001	0.172
European	7	0.178	1.46 (0.84, 2.52)	Random	(67.5)	0.005	0.73
	4	0.218	1.63 (0.75, 3.56)	Random	(78.9)	0.003	0.946
Caucasian	2	0.513	1.09 (0.85, 1.39)	Fixed	(0.0)	0.582	-
	2	0.513	1.09 (0.85, 1.39)	Fixed	(0.0)	0.582	-
GG versus GA+AA							
Overall	31	0.109	1.22 (0.96, 1.56)	Random	(50.1)	0.001	0.25
	20	0.752	1.05 (0.77, 1.44)	Random	(53.0)	0.003	0.446
African	5	0.828	0.98 (0.82, 1.18)	Fixed	(1.5)	0.398	0.644
	3	0.719	0.96 (0.79, 1.17)	Fixed	(0.0)	0.524	-
Asian	17	0.949	1.02 (0.61, 1.68)	Random	(54.7)	0.004	0.777
	11	0.447	0.75 (0.36, 1.56)	Random	(50.1)	0.029	0.005
European	7	0.001	1.80 (1.28, 2.54)	Fixed	(36.0)	0.154	0.503
	4	0.157	1.80 (0.80, 4.08)	Random	(56.5)	0.075	-
Caucasian	2	0.039	1.83 (1.03, 3.24)	Fixed	(0.0)	0.998	-
	2	0.039	1.83 (1.03, 3.24)	Fixed	(0.0)	0.998	-

OR - odds ratio, CI - confidence interval, I² - statistical variable of heterogeneity test, *exclude the studies deviating from Hardy-Weinberg equilibrium, †heterogeneity, ‡Egger's test

Table 3 - Meta-analysis of interleukin (IL)-10-819C/T polymorphism and tuberculosis risk as found in a study from China.

Genetic model and population	Study	*P*-value	OR (95% CI)	Statistical model	I² (%)	*P*-value[†]	*P*-value[‡]
C versus T							
Overall	21	0.155	0.96 (0.91, 1.01)	Fixed	(27.8)	0.116	0.86
	17	0.330	0.97 (0.92, 1.03)	Fixed	(30.4)	0.114	0.71
African	5	0.812	1.01 (0.94, 1.09)	Fixed	(0.0)	0.886	0.43
	4	0.612	1.02 (0.94, 1.10)	Fixed	(0.0)	0.992	-
Asian	11	0.004	0.89 (0.82, 0.96)	Fixed	(11.1)	0.339	0.869
	8	0.007	0.88 (0.81, 0.97)	Fixed	(5.9)	0.385	0.792
European	4	0.204	1.29 (0.87, 1.92)	Random	(57.6)	0.07	-
	4	0.204	1.29 (0.87, 1.92)	Random	(57.6)	0.07	-
Caucasian	1	0.936	1.01 (0.74, 1.39)	Fixed	-	-	-
	1	0.936	1.01 (0.74, 1.39)	Fixed	-	-	-
CC versus TT							
Overall	20	0.431	0.95 (0.85, 1.07)	Fixed	(11.7)	0.309	0.961
	16	0.715	0.98 (0.86, 1.11)	Fixed	(15.4)	0.278	0.854
African	5	0.691	1.03 (0.88, 1.21)	Fixed	(0.0)	0.509	0.619
	4	0.399	1.07 (0.91, 1.26)	Fixed	(0.0)	0.973	-
Asian	11	0.025	0.81 (0.67, 0.97)	Fixed	(0.0)	0.673	0.851
	8	0.025	0.79 (0.64, 0.97)	Fixed	(0.0)	0.562	0.682
European	4	0.105	1.63 (0.90, 2.94)	Fixed	(29.5)	0.235	-
	4	0.105	1.63 (0.90, 2.94)	Fixed	(29.5)	0.235	-
CT versus TT							
Overall	20	0.741	1.03 (0.86, 1.23)	Random	(64.5)	<0.001	0.314
	16	0.706	0.98 (0.89, 1.08)	Fixed	(14.0)	0.293	0.186
African	5	0.105	1.35 (0.94, 1.94)	Random	(74.8)	0.003	0.428
	4	0.250	1.09 (0.94, 1.27)	Fixed	(0.0)	0.646	-
Asian	11	0.191	0.87 (0.72, 1.07)	Random	(56.2)	0.011	0.517
	8	0.089	0.89 (0.78, 1.02)	Fixed	(19.7)	0.274	0.274
European	4	0.333	1.35 (0.74, 2.45)	Fixed	(0.0)	0.519	-
	4	0.333	1.35 (0.74, 2.45)	Fixed	(0.0)	0.519	-
CC+CT versus TT							
Overall	20	0.801	0.98 (0.84, 1.14)	Random	(54.8)	0.002	0.295
	16	0.446	0.96 (0.88, 1.06)	Fixed	(22.9)	0.193	0.195
African	5	0.065	1.14 (0.99, 1.30)	Fixed	(30.1)	0.221	0.401
	4	0.284	1.08 (0.94, 1.25)	Fixed	(0.0)	0.813	-
Asian	11	0.080	0.85 (0.71, 1.02)	Random	(51.8)	0.023	0.639
	8	0.024	0.87 (0.77, 0.98)	Fixed	(14.8)	0.314	0.476
European	4	0.154	1.51 (0.86, 2.68)	Fixed	(7.2)	0.357	-
	4	0.154	1.51 (0.86, 2.68)	Fixed	(7.2)	0.357	-
CC versus CT+TT							
Overall	20	0.173	0.90 (0.78, 1.05)	Random	(45.7)	0.014	0.524
	16	0.390	0.96 (0.87, 1.05)	Fixed	(11.8)	0.318	0.661
African	5	0.231	0.83 (0.61, 1.13)	Random	(78.4)	0.001	0.335
	4	0.906	0.99 (0.88, 1.11)	Fixed	(0.0)	0.875	-
Asian	11	0.085	0.86 (0.73, 1.02)	Fixed	(0.0)	0.642	0.47
	8	0.033	0.82 (0.68, 0.98)	Fixed	(0.0)	0.56	0.208
European	4	0.302	1.18 (0.86, 1.61)	Fixed	(47.4)	0.127	-
	4	0.302	1.18 (0.86, 1.61)	Fixed	(47.4)	0.127	-

OR - odds ratio, CI - confidence interval, I² - statistical variable of heterogeneity test, *exclude the studies deviating from Hardy-Weinberg equilibrium, [†]heterogeneity, [‡]Egger's test

polymorphism and TB risk (C versus T: OR - 0.96, 95% CI - 0.91-1.01; CC versus TT: OR- 0.95, 95% CI - 0.85-1.07; CT versus TT: OR- 1.03, 95% CI - 0.86-1.23; CC+CT versus TT: OR - 0.98, 95% CI - 0.84-1.14; CC versus CT+TT: OR - 0.90, 95% CI - 0.78-1.05). Excluding studies deviating from HWE did not affect the results (C versus T: OR - 0.97, 95% CI - 0.92-1.03; CC versus TT: OR - 0.98, 95% CI - 0.86-1.11; CT versus TT: OR - 0.98, 95% CI - 0.89-1.08; CC+CT versus TT: OR - 0.96, 95% CI - 0.88-1.06; CC versus CT+TT: OR- 0.96, 95% CI - 0.87-1.05). In the subgroup analyses by ethnicity, IL-10-819C/T polymorphism was associated with decreased TB risk among Asian descendants under 3 genetic models (C versus T: OR - 0.89, 95% CI - 0.82-0.96; CC versus TT: OR - 0.81, 95% CI - 0.67-0.97). The association was still significant after excluding studies deviating from HWE (C versus T: OR - 0.88, 95% CI - 0.81-0.97; CC versus TT: OR - 0.79, 95% CI - 0.64-0.97; CC+CT versus TT: OR - 0.87, 95% CI - 0.77-0.98; CC versus CT+TT: OR - 0.82, 95% CI - 0.68-0.98). While no significant association was found in other ethnicity in all tested models (**Table 3**). The heterogeneity was significant among some genetic models in the overall and subgroup analyses. However, most of heterogeneity was eliminated after excluding studies deviating from HWE (**Table 3**). Begg's and Egger's test suggested that publication bias was not apparent in all analyses concerning IL-10-819C/T polymorphism (**Table 3**).

Quantitative synthesis of IL-10-592C/A. The main results of the relationship between IL-10-592C/A polymorphism and TB risk are presented in **Table 4**. Similar to the other 2 genetic site polymorphism, the overall analysis of IL-10-592C/A polymorphism, including all ethnic groups, showed no significant association with TB risk (C versus A: OR - 0.97, 95% CI - 0.85-1.11; CC versus AA: OR - 0.89, 95% CI - 0.68-1.17; CA versus AA: OR - 0.94, 95% CI - 0.77-1.14; CC+CA versus AA: OR - 0.94, 95% CI - 0.76-1.16; CC versus CA+AA: OR - 0.94, 95% CI - 0.78-1.13). Removing the studies deviating from HWE yielded almost similar results (C versus A: OR - 1.00, 95% CI - 0.87-1.16; CC versus AA: OR - 0.94, 95% CI - 0.71-1.26; CA versus AA: OR - 0.93, 95% CI 0.76-1.13; CC+CA versus AA: OR - 0.94, 95% CI - 0.76-1.17; CC versus CA+AA: OR - 0.98, 95% CI - 0.80-1.21). Subgroup analyses were also performed by ethnicity. Decreased risk was observed among Asians in 3 genetic models (C versus A: OR - 0.79, 95% CI - 0.65-0.97; CC versus AA: OR - 0.57, 95% CI - 0.42-0.76; CC versus CA+AA: OR - 0.66, 95% CI - 0.51-0.86). When

removing the studies deviating from HWE in Asians, we found significant association in all 5 genetic models (C versus A: OR - 0.74, 95% CI - 0.65-0.85; CC versus AA: OR - 0.55, 95% CI - 0.41-0.75; CA versus AA: OR - 0.73, 95% CI - 0.60-0.89; CC+CA versus AA: OR - 0.69, 95% CI - 0.58-0.83; CC versus CA+AA: OR - 0.66, 95% CI - 0.51-0.86). While increased risk among Europeans in 2 genetic models (C versus A: OR - 1.31, 95% CI - 1.02-1.67; CC versus AA: OR - 1.88, 95% CI - 1.05-3.37) and Caucasian in 2 genetic models (C versus A: OR - 1.23, 95% CI - 1.06-1.42; CC versus CA+AA: OR - 1.45, 95% CI - 1.14-1.83) were observed in ethnicity-specific analyses. The results cannot be changed after excluding studies deviating from HWE among Europeans (C versus A: OR - 1.31, 95% CI - 1.02-1.67; CC versus AA: OR - 1.88, 95% CI - 1.05-3.37) and Caucasian (C versus A: OR - 1.25, 95% CI - 1.08-1.45; CC versus CA+AA: OR - 1.48, 95% CI - 1.16-1.89). No significant association was found among other populations (**Table 4**). Obvious heterogeneity was found in overall analyses. However, removing studies deviating from HWE, all subgroups exhibited homogeneity in all genetic models (**Table 4**). Begg's and Egger's test showed no evidence of publication bias in all analyses concerning IL-10-592C/A polymorphism (**Table 4**).

Discussion. At present, 3 meta-analyses have been conducted to assess the association between IL-10 polymorphisms and TB risk. Due to a relatively smaller study sample size, it is difficult for these previous studies to arrive at solid conclusions. Pacheco et al,[58] who conducted the first meta-analysis including only 8 studies did not find any significant association between IL-10-1082 G/A polymorphism and TB risk, whereas Zhang et al[59] reported an increased risk of TB in Europeans with IL-10-1082 in the genetic model (GG versus AA+AG). Recently, Liang et al[60] conducted a meta-analysis, and provided evidence that IL-10-1082G/A polymorphism was associated with TB risk in Europeans and Americans, and IL-10-819T/C and -592A/C polymorphisms could be risk factors for TB in Asians. Although the latter 2 meta-analyses,[59,60] which included 18 European, and 31 American studies have to some extent, amplified the power of test, they did not perform sensitivity analysis by excluding studies deviating from HWE to confirm the stability of results. Therefore, we carried out this meta-analysis on the basis of 37 eligible case-control studies to comprehensively, and rigorously evaluate the association between IL-10 polymorphisms and TB risk.

Table 4 - Meta-analysis of interleukin (IL)-10-592C/A polymorphism and tuberculosis risk as found in a study from China.

Genetic model and population	Study	*P*-value	OR (95% CI)	Statistical model	I² (%)	*P*-value†	*P*-value‡
C versus A							
Overall	18	0.639	0.97 (0.85, 1.11)	Random	(72.2)	<0.001	0.884
	14	0.980	1.00 (0.87, 1.16)	Random	(70.0)	<0.001	0.668
African	5	0.290	0.89 (0.73, 1.10)	Random	(76.8)	0.002	0.385
	3	0.933	1.00 (0.91, 1.11)	Fixed	(0.0)	0.958	-
Asian	6	0.026	0.79 (0.65, 0.97)	Random	(49.5)	0.078	0.53
	5	0.000	0.74 (0.65, 0.85)	Fixed	(32.7)	0.204	0.812
European	4	0.033	1.31 (1.02, 1.67)	Fixed	(41.8)	0.161	-
	4	0.033	1.31 (1.02, 1.67)	Fixed	(41.8)	0.161	-
Caucasian	3	0.005	1.23 (1.06, 1.42)	Fixed	(0.0)	0.674	-
	2	0.004	1.25 (1.08, 1.45)	Fixed	(0.0)	0.836	-
CC versus AA							
Overall	17	0.416	0.89 (0.68, 1.17)	Random	(61.8)	<0.001	0.85
	13	0.699	0.94 (0.71, 1.26)	Random	(61.0)	0.002	0.924
African	5	0.528	0.90 (0.63, 1.26)	Random	(63.4)	0.027	0.474
	3	0.655	1.05 (0.86, 1.28)	Fixed	(0.0)	0.997	0.454
Asian	6	0.000	0.57 (0.42, 0.76)	Fixed	(28.9)	0.218	0.604
	5	0.000	0.55 (0.41, 0.75)	Fixed	(32.3)	0.206	0.928
European	4	0.033	1.88 (1.05, 3.37)	Fixed	(1.9)	0.383	-
	4	0.033	1.88 (1.05, 3.37)	Fixed	(1.9)	0.383	0.032
Caucasian	2	0.104	1.31 (0.95, 1.80)	Fixed	(0.0)	0.360	-
	1	0.085	1.33 (0.96, 1.84)	Fixed	-	-	-
CA versus AA							
Overall	17	0.515	0.94 (0.77, 1.14)	Random	(49.6)	0.011	0.411
	13	0.450	0.93 (0.76, 1.13)	Random	(42.8)	0.051	0.392
African	5	0.897	0.98 (0.72, 1.33)	Random	(62.5)	0.031	0.627
	3	0.242	1.12 (0.93, 1.34)	Fixed	(0.0)	0.461	-
Asian	6	0.363	0.85 (0.60, 1.21)	Random	(51.4)	0.068	0.207
	5	0.002	0.73 (0.60, 0.89)	Fixed	(26.6)	0.244	0.47
European	4	0.189	1.49 (0.82, 2.69)	Fixed	(0.0)	0.590	-
	4	0.189	1.49 (0.82, 2.69)	Fixed	(0.0)	0.590	-
Caucasian	2	0.284	0.84 (0.61, 1.16)	Fixed	(0.0)	0.497	-
	1	0.325	0.85 (0.62, 1.17)	Fixed	-	-	
CC+CA versus AA							
Overall	17	0.546	0.94 (0.76, 1.16)	Random	(62.1)	<0.001	0.428
	13	0.587	0.94 (0.76, 1.17)	Random	(55.7)	0.008	0.388
African	5	0.654	0.93 (0.66, 1.30)	Random	(73.4)	0.005	0.663
	3	0.352	1.09 (0.91, 1.29)	Fixed	(0.0)	0.712	0.862
Asian	6	0.219	0.79 (0.55, 1.15)	Random	(58.6)	0.034	0.349
	5	0.000	0.69 (0.58, 0.83)	Fixed	(41.7)	0.143	0.715
European	4	0.063	1.71 (0.97, 2.99)	Fixed	(0.0)	0.497	-
	4	0.063	1.71 (0.97, 2.99)	Fixed	(0.0)	0.497	0.093
Caucasian	2	0.764	1.05 (0.78, 1.40)	Fixed	(0.0)	0.417	-
	1	0.697	1.06 (0.79, 1.42)	Fixed	-	-	-
CC versus CA+AA							
Overall	17	0.485	0.94 (0.78, 1.13)	Random	(58.5)	0.001	0.535
	13	0.887	0.98 (0.80, 1.21)	Random	(61.5)	0.002	0.799
African	5	0.175	0.92 (0.81, 1.04)	Fixed	(44.9)	0.123	0.417
	3	0.521	0.95 (0.83, 1.10)	Fixed	(0.0)	0.575	-
Asian	6	0.002	0.66 (0.51, 0.86)	Fixed	(0.0)	0.725	0.818
	5	0.002	0.66 (0.51, 0.86)	Fixed	(0.0)	0.593	0.662
European	4	0.098	1.30 (0.95, 1.79)	Fixed	(33.7)	0.210	-
	4	0.098	1.30 (0.95, 1.79)	Fixed	(33.7)	0.210	-
Caucasian	2	0.002	1.45 (1.14, 1.83)	Fixed	(0.0)	0.419	-
	1	0.001	1.48 (1.16, 1.89)	Fixed	-	-	-

OR - odds ratio, CI - confidence interval, I² - statistical variable of heterogeneity test, *exclude the studies deviating from Hardy-Weinberg equilibrium, †heterogeneity, ‡Egger's test

In terms of the IL-10-1082 G/A polymorphism, the results in pooling all studies showed no significant associations between the IL-10-1082 G/A polymorphism and TB risk. In the subsequent subgroup analysis, our initial pooling analyses found that this polymorphism in European group indicated an increased TB risk in 3 genetic models (allelic model, homozygote comparison, and recessive model), which is in consistency with Zhang et al's[59] and Liang et al's[60] meta-analysis. However, after excluding studies deviating from HWE during sensitivity analysis, our research failed to replicate this positive finding. As including studies deviating from HWE may lead to false-positive finding, those positive results should be interpreted with caution. Meanwhile, it is worth emphasizing that our meta-analysis showed an association between IL-10-1082 G/A polymorphism and TB risk in Caucasian descendants without between-study heterogeneity, which is also in consistency with the research conducted by Liang et al.[60] In view of the relatively small sample size of people were included in the pooling analysis of Caucasian subgroup, additional large studies are warranted to validate this finding.

Although pooled results of all the included studies demonstrated that IL-10-819C/T polymorphism has no substantial effect on the occurrence of TB, the finding that this polymorphism in 4 genetic models (allelic model, homozygote comparison, dominant model, and recessive model) was linked to protective effect on TB in Asian population was worth to be noted. It is a relatively solid result without between-study heterogeneity, and is also in accordance with the previous meta-analysis conducted by Liang et al.[60] While no significant association was found in other ethnicity in all tested models, which was also consistent with previous reports.[59,60] The IL-10-592C/A polymorphism was not linked to any obvious risk or protective effect on TB in all population. Interestingly, subgroup analyses showed that IL-10-592C/A polymorphism was associated with decreased susceptibility to TB in the Asian group, and increased susceptibility in European and Caucasian group, which were not reported by former meta-analyses.[58-60]

The reason why different association was observed in different ethnicity remained unclear. One possible explanation is the differences in the frequencies of the polymorphisms among diverse ethnicity, which may partly give rise to heterogeneity. Meanwhile, gene-gene interactions along with environmental factors could also contribute to the complexity of genetic effect. Thus, most often, variation in single genetic locus is insufficient to predict risk of disease.

The strength of our meta-analysis included a large sample size, comprehensive search strategy, and no language restrictions. As a result, our meta-analysis has more power to detect differences, and allow subgroup analysis. Additionally, we performed sensitive analysis by excluding studies deviating from HWE to confirm the stability of the results, which then may lead to more reliable conclusions.

Some limitations in this meta-analysis should also be addressed. Firstly, publication bias was apparent in the IL-10-1082 G/A genetic site under some genetic models among Asians. Secondly, some detailed information, such as HIV status, or TB severity was unavailable in most studies, which limited our further evaluation by performing stratified analysis according to those confounding factors. Thus, future studies should provide more information, such as the HIV status and TB severity, to promote further assessing of the association between IL-10 genetic polymorphism and TB risk. Thirdly, the small sample sizes in some subgroup analyses may not be the representative of the population. Therefore, the relationship between IL-10 genetic polymorphisms and TB should be confirmed in future studies.

In conclusion, this meta-analysis involving 18,553 participants evaluated the relationship between IL-10-1082/-819/-592 polymorphisms and risk of TB, which provided evidence that IL-10-819C/T and -592C/A polymorphisms are associated with TB susceptibility in Asians, and IL-10-592C/A polymorphism is related to TB susceptibility among Europeans, and IL-10-1082 G/A, -592C/A polymorphisms may be in association with TB susceptibility in Caucasian. Large-scale studies are warranted to be undertaken to confirm those relationship. Future studies should provide more information, such as the HIV status and TB severity, to promote further assessing of the association between IL-10 genetic polymorphism and TB risk.

References

1. World Health Organization. Tuberculosis (TB). Global tuberculosis report 2014. [Accessed 10 October 2014]. Geneva (CH): World Health Organization; 2014. Available from URL: http://www.who.int/tb/publications/global_report/en/index.html

2. Rosman MD, Oner-Eyupoglu AF. Clinical Presentation and Treatment of Tuberculosis. In: Fishman AP, editor. Fishman's Pulmonary Diseases and Disorders. New York (NY): McGraw-Hill; 1998. p. 2483-2502.

3. Bellamy R. Susceptibility to mycobacterial infection: the importance of host genetics. *Genes Immun* 2003; 4: 4-11.

4. He XY, Xiao L, Chen HB, Hao J, Li J, Wang YJ, et al. T regulatory cells and Th1/Th2 cytokines in peripheral blood from tuberculosis patients. *Eur J Clin Microbiol Infect Dis* 2010; 29: 643-650.

5. Ouyang W, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. *Annu Rev Immunol* 2011; 29: 71-109.

6. Redpath S, Ghazal P, Gascoigne NR. Hijacking and exploitation of IL-10 by intracellular pathogens. *Trends Microbiol* 2001; 9: 86-92.

7. Murray PJ, Young RA. Increased antimycobacterial immunity in interleukin-10-deficient mice. *Infect Immun* 1999; 67: 3087-3095.

8. Gil DP, Leon LG, Correa LI, Maya JR, Paris SC, Garcia LF, et al. Differential induction of apoptosis and necrosis in monocytes from patients with tuberculosis and healthy control subjects. *J Infect Dis* 2004; 189: 2120-2128.

9. Gong JH, Zhang M, Modlin RL, Linsley PS, Iyer D, Lin Y, et al. Interleukin-10 downregulates Mycobacterium tuberculosis-induced Th1 responses and CTLA-4 expression. *Infect Immun* 1996; 64: 913-918.

10. Turner J, Gonzalez-Juarrero M, Ellis DL, Basaraba RJ, Kipnis A, Orme IM, et al. In vivo IL-10 production reactivates chronic pulmonary tuberculosis in C57BL/6 mice. *J Immunol* 2002; 169: 6343-6351.

11. Rojas M, Olivier M, Gros P, Barrera LF, Garcia LF. TNF-alpha and IL-10 modulate the induction of apoptosis by virulent Mycobacterium tuberculosis in murine macrophages. *J Immunol* 1999; 162: 6122-6131.

12. Lin Y, Zhang M, Hofman FM, Gong J, Barnes PF. Absence of a prominent Th2 cytokine response in human tuberculosis. *Infect Immun* 1996; 64: 1351-1356.

13. Wang JY, Chang HC, Liu JL, Shu CC, Lee CH, Wang JT, et al. Expression of toll-like receptor 2 and plasma level of interleukin-10 are associated with outcome in tuberculosis. *Eur J Clin Microbiol Infect Dis* 2012; 31: 2327-2333.

14. Boussiotis VA, Tsai EY, Yunis EJ, Thim S, Delgado JC, Dascher CC, et al. IL-10-producing T cells suppress immune responses in anergic tuberculosis patients. *J Clin Invest* 2000; 105: 1317-1325.

15. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol* 2012; 32: 23-63.

16. Tobin DM, Roca FJ, Oh SF, McFarland R, Vickery TW, Ray JP, et al. Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. *Cell* 2012; 148: 434-446.

17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.

18. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-748.

19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-188.

20. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997; 315: 1533-1537.

21. Bellamy R, Ruwende C, Corrah T, McAdam KP, Whittle HC, Hill AV. Assessment of the interleukin 1 gene cluster and other candidate gene polymorphisms in host susceptibility to tuberculosis. *Tuber Lung Dis* 1998; 79: 83-89.

22. Trajkov D, Trajchevska M, Arsov T, Petlichkovski A, Strezova A, Efinska-Mladenovska O, et al. Association of 22 cytokine gene polymorphisms with tuberculosis in Macedonians. *Indian J Tuberc* 2009; 56: 117-131.

23. Shin HD, Park BL, Kim YH, Cheong HS, Lee IH, Park SK. Common interleukin 10 polymorphism associated with decreased risk of tuberculosis. *Exp Mol Med* 2005; 37: 128-132.

24. Ansari A, Talat N, Jamil B, Hasan Z, Razzaki T, Dawood G, et al. Cytokine gene polymorphisms across tuberculosis clinical spectrum in Pakistani patients. *PLoS One* 2009; 4: e4778.

25. Selvaraj P, Alagarasu K, Harishankar M, Vidyarani M, Nisha Rajeswari D, Narayanan PR. Cytokine gene polymorphisms and cytokine levels in pulmonary tuberculosis. *Cytokine* 2008; 43: 26-33.

26. Amirzargar AA, Rezaei N, Jabbari H, Danesh AA, Khosravi F, Hajabdolbaghi M, et al. Cytokine single nucleotide polymorphisms in Iranian patients with pulmonary tuberculosis. *Eur Cytokine Netw* 2006; 17: 84-89.

27. Delgado JC, Baena A, Thim S, Goldfeld AE. Ethnic-specific genetic associations with pulmonary tuberculosis. *J Infect Dis* 2002; 186: 1463-1468.

28. Taype CA, Shamsuzzaman S, Accinelli RA, Espinoza JR, Shaw MA. Genetic susceptibility to different clinical forms of tuberculosis in the Peruvian population. *Infect Genet Evol* 2010; 10: 495-504.

29. Scola L, Crivello A, Marino V, Gioia V, Serauto A, Candore G, et al. IL-10 and TNF-alpha polymorphisms in a sample of Sicilian patients affected by tuberculosis: implication for ageing and life span expectancy. *Mech Ageing Dev* 2003; 124: 569-572.

30. Thye T, Browne EN, Chinbuah MA, Gyapong J, Osei I, Owusu-Dabo E, et al. IL10 haplotype associated with tuberculin skin test response but not with pulmonary TB. *PLoS One* 2009; 4: e5420.

31. Lopez-Maderuelo D, Arnalich F, Serantes R, Gonzalez A, Codoceo R, Madero R, et al. Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2003; 167: 970-975.

32. Oral HB, Budak F, Uzaslan EK, Basturk B, Bekar A, Akalin H, et al. Interleukin-10 (IL-10) gene polymorphism as a potential host susceptibility factor in tuberculosis. *Cytokine* 2006; 35: 143-147.

33. Ates O, Musellim B, Ongen G, Topal-Sarikaya A. Interleukin-10 and tumor necrosis factor-alpha gene polymorphisms in tuberculosis. *J Clin Immunol* 2008; 28: 232-236.

34. Prabhu Anand S, Selvaraj P, Jawahar MS, Adhilakshmi AR, Narayanan PR. Interleukin-12B and interleukin-10 gene polymorphisms in pulmonary tuberculosis. *Indian J Med Res* 2007; 126: 135-138.

35. Wu F, Qu Y, Tang Y, Cao D, Sun P, Xia Z. Lack of association between cytokine gene polymorphisms and silicosis and pulmonary tuberculosis in Chinese iron miners. *J Occup Health* 2008; 50: 445-454.

36. Fitness J, Floyd S, Warndorff DK, Sichali L, Malema S, Crampin AC, et al. Large-scale candidate gene study of tuberculosis susceptibility in the Karonga district of northern Malawi. *Am J Trop Med Hyg* 2004; 71: 341-349.

37. Oh JH, Yang CS, Noh YK, Kweon YM, Jung SS, Son JW, et al. Polymorphisms of interleukin-10 and tumour necrosis factor-alpha genes are associated with newly diagnosed and recurrent pulmonary tuberculosis. *Respirology* 2007; 12: 594-598.

38. Ma ZM, Xiao P, Tang LG. [A study on the correlation between the polymorphism of interleukin 10 gene and susceptibility to pulmonary tuberculosis] *Guang Dong Yi Xue* 2007; 28: 1243-1245. Chinese

39. Garcia-Elorriaga G, Vera-Ramirez L, del Rey-Pineda G, Gonzalez-Bonilla C. -592 and -1082 interleukin-10 polymorphisms in pulmonary tuberculosis with type 2 diabetes. *Asian Pac J Trop Med* 2013; 6: 505-509.

40. Meenakshi P, Ramya S, Shruthi T, Lavanya J, Mohammed HH, Mohammed SA, et al. Association of IL-1beta +3954 C/T and IL-10-1082 G/A cytokine gene polymorphisms with susceptibility to tuberculosis. *Scand J Immunol* 2013; 78: 92-97.

41. Mhmoud N, Fahal A, van de Sande WJ. Association of IL-10 and CCL5 single nucleotide polymorphisms with tuberculosis in the Sudanese population. *Trop Med Int Health* 2013; 18: 1119-1127.

42. Ben-Selma W, Harizi H, Boukadida J. Association of TNF-alpha and IL-10 polymorphisms with tuberculosis in Tunisian populations. *Microbes Infect* 2011;13: 837-843.

43. Ulger M, Emekdas G, Aslan G, Tas D, Ilvan A, Tezcan S, et al. Determination of the cytokine gene polymorphism and genetic susceptibility in tuberculosis patients. *Mikrobiyol Bul* 2013; 47: 250-264. Turkish

44. Ansari A, Hasan Z, Dawood G, Hussain R. Differential combination of cytokine and interferon- gamma +874 T/A polymorphisms determines disease severity in pulmonary tuberculosis. *PLoS One* 2011; 6: e27848.

45. Akgunes A, Coban AY, Durupinar B. Human leucocyte antigens and cytokine gene polymorphisms and tuberculosis. *Indian J Med Microbiol* 2011; 29: 28-32.

46. Ramaseri Sunder S, Hanumanth SR, Nagaraju RT, Venkata SK, Suryadevara NC, Pydi SS, et al. IL-10 high producing genotype predisposes HIV infected individuals to TB infection. *Hum Immunol* 2012; 73: 605-611.

47. Mosaad YM, Soliman OE, Tawhid ZE, Sherif DM. Interferon-gamma +874 T/A and interleukin-10 -1082 A/G single nucleotide polymorphism in Egyptian children with tuberculosis. *Scand J Immunol* 2010; 72: 358-364.

48. Liang L, Zhao YL, Yue J, Liu JF, Han M, Wang H, et al. Interleukin-10 gene promoter polymorphisms and their protein production in pleural fluid in patients with tuberculosis. *FEMS Immunol Med Microbiol* 2011; 62: 84-90.

49. Yang Y, Li X, Cui W, Guan L, Shen F, Xu J, et al. Potential association of pulmonary tuberculosis with genetic polymorphisms of toll-like receptor 9 and interferon-gamma in a Chinese population. *BMC Infect Dis* 2013; 13: 511.

50. Ma MJ, Xie LP, Wu SC, Tang F, Li H, Zhang ZS, 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: 1005-1010.

51. Yang H, Liang ZH, Liu XL, Wang F. [Association between polymorphisms of interleukin-10, interferon-gamma gene and the susceptibility to pulmonary tuberculosis] *Zhonghua Liu Xing Bing Xue Za Zhi* 2010; 31: 155-158. Chinese

52. Muhammad SA, Sadia A, Amna S, Sajjad A, Zia URF, Tahir A, et al. Interleukin-10 gene promoter polymorphism as a potential host susceptibility factor in Pakistani patients with pulmonary tuberculosis. *African Journal of Biotechnology* 2011;10: 14706-14710.

53. Liu XX, Sun YH, Guo M, Feng FM. [Study on the relationship of interleukin-10 genetic polymorphisms with the susceptibility of pulmonary tuberculosis] *Modern Preventive Medicine* 2009; 36: 1827-1830. Chinese

54. Henao MI, Montes C, Paris SC, Garcia LF. Cytokine gene polymorphisms in Colombian patients with different clinical presentations of tuberculosis. *Tuberculosis (Edinb)* 2006; 86: 11-19.

55. Mei LQC, Zha D, Huang LP, Duo LN, Lu X.J, Ying BW, Fan H. [Study on association between interleukin-10 gene polymorphism with pulmonary tuberculosis in Tibetans] *Modern Preventive Medicine* 2012; 39: 3607-3610. Chinese

56. Xin DS, Jiang LF, Yang XM, Guo W, Fu FX. [A case-control study on the association between IL-10 genetic polymorphisms and susceptibility to pulmonary tuberculosis] *China Healthcare & Nutrition* 2012; 11: 68-70. Chinese

57. Qi H, Sun L, Jin YQ, Shen C, Chu P, Wang SF, et al. rs2243268 and rs2243274 of Interleukin-4 (IL-4) gene are associated with reduced risk for extrapulmonary and severe tuberculosis in Chinese Han children. *Infect Genet Evol* 2014; 23: 121-128.

58. Pacheco AG, Cardoso CC, Moraes MO. IFNG +874T/A, IL10 -1082G/A and TNF -308G/A polymorphisms in association with tuberculosis susceptibility: a meta-analysis study. *Hum Genet* 2008; 123: 477-484.

59. Zhang J, Chen Y, Nie XB, Wu WH, Zhang H, Zhang M, et al. Interleukin-10 polymorphisms and tuberculosis susceptibility: a meta-analysis. *Int J Tuberc Lung Dis* 2011; 15: 594-601.

60. Liang B, Guo Y, Li Y, Kong H. Association between IL-10 gene polymorphisms and susceptibility of tuberculosis: evidence based on a meta-analysis. *PLoS One* 2014; 9: e88448.