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IL-10 Polymorphisms and Tuberculosis Susceptibility: An Updated Meta-Analysis

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Purpose: The association of interleukin-10 (*IL-10*) polymorphisms (-1082G/A, -819C/T, -592A/C) and interleukin-6 (*IL-6*) polymorphisms (-174G/C) with tuberculosis (TB) risk has been widely reported. However, the results are controversial. To clarify the role of these polymorphisms in TB, we performed a meta-analysis of all available and relevant published studies.

Materials and Methods: Based on comprehensive searches of the PubMed, Medline, Embase, Web of Science, Elsevier Science Direct and Cochrane Library database, we identified outcome data from all articles estimating the association between *IL-10* and *IL-6* polymorphisms and TB risk.

Results: The results indicated significant association of the allele model, heterozygous model and dominant model of *IL-6* -174G/C polymorphism with decreased risk of TB. In the stratified analysis by ethnicity, significantly increased risk was observed for *IL-10* -1082G/A polymorphism in Europeans under recessive model, for *IL-10* -819C/T polymorphism in Asians under heterozygous model and dominant model and *IL-10* -592A/C polymorphism in Asians under Allele model, homozygous model and recessive model. Moreover, significantly decreased risk of TB was associated with Asians for *IL-6* -174C/G polymorphism in allele model, heterozygous model and dominant model. We also performed the analyses by sample types in *IL-10* -1082G/A polymorphism, and observed significantly increased TB risk in mixed group under homozygous model.

Conclusion: The results suggested that the *IL-10* -1082G/A polymorphism is associated with increased TB risk in Europeans, while *IL-10* -819C/T and *IL-10* -592A/C polymorphisms in Asians. However, *IL-6* -174G/C polymorphism might be a genetic risk factor that decreases TB susceptibility in Asians.

Key Words: *IL-10*, *IL-6*, polymorphism, tuberculosis, susceptibility, meta-analysis

INTRODUCTION

Tuberculosis (TB) is one of the important leading causes of death in humans, and it remains a serious public health obstacle in the developing countries. It is estimated that 1.4 million people annually die due to this treatable disease and 9 million incident cases of TB are estimated globally.[1] According to the report, Mycobacterium tuberculosis (MTB) infect about one-third of population; however, only approximately one-tenth of those infected will ever develop active TB, which indicate that MTB infection is the result of the interplay between host genetic susceptibility and environmental factors.[2]

Interleukin-10 (IL-10) is a multifunctional regulatory cytokine of inflammatory responses. Increasing numbers of studies[3] have demonstrated that IL-10 acts as a general inhibitor of proliferative and cytokine responses of both T helper (Th) 1 and Th2 cells *in vitro* and *in vivo*. IL-10 plays an anti-inflammatory action by suppressing the production of cytokines such as IL-1α, IL-1β, IL-6, IL-8, IL-12, and tumor necrosis factor-alpha in activated macrophage and interferon gamma in T cells. The *IL-10* gene is located on chromosome 1 (1q31-1q32) with five exons. The promoter region of *IL-10* gene has been found to be

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highly polymorphic and its many polymorphisms have been identified.[4] In the past few years, the impact of three common polymorphisms in the promoter of *IL-10* gene -592A/C, -1082 G/A, and -819C/T on susceptibility to TB have been reported, and results suggested that these polymorphisms contribute to the risk of TB by affecting IL-10 transcription level, but the findings are controversial.

The human interleukin-6 (*IL-6*) gene is located at 7p21-24 locus with an upstream promoter containing 303 bp. IL-6 is a pleiotropic cytokine, secreted as a T-cell derived factor by a variety of cell types including lymphocytes, monocytes, and endothelial cells. It has endocrine as well as paracrine and autocrine actions implicated in several physiologic and pathologic processes including immunity and inflammation, activation of fibroblasts, mast cells, endothelial cells, monocytes, and keratinocytes.[5] Furthermore, the genetic polymorphism in the *IL-6* promoter (-174G/C) that influences its transcription rate might play a crucial role in host immunity and susceptibility to TB.[6]

A relatively large number of studies found the association between *IL-10* and *IL-6* polymorphisms and TB risk, however, the results have been inconsistent and inconclusive due to limited sample sizes and different study populations. Therefore, we performed this meta-analysis on all eligible case-control studies to estimate the effect of polymorphisms in the *IL-10* and *IL-6* genes on the risk of TB.

MATERIALS AND METHODS

Identification of relevant studies

Relevant publications were identified with a literature search using terms "*IL-10*" or "Interleukin-10" or "*IL-6*" or "Interleukin-6" and "tuberculosis" or "TB" or "TB infection" or "TB disease" and "polymorphism" or "genotype" or "variant" in the PubMed, Medline, Embase, Web of Science, Elsevier Science Direct and Cochrane Library database (the last search update was 1 February 2014), and the search was limited to English-language journals. Additional studies were identified by a manual search of the references of original studies. The following criteria were used for inclusion in the analysis: 1) a case-control or cohort design was used and 2) studies contained available genotype frequencies. The major reasons for exclusion of studies were: no usable data were reported.

Data extraction and quality assessment

Two investigators independently extracted data and jointly reached a consensus on all of the studies researched. The following data were collected from each study: first author's name, publication year, original country, ethnicity, number of cases and controls, genotype frequencies for cases and controls, Hardy-Weinberg equilibrium (HWE) of controls and Newcastle-Ottawa Scale (NOS).[7] Star symbol was used to denote the quality, based on 3 aspects of the study: selection, comparability, and exposure. Studies with a score of 7 stars or greater were considered to be of high quality.

Statistical analysis

The risks [odds ratios (ORs), and 95% confidence intervals (95% CIs)] of TB associated with *IL-10* and *IL-6* polymorphisms were estimated for each study based on extracted genotype data. The statistical significance of the pooled OR was determined using the Z-test. Heterogeneity assumption was examined by the Cochran's Q-test. If Q-test indicated $p<0.10$, thus indicating a lack of heterogeneity among studies, then the fixed effect model was used (the Mantel-Haenszel method).[8] Otherwise, the random-effects model (the DerSimonian and Laird method)[9] was performed. Sensitivity analysis was mainly performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted to reflect the influence of the individual data set on the pooled OR. Asymmetry funnel plots were inspected to assess potential publication bias. The Egger's linear regression test was also used to assess publication bias statistically. All the above statistical analyses were performed by using the software Stata Version 12.0 (Stata Corporation, College Station, TX, USA) and *p* values were two-tailed.

RESULTS

Literature search and characteristics of eligible studies

The flow chart that displays the study selection process is shown in Fig. 1. The search of the selected databases retrieved 30 potentially relevant articles, including 7800 cases and 8793

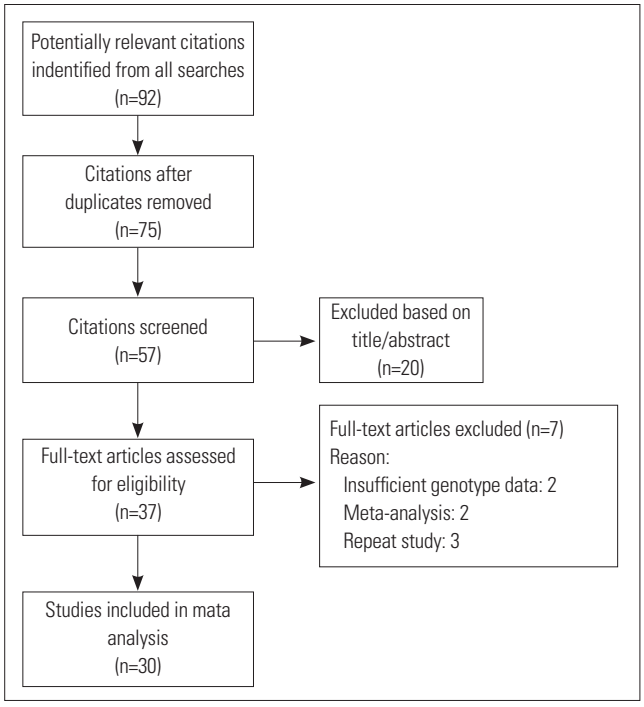

Fig. 1. Flow diagram for study selection.

Table 1. Baseline Characteristics of the 30 Eligible Studies Included in This Meta-Analysis

Study	Yr	Male patients (%)	Mean age (yrs)		Sample types	Sample size		SNP studied	Clinical diagnoses performed	Control source	Sample tested	Genotyping method	NOS score	P-HWE for controls
			Cases	Controls		Cases	Control							
IL-10														
Bellamy, et al.[10]	1998	67.4	34.7±13.2	30.3±7.5	PTB	401	408	-1082G/A, -819C/T, -592A/C	Acidfast, bacilli (AFB)	HB	Blood	PCR-slot-blotting	7	0.824
Delgado, et al.[11]	2002	37.3	42.2±14.1	37.5±12.9	PTB	356	106	-1082G/A	Sputum smear, medical history, physical examination	HB	Blood	RFLP-PCR	9	<0.001
López-Maderuelo, et al.[12]	2003	NR	NR	NR	PTB	113	100	-1082G/A	Culture, radiologic diagnosed	HB	Blood	ARMS-PCR	8	0.949
Scola, et al.[13]	2003	NR	35–60	NR	PTB	45	114	-1082G/A	Clinical history, radiologic diagnosed	PB	Blood	ARMS-PCR	7	<0.001
Fitness, et al.[14]	2004	NR	NR	NR	PTB	210	705	-1082G/A, -819C/T, -592A/C	Culture, smear, history	HB	Blood	ARMS-PCR	7	0.524
Shin, et al.[15]	2005	NR	46.9 (18–86)	56.1 (50–81)	PTB	450	851	-1082G/A, -592A/C	AFB	HB	Blood	Single-base extension methods	8	0.168
Amirzargar, et al.[6]	2006	NR	NR	NR	PTB	41	123	-1082G/A, -819C/T, -592A/C	AFB, chest X-ray (CXR)	HB	Blood	PCR-SSP	8	<0.001
Oral, et al.[16]	2006	NR	NR	NR	PTB, EPTB	81	50	-1082G/A, -819C/T, -592A/C	Staining of sputum smears, culture, biopsy, radiography	HB	Blood	PCR-SSP	9	0.06
Henao, et al.[17]	2006	57.9	15–70	17–55	PTB, EPTB	190	135	-1082G/A, -819C/T, -592A/C	Ziehl-Nielssen staining of sputum smears, culture, biopsy, CXR, clinical history	HB	Blood	PCR-SSP	9	0.94
Oh, et al.[18]	2007	68.9	17–88	45.8 (18–81)	PTB	145	117	-1082G/A	Staining of sputum smears, culture, radiography	HB	Blood	ARMS-PCR	8	0.612
Prabhu Anand, et al.[19]	2007	56.8	35.5±12.3	29.7±9.5	PTB	132	143	-1082G/A	Staining of sputum smears, culture, radiography	HB	Blood	PCR-RFLP	8	0.123
Ates, et al.[20]	2008	62	47.84±12.6	54.1±7.2	PTB, EPTB	128	80	-1082G/A, -819C/T, -592A/C	Radiographic, clinical presentation, smears, culture	HB	Blood	ARMS-PCR	9	0.978
Selvaraj, et al.[21]	2008	71.7	Male: 35.3±10.5, female: 29.2±10.3	Male: 32±8.1, female: 27.1±8.6	PTB	155	183	-1082G/A, -819C/T,	Radiographic, clinical presentation, smears, culture	PB	Blood	PCR-RFLP	7	0.204
Wu, et al.[22]	2008	NR	NR	NR	PTB	61	122	-1082G/A, -819C/T, -592A/C	Radiographic, clinical presentation, smears, culture	HB	Blood	PCR-RFLP	7	0.379
Ansari, et al.[23]	2009	NR	NR	NR	PTB	188	188	-1082G/A	Microscopy, culture, histology, imaging	PB	Blood	ARMS-PCR	8	<0.001
Thye, et al.[24]	2009	NR	NR	NR	PTB	2010	2346	-1082G/A, -819C/T, -592A/C	Smears, culture	PB	Blood	FRET	8	0.542
Trajkov, et al.[25]	2009	NR	20–59	NR	PTB	75	299	-1082G/A, -819C/T, -592A/C	WHO based	PB	Blood	PCR-SSP	7	<0.001
Taype, et al.[26]	2010	97.6	29.01±11.42	32.56±9.39	PTB, EPTB	626	513	-1082G/A, -592A/C	Smears, culture, biopsy, clinical	HB	Blood	Taqman PCR	9	0.142

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Table 1. Baseline Characteristics of the 30 Eligible Studies Included in This Meta-Analysis (Continued)

Study	Yr	Male patients (%)	Mean age (yrs)		Sample types	Sample size		SNP studied	Clinical diagnoses performed	Control source	Sample tested	Genotyping method	NOS score	P-HWE for controls
			Cases	Controls		Cases	Control							
IL-10														
Mosaad, et al.[27]	2010	67.3	0.5 (0.025–1.5)	NR (0.047–1.5)	PTB, EPTB	110	118	-1082G/A	Smear, culture	HB	Blood	ARMS-PCR	9	<0.001
Ma, et al.[28]	2010	27.8	34.75±16.67	38.17±17.39	PTB	543	544	-819C/T	Radiographic, smears, culture	HB	Blood	ARMS-PCR	9	0.491
Ben-Selma, et al.[29]	2011	51.9	PTB: 44, EPTB: 39	35	PTB, EPTB	131	95	-1082G/A, -819C/T, -592A/C	Sputum smear, CXR, radiologic, histologic grounds	HB	Blood	PCR-RFLP	9	<0.05
Liang, et al.[30]	2011	NR	NR	NR	PTB, EPTB	235	78	-1082G/A, -819C/T, -592A/C	Radiographic, biopsy, clinical presentation, smears, culture	HB	Blood	SNaPshot assay	9	0.589
Ramaseri Sunder, et al.[31]	2012	NR	NR	NR	PTB, EPTB	104	102	-1082G/A	Sputum smear, CXR, biopsy, Fine Needle Aspiration Cytology (FNAC)	HB	Blood	ARMS-PCR	8	0.057
Spinassé, et al.[32]	2012	NR	NR	NR	PTB	221	271	-1082G/A, -819C/T, -592A/C	Culture	HB	Blood	Sequencing	7	0.189
García-Elorriaga, et al.[33]	2013	38.9	38–65	26–41	PTB	77	60	-1082G/A, -592A/C	WHO based	HB	Blood	Taqman PCR	7	0.728
Ulger, et al.[34]	2013	84.5	32.57±15.94	29.40±11.56	PTB, EPTB	84	110	-1082G/A	Smear, culture	HB	Blood	PCR-RFLP	8	<0.001
Meenakshi, et al.[35]	2013	50	27.4±13.9	30±10.7	PTB	100	100	-1082G/A	Radiographic, sputum culture, AFB, histocytological examination	HB	Blood	ARMS-PCR	8	0.058
Mhmoud, et al.[36]	2013	69.6	36.9 (15–89)	31.2 (17–85)	PTB	191	206	-819C/T, -592A/C	Culture, smear	HB	Blood	PCR-RFLP	8	<0.001
IL-6														
Oral, et al.[16]	2006	NR	NR	NR	PTB, EPTB	81	49	-174G/C	Staining of sputum smears, culture, biopsy, radiography	HB	Blood	PCR-SSP	9	<0.05
Henao, et al.[17]	2006	57.9	15–70	17–55	PTB, EPTB	190	135	-174G/C	Ziehl-Nielssen staining of sputum smears, culture, biopsy, CXR, clinical history	HB	Blood	PCR-SSP	9	0.689
Amirzargar, et al.[6]	2006	NR	NR	NR	PTB	40	119	-174G/C	AFB, CXR	HB	Blood	PCR-SSP	8	<0.05
Selvaraj, et al.[21]	2008	71.7	Male: 35.3±10.5, female: 29.2±10.3	Male: 32±8.1, female: 27.1±8.6	PTB	160	183	-174G/C	Radiographic, clinical presentation, smears, culture	PB	Blood	PCR-RFLP	7	0.419
Trajkov, et al.[25]	2009	NR	20–59	NR	PTB	75	301	-174G/C	WHO based	PB	Blood	PCR-SSP	7	0.492
Ansari, et al.[37]	2011	NR	Minimal/ moderate disease: 32.4±15.9; advanced disease: 27±17.0	28.3±12.1	PTB	97	166	-174G/C	Radiographic, smears, culture	PB	Blood	ARMS-PCR	8	0.567
Zhang, et al.[38]	2012	62.0	38.64±18.44	36.92±16.52	PTB	495	358	-174G/C	Radiographic, smears, culture	HB	Blood	Mass spectrometry	8	0.979

NR, not report; PTB, pulmonary tuberculosis; EPTB, extra-pulmonary tuberculosis; SNP, single nucleotide polymorphism; PB, population-based controls; HB, hospital-based controls; PCR, polymerase chain reaction; SSP, sequence-specific primers; ARMS, amplification refractory mutation system; RFLP, restriction fragment length polymorphism; NOS, newcastle-ottawa scale; C, confirmed to HWE; HWE, Hardy-Weinberg equilibrium.

Table 2. Genotype and Allele Distributions of *IL-10* and *IL-6* Polymorphisms in Cases and Controls

Polymorphisms	Study	Country	Ethnicity	Case			Control			Case		Control	
				GG	AG	AA	GG	AG	AA	G	A	G	A
IL-10-1082G/A	Bellamy, et al.[10]	Gambia	African	51	185	165	45	184	179	287	515	274	542
	Delgado, et al.[11]	Cambodia	Asian	11	259	86	3	64	39	281	431	70	142
	López-Maderuelo, et al.[12]	Spain	European	33	47	33	29	50	21	113	113	108	92
	Scola, et al.[13]	Italy	European	17	22	6	24	77	13	56	34	125	103
	Fitness, et al.[14]	Malawi	African	23	78	69	87	251	203	124	216	425	657
	Shin, et al.[15]	Korea	Asian	2	53	394	9	124	718	57	841	142	1560
	Amirzargar, et al.[6]	Iran	Asian	2	31	7	5	79	18	35	45	89	115
	Oral, et al.[16]	Turkey	European	10	41	30	5	13	32	61	101	23	77
	Henao, et al.[17]	Colombia	American	32	92	66	26	66	43	156	224	118	152
	Oh, et al.[18]	Korea	Asian	4	43	98	19	53	45	51	239	91	143
	Prabhu, et al.[19]	India	Asian	3	55	74	6	61	73	61	203	73	207
	Ates, et al.[20]	Turkey	European	26	65	37	6	32	42	117	139	44	116
	Selvaraj, et al.[21]	India	Asian	5	42	102	6	69	108	52	246	81	285
	Wu, et al.[22]	China	Asian	1	12	48	0	18	104	14	108	18	226
	Ansari, et al.[23]	Pakistan	Asian	27	132	29	20	136	32	186	190	176	200
	Thye, et al.[24]	Ghana	African	117	631	793	160	783	1025	865	2217	1103	2833
	Trajkov, et al.[25]	Macedonia	European	10	48	17	17	212	70	68	82	246	352
	Taype, et al.[26]	Peru	American	22	187	414	10	153	347	231	1015	173	847
	Mosaad, et al.[27]	Egypt	African	16	92	2	22	88	8	124	96	132	104
	Ben-Selma, et al.[29]	Tunisian	African	21	65	45	9	26	60	168.8	155	44	146
	Liang, et al.[30]	China	Asian	0	28	207	0	9	69	28	442	9	147
	Ramaseri Sunder, et al.[31]	India	Asian	3	25	76	2	43	57	31	177	47	157
	Spinassé, et al.[32]	Brazil	American	24	100	97	31	107	133	148	294	169	373
	García-Elorriaga, et al.[33]	Mexico	American	54	20	3	31	25	4	128	26	87	33
	Ulger, et al.[34]	Turkey	European	0	84	0	1	104	5	84	84	106	114
	Meenakshi, et al.[35]	India	Asian	4	81	15	16	59	25	89	111	91	109
Polymorphisms	**Study**	**Country**	**Ethnicity**	**Case**			**Control**			**Case**		**Control**	
				TT	**TC**	**CC**	**TT**	**TC**	**CC**	**T**	**C**	**T**	**C**
IL-10-819C/T	Bellamy, et al.[10]	Gambia	African	89	192	120	88	206	114	370	432	382	434
	Fitness, et al.[14]	Malawi	African	27	98	85	108	303	287	152	268	519	877
	Amirzargar, et al.[6]	Iran	Asian	2	20	19	9	52	62	24	58	70	176
	Oral, et al.[16]	Turkey	European	10	23	48	7	19	24	43	119	33	67
	Henao, et al.[17]	Colombia	American	32	92	66	21	64	50	156	224	106	164
	Ates, et al.[20]	Turkey	European	7	58	63	8	36	36	72	184	52	108
	Selvaraj, et al.[21]	India	Asian	45	86	24	56	82	45	176	134	194	172
	Wu, et al.[22]	China	Asian	24	34	3	50	62	10	82	40	162	82
	Thye, et al.[24]	Ghana	African	267	762	515	365	942	665	1296	1792	1672	2272
	Trajkov, et al.[25]	Macedonia	European	5	35	35	19	125	155	45	105	163	435
	Ma, et al.[28]	China	Asian	229	256	58	230	253	61	714	372	713	375
	Ben-Selma, et al.[29]	Tunisian	African	11	65	55	10	42	43	87	175	62	128
	Liang, et al.[30]	China	Asian	123	90	22	35	31	12	336	134	101	55
	Spinassé, et al.[32]	Brazil	American	32	100	89	38	124	109	164	278	200	342
	Mhmoud, et al.[36]	Sudan	African	42	126	23	70	73	63	210	172	213	199
Polymorphisms	**Study**	**Country**	**Ethnicity**	**Case**			**Control**			**Case**		**Control**	
				AA	**AC**	**CC**	**AA**	**AC**	**CC**	**A**	**C**	**A**	**C**
IL-10-592A/C	Bellamy, et al.[10]	Gambia	African	89	192	120	88	206	114	370	432	382	434
	Fitness, et al.[14]	Malawi	African	27	98	85	107	301	297	152	268	515	895
	Shin, et al.[15]	Korea	Asian	238	173	39	376	384	91	649	251	1136	566
	Amirzargar, et al.[6]	Iran	Asian	2	20	18	9	52	62	24	56	70	176

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Table 2. Genotype and Allele Distributions of *IL-10* and *IL-6* Polymorphisms in Cases and Controls (Continued)

Polymorphisms	Study	Country	Ethnicity	Case			Control			Case		Control	
				AA	AC	CC	AA	AC	CC	A	C	A	C
	Oral, et al.[16]	Turkey	European	10	23	48	7	19	24	43	119	33	67
	Henao, et al.[17]	Colombia	American	72	89	29	41	67	27	233	147	149	121
	Ates, et al.[20]	Turkey	European	7	58	63	8	36	36	72	184	52	108
	Wu, et al.[22]	China	Asian	24	34	3	50	62	10	82	40	162	82
	Thye, et al.[24]	Ghana	African	172	532	321	269	696	480	876	1174	1234	1656
	Trajkov, et al.[25]	Macedonia	European	5	31	39	28	117	154	41	109	173	425
	Taype, et al.[26]	Peru	American	117	218	264	105	230	178	452	746	440	586
	Ben-selma, et al.[29]	Tunisian	African	12	63	56	10	42	43	87	175	62	128
	Liang, et al.[30]	China	Asian	123	90	22	35	31	12	336	134	101	55
	Spinassé, et al.[32]	Brazil	American	34	102	85	37	127	107	170	272	201	341
	García-elorriaga, et al.[33]	Mexico	American	1	57	19	1	42	17	59	95	44	76
	Mhmoud, et al.[36]	Sudan	African	127	47	17	100	68	38	301	81	268	144
Polymorphisms	**Study**	**Country**	**Ethnicity**	**Case**			**Control**			**Case**		**Control**	
				CC	CG	GG	CC	CG	GG	C	G	C	G
IL-6 -174G/C	Oral, et al.[16]	Turkey	European	6	27	48	9	13	27	39	123	31	67
	Henao, et al.[17]	Colombia	American	11	73	106	13	61	61	95	285	87	183
	Amirzargar, et al.[6]	Iran	Asian	4	13	23	10	71	38	21	59	91	147
	Selvaraj, et al.[21]	India	Asian	3	35	122	3	51	129	41	279	57	309
	Trajkov, et al.[25]	Macedonia	European	8	31	36	25	132	144	47	103	182	420
	Ansari, et al.[37]	Pakistan	Asian	4	24	69	10	56	100	32	162	76	256
	Zhang, et al.[38]	China	Asian	0	4	491	0	1	357	4	986	1	715

IL-10, interleukin 10; *IL-6*, interleukin 6.

controls, according to inclusion and exclusion criteria. There are 26 case-control studies concerning *IL-10* -1082G/A polymorphism,[6,10-27,29-35] 15 case-control studies for *IL-10* -819C/T polymorphism,[6,10,14,16,17,20-22,24,25,28-30,32,36] 16 case-control studies for *IL-10* -592A/C polymorphism,[6,10,14-17,20,21,24-26,29,30,32,33,36] and 7 case-control studies about *IL-6* -174G/C polymorphism.[6,16,17,21,25,37,38] Among the 30 eligible studies, 14 of them were of Asians,[6,11,15,18,19,21-23,28,30,31,35,37,38] 6 studies were of Europeans,[12,13,16,20,25,34] 6 studies were of Africans,[10,14,24,27,29,36] and 4 studies were of Americans.[17,26,32,33] The NOS scores ranged from 7 to 9, indicating that the methodological quality was generally good. The detailed characteristics of the eligible studies included in this meta-analysis are shown in Table 1, and the genotype and allele distributions of all four polymorphisms are shown in Table 2. The genotype distributions among the controls of all studies were consistent with the HWE except for eight studies for the *IL-10* -1082G/A,[6,11,13,23,25,27,29,34] one study for the *IL-10* -819C/T,[36] three studies for the *IL-10* -592A/C,[14,33,36] and two studies for the *IL-6* -174G/C (Table 1).[6,16]

Quantitative synthesis

The summary of the meta-analysis for *IL-10* -1082G/A, -819C/T, -592A/C, and *IL-6* -174G/C polymorphisms and tuberculosis susceptibility is shown in Table 3.

Analysis of *IL-10* -1082G/A and TB susceptibility

In all, twenty-six studies consisted of 5949 cases and 6948 controls, and assessed the potential influence of the *IL-10* -1082G/A polymorphism with TB susceptibility. Random effects models were used to calculate the pooled OR in all genetic models. Overall, the combined results showed no significant association in all genetic models (Fig. 2A-E). In the stratified analysis by ethnicity, *IL-10* -1082G/A polymorphism was associated with a significantly increased risk of TB in European group under recessive model (GG vs. AG+AA: OR=1.69, 95% CI=1.19–2.39). However, no significant association was found in American, Asian and African populations in all tested models. On subgroup analysis by sample types, significantly increased TB risk was observed under homozygous model (GG vs. AA: OR=2.00, 95% CI=1.16–3.45) in PTB and extra-pulmonary tuberculosis (EPTB) mixed group. The results are shown in Table 3.

Analysis of *IL-10* -819C/T and TB susceptibility

As for *IL-10* -819C/T, there were fifteen studies involving 4207 cases and 5264 controls for data synthesis in our meta-analysis. The results showed that *IL-10* -819C/T polymorphism was not significantly associated with the risk of TB in all genetic models (Fig. 2F-J). In the stratified analyses by ethnicity and control source for the -819C/T polymorphism, a significantly increased risk was observed among Asians in heterozygous model and dominant model (TC vs. CC: OR=1.34, 95% CI=1.02–1.77; TT+TC vs. CC: OR=1.31, 95% CI=1.01–1.70). The results are shown in Table 3.

Table 3. Determination of the Genetic Effects of *IL-10* and *IL-6* Polymorphisms on TB and Subgroup Analysis

	Allele model		Homozygous model		Heterozygous model		Dominant model		Recessive model	
	Effect model OR (95% CI)	*p* value	Effect model OR (95% CI)	*p* value	Effect model OR (95% CI)	*p* value	Effect model OR (95% CI)	*p* value	Effect model OR (95% CI)	*p* value
IL-10 -1082G/A	G allele vs. A allele		GG vs. AA		AG vs. AA		GG+AG vs. AA		GG vs. AG+AA	
Ethnicity										
Overall	1.05 (0.93, 1.19)	0.423	1.15 (0.87, 1.51)	0.320	1.08 (0.90, 1.29)	0.393	1.09 (0.91, 1.31)	0.335	1.09 (0.87, 1.38)	0.448
European	1.34 (1.00, 1.80)	0.054	1.88 (0.93, 3.80)	0.079	1.35 (0.70, 2.63)	0.369	1.49 (0.79, 2.79)	0.215	F1.69 (1.19, 2.39)	0.003
American	F1.10 (0.95, 1.27)	0.201	F1.16 (0.81, 1.67)	0.421	F1.07 (0.88, 1.30)	0.509	F1.09 (0.90, 1,31)	0.372	F1.23 (0.90, 1.68)	0.203
Asian	0.85 (0.67, 1.09)	0.209	0.69 (0.36, 1.36)	0.285	0.91 (0.66, 1.26)	0.940	0.89 (0.63, 1.25)	0.494	0.67 (0.36, 1.26)	0.212
African	1.12 (0.91, 1.38)	0.289	1.20 (0.81, 1.77)	0.369	1.32 (0.93, 1.87)	0.126	1.31 (0.92, 1.88)	0.131	F0.97 (0.81, 1.17)	0.761
Sample types										
PTB	0.98 (0.85, 1.12)	0.726	0.93 (0.70, 1.25)	0.646	0.97 (0.81, 1.15)	0.691	0.96 (0.80, 1.15)	0.651	1.01 (0.76, 1.34)	0.958
PTB+EPTB	1.23 (0.94, 1.62)	0.130	2.00 (1.16, 3.45)	0.013	1.53 (0.95, 2.49)	0.084	1.56 (0.97, 2.52)	0.067	1.31 (0.89, 1.93)	0.176
IL-10 -819C/T	T allele vs. C allele		TT vs. CC		TC vs. CC		TT+TC vs. CC		TT vs. TC+CC	
Ethnicity										
Overall	F1.01 (0.95, 1.07)	0.788	F1.01 (0.89, 1.15)	0.834	1.21 (1.00, 1.46)	0.056	1.14 (0.98, 1.34)	0.099	F0.93 (0.84, 1.03)	0.164
European	F0.92 (0.71, 1.19)	0.512	F0.75 (0.40, 1.42)	0.380	F0.97 (0.68, 1.37)	0.846	0.93 (0.67, 1.30)	0.678	F0.79 (0.43, 1.44)	0.438
American	F1.04 (0.85, 1.27)	0.732	F1.08 (0.71, 1.65)	0.721	F1.03 (0.76, 1.39)	0.870	F1.04 (0.78, 1.38)	0.799	F1.06 (0.72, 1.57)	0.756
Asian	F1.08 (0.95, 1.23)	0.265	F1.24 (0.92, 1.67)	0.157	F1.34 (1.02, 1.77)	0.035	F1.31 (1.01, 1.70)	0.043	F1.01 (0.84, 1.22)	0.897
African	F0.99 (0.92, 1.07)	0.812	F0.97 (0.83, 1.13)	0.691	1.34 (0.90, 2.00)	0.148	1.21 (0.89, 1.64)	0.231	F0.88 (0.77, 1.01)	0.065
Control source										
HB	F1.01 (0.93, 1.10)	0.785	F1.04 (0.87, 1.24)	0.685	1.20 (0.92, 1.55)	0.175	1.13 (0.92, 1.39)	0.237	F0.93 (0.81, 1.07)	0.310
PB	F1.01 (0.92, 1.09)	0.919	F0.99 (0.82, 1.19)	0.908	1.26 (0.89, 1.78)	0.201	1.20 (0.88, 1.64)	0.258	F0.92 (0.79, 0.84)	0.339
IL-10 -592A/C	A allele vs. C allele		AA vs. CC		AC vs. CC		AA+AC vs. CC		AA vs. AC+CC	
Ethnicity										
Overall	1.07 (0.95, 1.19)	0.270	1.09 (0.89, 1.33)	0.401	F1.01 (0.91, 1.12)	0.839	1.06 (0.91, 1.22)	0.474	1.09 (0.93, 1.29)	0.291
European	F0.84 (0.65, 1.09)	0.181	F0.64 (0.35, 1.18)	0.153	F0.90 (0.63, 1.27)	0.536	F0.85 (0.61, 1.18)	0.323	F0.68 (0.38, 1.23)	0.204
American	1.01 (0.80, 1.28)	0.918	F0.93 (0.72, 1.20)	0.595	0.91 (0.64, 1.31)	0.623	0.97 (0.67, 1.39)	0.859	F1.07 (0.86, 1.34)	0.545
Asian	F1.26 (1.08, 1.45)	0.002	F1.50 (1.07, 2.12)	0.020	F1.21 (0.88, 1.67)	0.250	F1.35 (0.99, 1.83)	0.058	F1.33 (1.10, 1.62)	0.004
African	1.12 (0.91, 1.37)	0.290	1.12 (0.79, 1.58)	0.528	F1.11 (0.97, 1.27)	0.144	F1.09 (0.96, 1.24)	0.175	1.08 (0.77, 1.52)	0.654
Control source										
HB	1.08 (0.94, 1.24)	0.254	1.14 (0.90, 1.45)	0.289	F0.95 (0.84, 1.08)	0.429	1.07 (0.89, 1.29)	0.464	1.15 (0.97, 1.37)	0.111
PB	1.00 (0.89, 1.11)	0.933	0.94 (0.75, 1.19)	0.607	F1.13 (0.95, 1.34)	0.154	1.08 (0.91, 1.22)	0.359	0.87 (0.71, 1.07)	0.194
IL-6 -174G/C	C allele vs. G allele		CC vs. GG		CG vs. GG		CC+CG vs. GG		CC vs. CG+GG	
Overall	F0.77 (0.64, 0.91)	0.003	F0.67 (0.43, 1.05)	0.078	F0.72 (0.57, 0.90)	0.005	F0.71 (0.57, 0.88)	0.002	F0.77 (0.50, 1.19)	0.243
European	F0.92 (0.67, 1.26)	0.594	0.73 (0.22, 2.43)	0.610	F1.00 (0.64, 1.57)	0.987	F0.94 (0.62, 1.42)	0.773	0.72 (0.20, 2.59)	0.615
Asian	F0.71 (0.54, 0.93)	0.013	F0.69 (0.32, 1.48)	0.343	F0.61 (0.44, 0.85)	0.004	F0.63 (0.46, 0.86)	0.004	F0.93 (0.44, 1.97)	0.855

TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extra-pulmonary tuberculosis; PB, population-based controls; HB, hospital-based controls; R, random effect model; F, fixed effect model; *IL-10*, interleukin 10; *IL-6*, interleukin 6; CI, confidence interval; OR, odds ratio.

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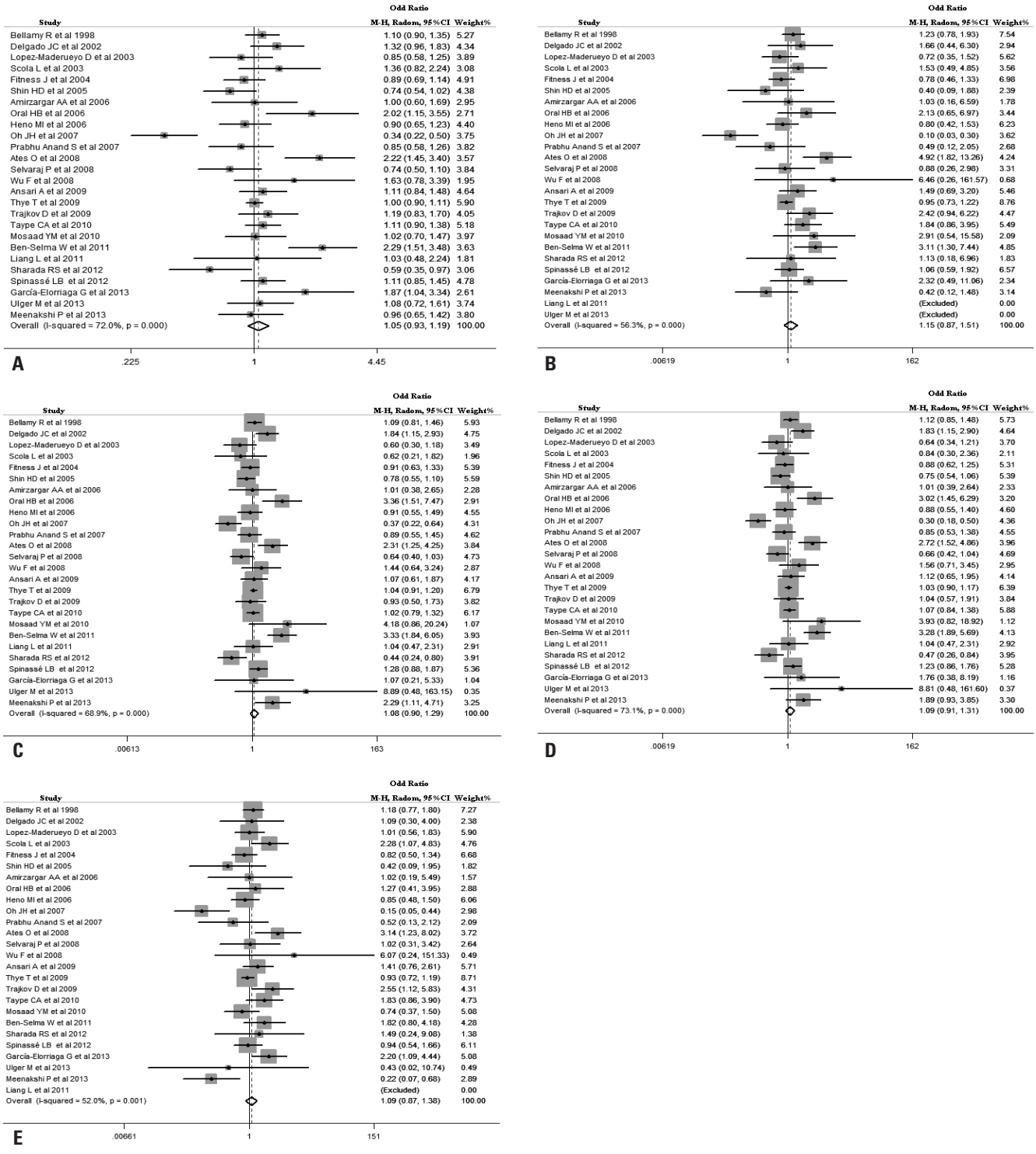

Fig. 2. Forest plot of the overall risk of TB associated with the *IL-10* -1082G/A and -819C/T polymorphism in all genetic models. Bars represent 95% CI and boxes represent OR values. The size of each box indicates the weight of the study in the pooled results. (A-E) Allele vs. A allele, GG vs. AA, AG vs. AA, GG+AG vs. AA, GG vs. AG+AA for -1082G/A. TB, tuberculosis; *IL-10*, interleukin 10; CI, confidence interval; OR, odds ratio.

Analysis of *IL-10* -592A/C and TB susceptibility

In total, sixteen studies including 4115 cases and 5441 controls examined the relationship between the *IL-10* -592A/C polymorphism and TB susceptibility. As shown in Table 3, we failed to find the association between the *IL-10* -592A/C polymorphism and TB risk in all genetic models. In the stratified analyses for the *IL-10* -592A/C polymorphism, a significantly increased risk was observed among Asians in allele model (A allele vs. C allele: OR=1.26, 95% CI=1.08−1.28), homozygous model (AA vs. CC: OR=1.50, 95% CI=1.07−2.12), and recessive

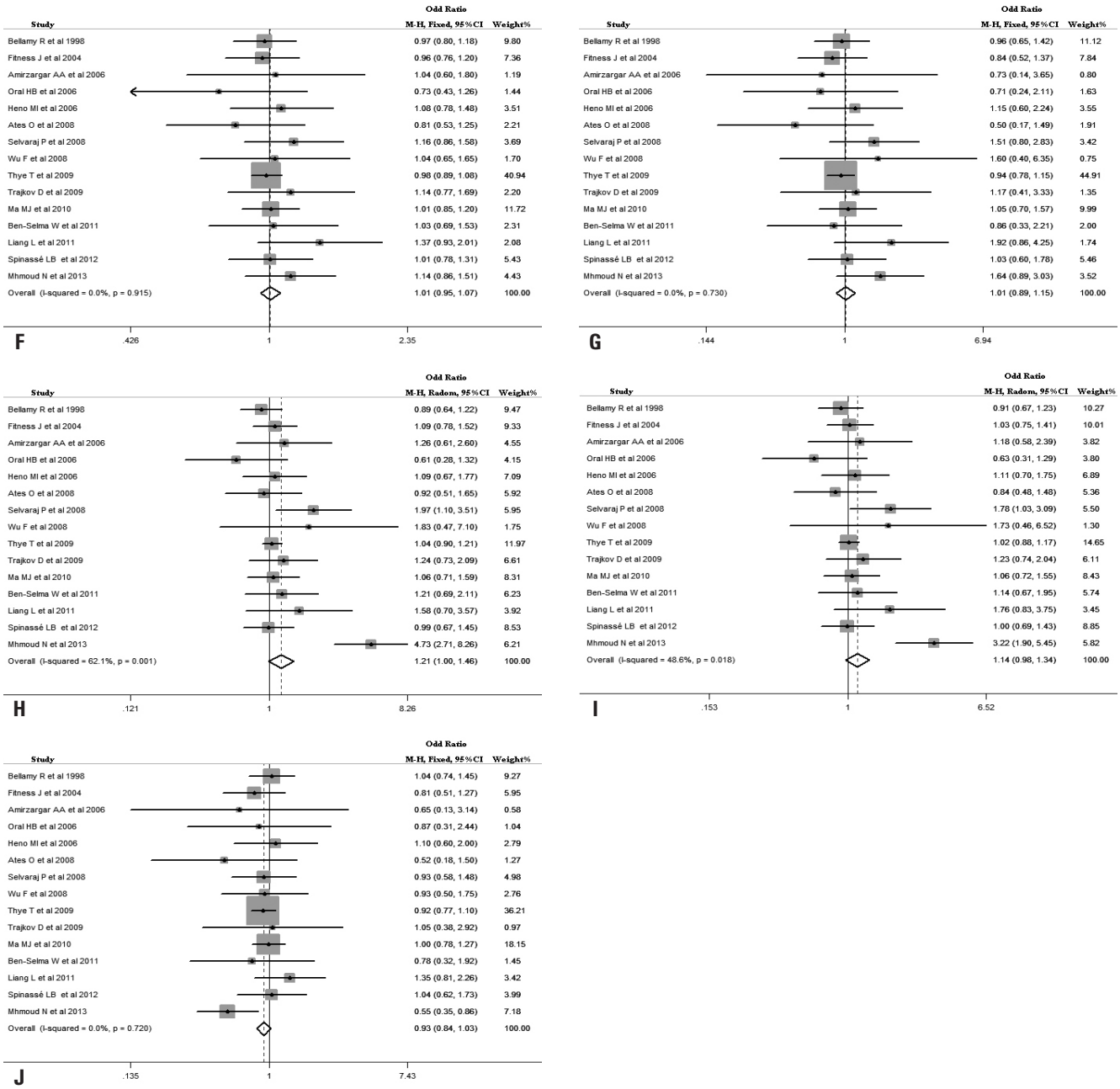

Fig. 2. Forest plot of the overall risk of TB associated with the *IL-10* -1082G/A and -819C/T polymorphism in all genetic models. Bars represent 95% CI and boxes represent OR values. The size of each box indicates the weight of the study in the pooled results. (F-J) T allele vs. C allele, TT vs. CC, TC vs. CC, TT+TC vs. CC, TT vs. TC+CC for -819C/T. TB, tuberculosis; *IL-10*, interleukin 10; CI, confidence interval; OR, odds ratio.

model (AA vs. AC+CC: OR=1.33, 95% CI=1.10–1.62) (Table 3).

Analysis of *IL-6* -174G/C and TB susceptibility

A total of 1138 cases and 1311 controls from seven case-control studies were included for data synthesis. A decreased risk between *IL-6* -174G/C polymorphism and the risk of TB was observed in Allele model (C allele vs. G allele: OR=0.77, 95% CI=0.64–0.91), heterozygous model (CC vs. GG: OR=0.72, 95% CI=0.57–0.90), and dominant genetic model (CC+CG vs. GG: OR=0.71, 95% CI=0.57–0.88). In the stratified analysis by ethnicity, *IL-6* -174G/C polymorphism was associated with a significantly decreased risk of TB in Asian populations in Allele model (C allele vs. G allele: OR=0.71, 95% CI=0.54–0.93), heterozygous model (CC vs. GG: OR=0.61, 95% CI=0.44–0.85), and dominant genetic model (CC+CG vs. GG: OR=0.63, 95% CI=0.46–0.86). The results are shown in Table 3.

Heterogeneity analysis

There were statistically significant heterogeneity in all genetic models for *IL-10* -1082G/A polymorphism, heterozygous mod-

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el and dominant model for *IL-10* -819C/T polymorphism, and all genetic models except for heterozygous model for *IL-10* -592A/C (Table 3). To elucidate the heterogeneity, Galbraith plots were performed in these genetic models. When the studies which were outliers in some genetic models were excluded respectively, all I^2 values were less than 50%, and $P_{heterogeneity}$ were greater than 0.1 (Fig. 3, Table 4). The significance of pooled OR in all genetic models was not influenced after excluding the studies. By meta-regression analysis, the heterogeneity sources were attributable to the sample types, ethnicity, control source, and the genotyping method. Ethnicity and sample types might be predominant sources of heterogeneity in *IL-10* -1082G/A polymorphism, and ethnicity and control source in both *IL-10* -819C/T and *IL-10* -592A/C polymorphisms (Table 5).

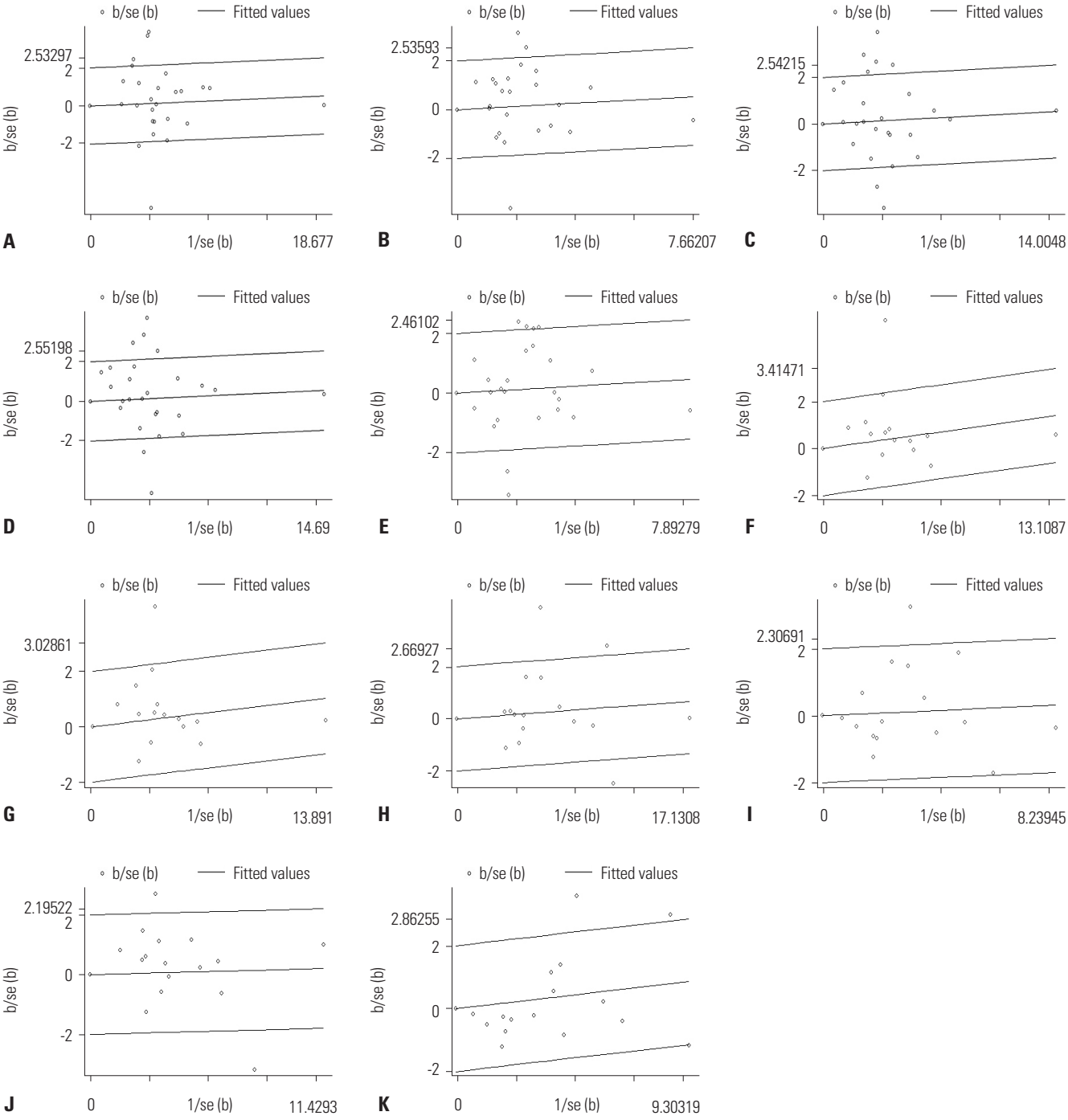

Fig. 3. Galbraith plot of *IL-10* promoter polymorphism and TB risk. (A-E) The five studies[18,20,22,31,33] in G vs. A, three studies[20,22,31] in GG vs. AA, seven studies[13,18,20,22,31,33,37] in AG vs. AA, six studies[13,18,20,22,31,33] in GG+AG vs. AA, and five studies[20,22,27,35,37] in GG vs. AG+AA were outliers for -1082G/A. (F and G) The one study[38] in TC vs. CC and one study[38] in TT+TC vs. CC for -819C/T. (H-K) The three studies[26,28,38] in A vs. C, one study[38] in AA vs. CC, one study[38] in AA+AC vs. CC, and two studies[17,38] in AA vs. AC+CC for -592A/C. TB, tuberculosis; *IL-10*, interleukin 10.

Sensitivity analysis

Sensitivity analysis was performed by sequentially excluding individual studies, including studies which was not in agreement with HWE. Statistically similar results were obtained in all genetic models after sequentially excluding each study, indicating the stability of our data.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in the all genetic models. In all genetic models, Egger's test also did not show any significant statistical evidence of publication bias, indicating low risk of publication bias in this meta-analysis (Fig. 4, Table 6).

DISCUSSION

This is not the first meta-analysis to assess the associations between three polymorphisms (-1082G/A, -819C/T, and -592A/C) in the *IL-10* gene promoter and the risk of TB. We found that the results of our meta-analysis are inconsistent with a recent study of Liang, et al.[39] in which some following shortcomings were found : 1) the NOS scores of 3 Chinese articles included were lower than 7 stars through quality assessment, 2) two studies that meet the inclusion criterion were excluded (Ma, et al.,[28] Spinassé, et al.[32]), 3) the choice of genetic models was incorrect, 4) heterogeneity analysis and sensitivity analysis were missing, and 5) some extracted data was not accurate enough. Therefore, we performed this meta-analysis to examine the association between three *IL-10* and *IL-6* polymorphisms and TB risk again. Our meta-analysis results indicated that the presence of the *IL-10* -1082G/A, -819C/T, and -592A/C polymorphisms was not associated with the risk of TB in all genetic models. On the other hand, the *IL-6* -174G/C polymorphism might be associated with an decreased risk of TB in some genetic models (C allele vs. G allele: OR=0.77, 95% CI=0.64–0.91, p=0.003; CC vs. GG: OR=0.72, 95% CI=0.57–0.90, p=0.005; CC+CG vs. GG: OR=0.71, 95% CI=0.57–0.88, p=0.002).

We also carried out subgroup analysis based on ethnicity, sample types and control source in consideration of obvious heterogeneity. In the stratiied analysis by ethnicity, we observed significantly increased TB risk associated with the *IL-10* -1082G/A polymorphism in recessive model in Europeans, *IL-10* -819C/T polymorphism in Asians in heterozygous model and dominant model, *IL-10* -592A/C polymorphism in Asians in Allele model, homozygous model and recessive model respectively, and a decreased TB risk associated with *IL-6* -174G/C polymorphism was found in allele model, heterozygous model and dominant model in Asians. Different genetic background and environmental exposures might contribute to this ethnic difference. Subgroup analysis based on sample types suggested that *IL-10* -1082G/A polymorphism may be related with an increased risk of TB in homozygous model in the PTB+EPTB mixed sample. The results of subgroup analysis by control source revealed no signiicant association with TB susceptibility among *IL-10* and *IL-6* polymorphisms.

In our meta-analysis, obvious heterogeneity was observed for *IL-10* -1082G/A polymorphism in all genetic models, -819C/T polymorphism in heterozygous model and dominant model, and -592A/C polymorphism in all genetic models except for

Table 4. Meta-Analyses of *IL-10* Polymorphisms and Risk of TB after Omitting the Studies

Polymorphisms	Omitted studies	OR (95% CI)	Z	P_{OR}	I^2 (%)	$P_{heterogeneity}$	Effect model
IL-10 -1082G/A							
G vs. A	Ates, et al.;[20] García-Elorriaga, et al.;[33] Oh, et al.;[18] Ramaseri Sunder, et al.;[31] Wu, et al.[22]	1.02 (0.96, 1.09)	0.69	0.488	9.4	0.336	F
GG vs. AA	Ates, et al.;[20] Ramaseri Sunder, et al.;[31] Wu, et al.[22]	1.04 (0.90, 1.21)	0.54	0.588	2.2	0.430	F
AG vs. AA	Ansari, et al.;[37] Ates, et al.;[20] García-Elorriaga, et al.;[33] Oh, et al.;[18] Ramaseri Sunder, et al.;[31] Scola, et al.;[13] Wu, et al.[22]	1.00 (0.92, 1.09)	0.01	0.989	0.0	0.486	F
GG+AG vs. AA	Ates, et al.;[20] García-Elorriaga, et al.;[33] Oh, et al.;[18] Ramaseri Sunder, et al.;[31] Scola, et al.;[13] Wu, et al.[22]	1.01 (0.93, 1.10)	0.25	0.802	11.6	0.311	F
GG vs. AG+AA	Ansari, et al.;[37] Ates, et al.;[20] Meenakshi, et al.;[35] Mosaad, et al.;[27] Wu, et al.[22]	1.03 (0.90, 1.19)	0.46	0.645	0.0	0.623	F
IL-10 -819C/T							F
TC vs. CC	Zhang, et al.[38]	1.06 (0.96, 1.17)	1.19	0.234	0.0	0.671	F
TT+TC vs. CC	Zhang, et al.[38]	1.04 (0.95, 1.14)	0.80	0.424	0.0	0.683	F
IL-10 -592A/C							F
A vs. C	Ma, et al.;[28] Taype, et al.;[26] Zhang, et al.[38]	1.08 (0.99, 1.17)	1.78	0.075	3.7	0.409	F
AA vs. CC	Zhang, et al.[38]	0.99 (0.87, 1.13)	0.11	0.913	5.9	0.386	F
AA+AC vs. CC	Zhang, et al.[38]	1.00 (0.91, 1.10)	0.08	0.936	29.1	0.138	F
AA vs. AC+CC	Henao, et al.;[17] Zhang, et al.[38]	0.96 (0.85, 1.09)	0.63	0.526	0.0	0.845	F

TB, tuberculosis; CI, confidence interval; OR, odds ratio; $P_{heterogeneity}$, p value of Q test for heterogeneity; F, fixed-effect models; *IL-10*, interleukin 10.

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heterozygous model, whereas there was no obvious heterogeneity for *IL-6* -174G/C polymorphism. Then, we used the Galbraith plots to explore the sources of heterogeneity. We found that all the I^2 values were less than 50% and $P_{heterogeneity}$ were greater than 0.1 after excluding some studies, thus indicating that these studies might be the major source of the heterogeneity for the *IL-10* -1082G/A, -819C/T, and -592A/C polymorphisms. Owing to the limited number of studies in this meta-analysis, we restricted meta-regression analysis to four factors (sample types, ethnicity, control source, and genotyping method), which are the most likely to cause the heterogeneity between studies. Although the four above-mentioned factors had no significant impact on the heterogeneity except sample types factor for *IL-10* -1082G/A in homozygous model, the results of subgroup analyses revealed that the ethnicity and sample type might contribute to the potential heterogeneity.

Some limitations of this meta-analysis exist which should be considered when interpreting the present results. Firstly, heterogeneity is a potential problem when interpreting the results of meta-analysis. Significant heterogeneity existed among some comparisons, especially for *IL-10* -1082G/A and -592A/C polymorphisms. Secondly, this meta-analysis included the only published studies and publication bias may occur, although our results of publication bias showed no significance. Thirdly, host genetic susceptibility, environment factors and other factors might contribute to the pathogenesis of TB. Although many other factors such as age or gender may play a profound role in the development of TB, we did not make subgroup analysis based on these factors as data is not sufficient. Finally, some genetic polymorphisms of studies deviant from HWE were included in this meta-analysis, which suggested that there was potential bias during control selection or genotyping errors.

In conclusion, our meta-analysis suggested that *IL-10* -1082G/A, -819C/T, and -592A/C polymorphisms had no association with TB risk in general population, while the *IL-6* -174G/C polymorphism was signiicantly associated with decreased risk of TB in all genetic models except for recessive model. In the subgroup analysis, *IL-10* -1082G/A polymorphism was associated with TB risk in Europeans in recessive model, and *IL-10* -592A/C polymorphisms were significantly associated with TB risk in Asians in Allele model, homozygous model and recessive model, respectively, and a decreased TB risk associated with *IL-6* -174G/C polymorphism was found in allele model, heterozygous model and dominant model in Asians. Furthermore, *IL-10* -1082G/A polymorphism was as-

Table 5. Multivariate Meta-Regression Analyses of Potential Source of Heterogeneity

Heterogeneity factors	Coefficient	SE	t	*p* value	95% CI	
					LL	UL
Sample types						
IL-10 -1082G/A	0.234, 0.924, 0.407,	0.183, 0.361, 0.278,	1.28, 2.56, 1.46,	0.215, 0.019, 0.158,	-0.146, 0.170, -0.171,	0.614, 1.679, 0.985,
(AM, HoM, HeM, DM, RM)	0.433, 0.457	0.279, 0.289	1.55, 1.58	0.136, 0.130	-0.148, -0.146	1.014, 1.061
IL-10 -819C/T (HeM, DM)	-0.119, -0.071	0.345, 0.285	-0.35, -0.25	0.737, 0.808	-0.887, -0.706	0.649, 0.564
IL-10 -592A/C	-0.091, -0.104,	0.158, 0.316,	-0.57, -0.33,	0.577, 0.748,	-0.438, -0.800,	0.256, 0.592,
(AM, HoM, DM, RM)	-0.162, -0.055	0.203, 0.235	-0.80, -0.23	0.440, 0.819	-0.609, -0.572	0.284, 0.462
Ethnicity						
IL-10 -1082G/A	-0.082, -0.118, 0.014,	0.077, 0.141, 0.124,	-1.07, -0.83, 0.11,	0.298, 0.415, 0.910,	-0.241, -0.413, -0.244,	0.077, 0.177, 0.272,
(AM, HoM, HeM, DM, RM)	-0.031, -0.223	0.124, 0.108	-0.25, -2.06	0.804, 0.052	-0.290, -0.448	0.227, 0.002
IL-10 -819C/T (HeM, DM)	0.116, 0.082	0.141, 0.115	0.82, 0.71	0.433, 0.493	-0.120, -0.175	0.431, 0.339
IL-10 -592A/C	0.067, 0.106,	0.067, 0.137,	1.00, 0.78,	0.339, 0.453,	-0.081, -0.195,	0.215, 0,407,
(AM, HoM, DM, RM)	0.084, 0.062	0.082, 0.110	1.02, 0.57	0.329, 0.583	-0.097, -0.179	0.264, 0.304
Control source						
IL-10 -1082G/A	0.093, 0.528, -0.137,	0.207, 0.366, 0.308,	0.45, 1.44, -0.44,	0.659, 0.166, 0.661,	-0.338, -0.239, -0.776,	0.524, 1.295, 0.503,
(AM, HoM, HeM, DM, RM)	-0.057, 0.545	0.311, 0.295	-0.18, 1.85	0.855, 0.080	-0.705, -0.070	0.590, 1.161
IL-10 -819C/T (HeM, DM)	0.053, 0.051	0.363, 0.294	0.14, 0.17	0.888, 0.867	-0.757, -0.605	0.862, 0.707
IL-10 -592A/C	-0.157, -0.368,	0.191, 0.362,	-0.82, -1.02,	0.429, 0.331,	-0.577, -1.165,	0.263, 0.429,
(AM, HoM, DM, RM)	-0.090, -0.395	0.225, 0.265	-0.40, -1.49	0.697, 0.165	-0.585, -0.978	0.405, 0.189
Genotyping method						
IL-10 -1082G/A	0.075, 0.124, 0.051,	0.064, 0.121, 0.098,	1.17, 1.02, 0.52,	0.254, 0.319, 0.606,	-0.058, -0.129, -0.152,	0.209, 0.376, 0.254,
(AM, HoM, HeM, DM, RM)	0.068, 0.137	0.099, 0.095	0.69, 1.44	0.499, 0.164	-0.137, -0.061	0.273, 0.335
IL-10 -819C/T (HeM, DM)	0.006, 0.022	0.131, 0.106	0.05, 0.21	0.965, 0.840	-0.285, -0.214	0.297, 0.257
IL-10 -592A/C	0.015, 0.074,	0.060, 0.117,	0.24, 0.63,	0.813, 0.538,	-0.118, -0.183,	0.147, 0.331,
(AM, HoM, DM, RM)	-0.024, 0.090	0.073, 0.089	-0.32, 1.01	0.752, 0.336	-0.185, -0.107	0.137, 0.286

SE, standard error; CI, confidence interval; UL, upper limit; LL, lower limit; AM, allele model; HoM, homozygous model; HeM, heterozygous model; DM, dominant model; RM, recessive model; *IL-10*, interleukin 10.

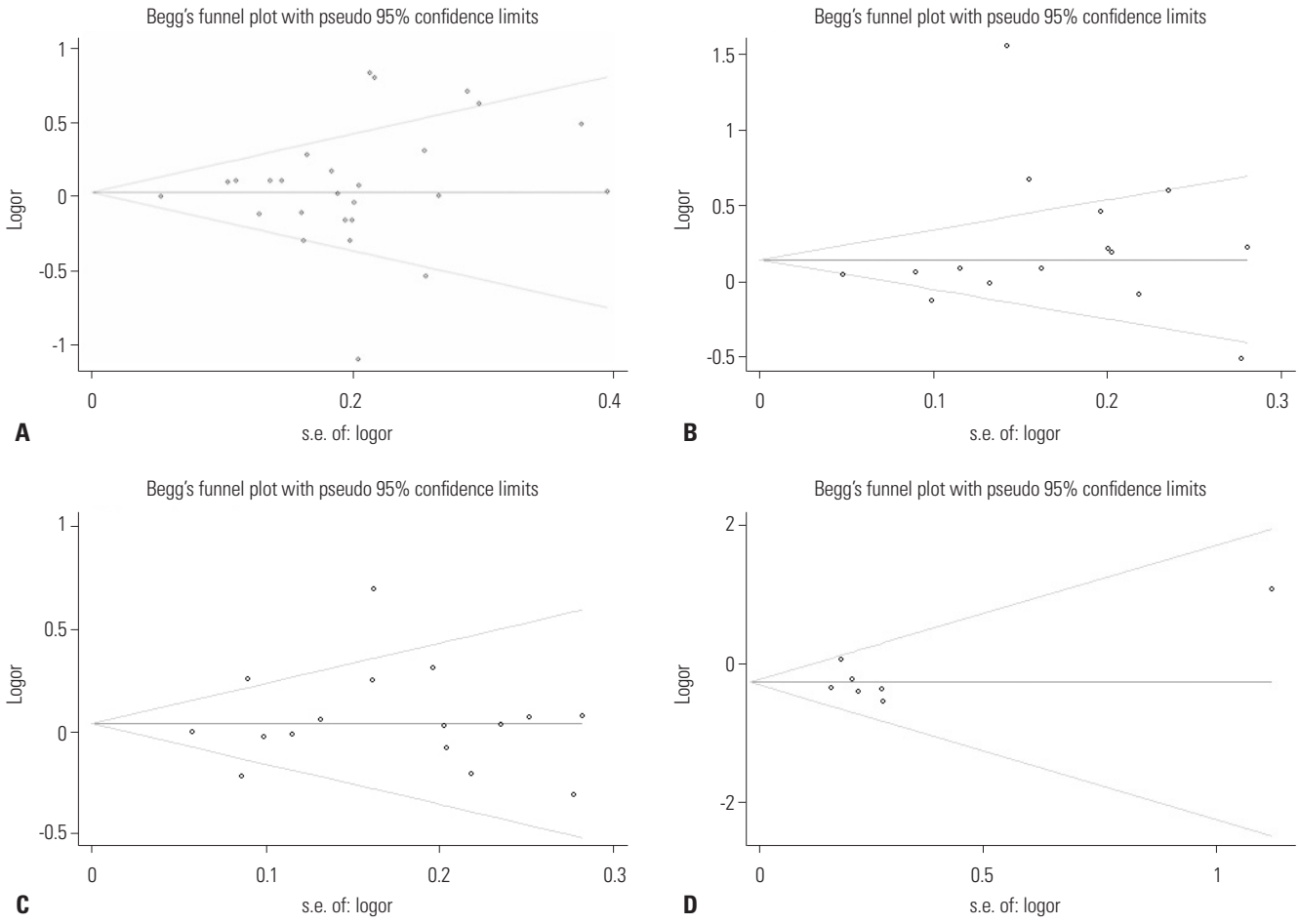

Fig. 4. Funnel plot for publication bias of the meta-analysis of tuberculosis risk and *IL-10* polymorphisms in allele genetic model comparison. (A) *IL-10* -1082G/A polymorphism. (B) *IL-10* -819C/T polymorphism. (C) *IL-10* -592A/C polymorphism. (D) *IL-6* -174G/C polymorphism. *IL-10*, interleukin 10; *IL-6*, interleukin 6.

Table 6. Publication Bias of *IL-10* -1082G/A, *IL-10* -819C/T, and *IL-10* -592A/C Polymorphisms in all Genetic Models

Polymorphisms	$Z_{Begg's}$	$P_{Begg's}$	$t_{Egger's}$	$P_{Egger's}$
IL-10 -1082G/A (AM, HoM, HeM, DM, RM)	0.93, 0.47, 1.01, 1.28, 0.35	0.355, 0.637, 0.311, 0.201, 0.726	0.60, 0.79, 0.82, 0.95, 0.21	0.555, 0.436, 0.418, 0.352. 0.839
IL-10 -819C/T (AM, HoM, HeM, DM, RM)	0.99, 0.10, 1.88, 1.78, 0.99	0.322, 0.921, 0.060, 0.075, 0.322	1.04, 0.80, 1.30, 1.28, -0.68	0.317, 0.438, 0.217, 0.221, 0.511
IL-10 -592A/C (AM, HoM, HeM, DM, RM)	0.23, 0.32, 1.22, 1.31, 0.59	0.822, 0.753, 0.224, 0.192, 0.558	0.59, 0.57, 0.90, 1.36, -0.68	0.564, 0.575, 0.385, 0.195, 0.505
IL-6 -174G/C (AM, HoM, HeM, DM, RM)	0.30, 0.75, 0.90, 0.00, 0.38	0.764, 0.452, 0.368, 1.000, 0.707	0.57, -0.09, 0.57, 0.51, 0.07	0.596, 0.934, 0.592, 0.634, 0.945

AM, allele model; HoM, homozygous model; HeM, heterozygous model; DM, dominant model; RM, recessive model; *IL-10*, interleukin 10; *IL-6*, interleukin 6.

sociated also with an increased risk of TB in homozygous model in the PTB+EPTB mixed sample. However, additional well-designed and larger scale primary studies in populations with different ethnicities are required to further evaluate the *IL-10* and *IL-6* gene polymorphisms with TB risk in future.

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REFERENCES

1. Gouzy A, Nigou J, Gilleron M, Neyrolles O, Tailleux L, Gordon SV. Tuberculosis 2012: biology, pathogenesis and intervention strategies; an update from the city of light. Res Microbiol 2013;164:270-80.
2. Hill AV. Aspects of genetic susceptibility to human infectious diseases. Annu Rev Genet 2006;40:469-86.
3. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T

http://dx.doi.org/10.3349/ymj.2015.56.5.1274

lymphocytes. Nature 1996;383:787-93.
4. Howell WM, Rose-Zerilli MJ. Cytokine gene polymorphisms, cancer susceptibility, and prognosis. J Nutr 2007;137(1 Suppl):194S-9S.
5. Van Snick J. Interleukin-6: an overview. Annu Rev Immunol 1990;8:253-78.
6. 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;17:84-9.
7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
8. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
10. 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;79:83-9.
11. Delgado JC, Baena A, Thim S, Goldfeld AE. Ethnic-specific genetic associations with pulmonary tuberculosis. J Infect Dis 2002;186:1463-8.
12. López-Maderuelo D, Arnalich F, Serantes R, González A, Codoceo R, Madero R, et al. Interferon-gamma and interleukin-10 gene polymorphisms in pulmonary tuberculosis. Am J Respir Crit Care Med 2003;167:970-5.
13. 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;124:569-72.
14. 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;71:341-9.
15. 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;37:128-32.
16. Oral HB, Budak F, Uzaslan EK, Baştürk B, Bekar A, Akalin H, et al. Interleukin-10 (IL-10) gene polymorphism as a potential host susceptibility factor in tuberculosis. Cytokine 2006;35:143-7.
17. Henao MI, Montes C, París SC, García LF. Cytokine gene polymorphisms in Colombian patients with different clinical presentations of tuberculosis. Tuberculosis (Edinb) 2006;86:11-9.
18. 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;12:594-8.
19. Prabhu Anand S, Selvaraj P, Jawahar MS, Adhilakshmi AR, Narayanan PR. Interleukin-12B & interleukin-10 gene polymorphisms in pulmonary tuberculosis. Indian J Med Res 2007;126:135-8.
20. Ates O, Musellim B, Ongen G, Topal-Sarikaya A. Interleukin-10 and tumor necrosis factor-alpha gene polymorphisms in tuberculosis. J Clin Immunol 2008;28:232-6.
21. 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.
22. 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;50:445-54.
23. 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.
24. 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.
25. 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;56:117-31.
26. 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.
27. 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;72:358-64.
28. Ma MJ, Xie LP, Wu SC, Tang F, Li H, Zhang ZS, et al. Toll-like receptors, tumor necrosis factor-α, and interleukin-10 gene polymorphisms in risk of pulmonary tuberculosis and disease severity. Hum Immunol 2010;71:1005-10.
29. Ben-Selma W, Harizi H, Boukadida J. Association of TNF-α and IL-10 polymorphisms with tuberculosis in Tunisian populations. Microbes Infect 2011;13:837-43.
30. 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.
31. 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;73:605-11.
32. Spinassé LB, Miranda AB, Santos AR, Mello FCQ, Lapa e Silva JR, Lopes MQP, et al. Partial Mapping of the IL-10 Promoter Region: Identification of New SNPs and Association with Tuberculosis Outcome in Brazilians. In: Cardona PJ, editor. Understanding Tuberculosis-Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity. INTECH Open Access Publisher; 2012. p.357-66.
33. García-Elorriaga G, Vera-Ramírez L, del Rey-Pineda G, González-Bonilla C. -592 and -1082 interleukin-10 polymorphisms in pulmonary tuberculosis with type 2 diabetes. Asian Pac J Trop Med 2013;6:505-9.
34. Ulger M, Emekdaş G, Aslan G, Taş D, Ilvan A, Tezcan S, et al. [Determination of the cytokine gene polymorphism and genetic susceptibility in tuberculosis patients]. Mikrobiyol Bul 2013;47:250-64.
35. Meenakshi P, Ramya S, Shruthi T, Lavanya J, Mohammed HH, Mohammed SA, et al. Association of IL-1β +3954 C/T and IL-10-1082 G/A cytokine gene polymorphisms with susceptibility to tuberculosis. Scand J Immunol 2013;78:92-7.
36. 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;18:1119-27.
37. Ansari A, Hasan Z, Dawood G, Hussain R. Differential combination of cytokine and interferon- γ +874 T/A polymorphisms determines disease severity in pulmonary tuberculosis. PLoS One 2011;6:e27848.
38. Zhang G, Zhou B, Wang W, Zhang M, Zhao Y, Wang Z, et al. A functional single-nucleotide polymorphism in the promoter of the gene encoding interleukin 6 is associated with susceptibility to tuberculosis. J Infect Dis 2012;205:1697-704.
39. 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.