



An updated meta-analysis of transforming growth factor- β 1 gene: Three well-characterized polymorphisms with asthma



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ABSTRACT

The association between TGF- β 1 polymorphisms and asthma risk has been widely reported, but results were controversial. We performed this meta-analysis based on the Preferred Reporting Items for Systematic Reviews and meta-analyses statement (PRISMA). Electronic database of Pub Med, Web of Science, CBM, and CNKI were searched for eligible articles published up to September, 2013. The effect summary odds ratio (OR) and 95% confidence intervals were obtained. Finally, a total of 20 articles were identified, 17 studies with 3694 cases and 5613 controls for C-509T polymorphism, 7 studies with 1109 cases and 1098 controls for T869C polymorphism and 5 studies with 849 cases and 829 controls for G915C polymorphism. For C-509T, significant associations with asthma were found in Asians (TT + TC vs. CC: $P = 0.004$, OR = 1.43, 95%CI = 1.12–1.81, $P_{\text{heterogeneity}} = 0.001$) and in Caucasians ($P = 0.05$, OR = 1.16, 95%CI = 1.00–1.34, $P_{\text{heterogeneity}} = 0.36$). With respect to T869C, a small significant association was observed in overall analysis of allele contrasts (C vs. T: OR = 1.14, 95%CI: 1.01–1.29, $P = 0.03$) and homozygote comparison (CC vs. TT: OR = 1.29, 95%CI: 1.00–1.65, $P = 0.05$), but no significant risks were found among Caucasian population and Asian population. For G915C polymorphism, no significant association with asthma risk was demonstrated in overall analysis and subgroup analyses according to ethnicity for all genetic models. This meta-analysis suggested that TGF- β 1 C-509T and T869C polymorphisms may be risk factors for asthma.

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1. Introduction

Asthma is a chronic respiratory disease which is characterized by variable airway obstructions caused by bronchial hyper-reactivity [1]. The development of asthma is determined by the interaction between host genetic susceptibility and environment (exposure to tobacco smoke, air pollution, allergens and infections, etc.) [2]. A complete understanding of the genetic risk factors for asthma is essential for the design of new therapeutic or preventive strategies for asthma, which can reduce the burden of disease. And currently, STAT6, IL-4, IL-13, RAD50 and ADAM33 have been consistently reported in asthma susceptibility [3–7].

Asthma is a chronic inflammatory and remodeling disorder of the airways and many cytokines contribute to the different pathogenesis features of asthma [8]. Transforming growth factor- β 1 (TGF- β 1) is one of the main mediators involved in tissue remodeling in the asthmatic lung. Several studies have shown that TGF- β 1 plays an important role in most of the cellular biological processes leading to airway remodeling [9–10]. An increased expression of TGF- β 1 has been described in asthma patients compared with normal subjects [11–14]. TGF- β 1 protein levels are predominantly under genetic control [15]. The TGF- β 1 gene, located on chromosome 19q13.1–3, contains several single nucleotide polymorphisms [C-509T (rs1800469), G915C (G25C) (rs1800471) and T869C (T10C) (rs1982073)] [16]. Several molecular epidemiological studies have investigated the potential role of TGF- β 1 polymorphisms in asthma development. However, the results were inconclusive and conflicting. These controversial findings may be caused by the limitations of individual studies, such as the small sample and low statistic power.

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In 2010, in order to clarify the effect of factor- $\beta 1$ polymorphisms (C-509T, G915C) on the risk of developing asthma, Zhang YG et al. performed a meta-analysis which only contained 14 studies and did not analyze the association between of T869C polymorphism and asthma [17]. While, an expanding body of literature assessing the association between the factor- $\beta 1$ polymorphisms and asthma had been published since 2009. Recently, another meta-analysis reported by Che et al. concluded that TGF- $\beta 1$ C-509T and T869C polymorphisms may be risk factors for asthma susceptibility [18]. Three studies failed to include in later meta-analysis [19–21] and some studies in their meta-analysis was not in Hardy–Weinberg equation (HWE), which might make their conclusions questionable. Therefore, we performed an updated meta-analysis of published studies to pool results between studies.

2. Materials and methods

This meta-analysis was carried out according to Preferred Reporting Items for Systematic Reviews and meta-Analyses guidelines (<http://links.lww.com/MD/A844>) [22].

2.1. Literature search strategy

A comprehensive search was performed to search the electronic databases of Pub Med, Web of Science, the Chinese Biomedical Database (CBM), and the Chinese National Knowledge Infrastructure (CNKI) with different combinations: “asthma or asthmatic” and “TGF- $\beta 1$ or transforming growth factor beta” and “polymorphism or variant”. The language of publication was only in English and Chinese. The retrieved abstracts were read to identify studies examining the genotype association between TGF- $\beta 1$ polymorphisms and asthma. An upper date limit of September 2013 was applied; however, no lower date limit was set. In addition, all references cited were reviewed to identify additional studies.

2.2. Inclusion criteria

We reviewed the titles and abstracts of all citations and retrieved literature. The following inclusion criteria was used for literature selection: (1) the publication was a case-control study referring to the association between TGF- $\beta 1$ polymorphisms (C-509T, G915C or T869C) and asthma risk; (2) data were available on genotype distributions for calculating the odds ratio (OR) with its 95% confidence interval (CI) or sufficient data that could allow us to calculate the corresponding estimate effect [OR, (95% CI)], and (3) there was no deviation from Hardy–Weinberg equilibrium (HWE) among the controls. When more than one of the same patient population was included in several publications, only the most recent or complete study was included in the meta-analysis.

2.3. Data extraction

The following information was independently extracted from the included studies: first author, year of publication, ethnic of study population, age of the population, language, and the frequency of alleles and genotypes in cases and controls. Data were extracted independently by the two investigators from the included studies. Discrepancies were resolved by discussion and consensus with all the authors. Ethnicity was categorized as Asians and Caucasians.

2.4. Statistical analysis

Crude ORs with their 95% CIs were used to assess the strength of association between the TGF- $\beta 1$ polymorphisms and asthma risk.

The significance of association for dominant model (C-509T: TT + TC vs. CC, T869C: CC + CT vs. TT, and G915C: CC + CG vs. GG) was evaluated for each study separately [23]. Heterogeneity test was assessed by chi-square-based Q-test and I^2 test [24]. In our study, two models of meta-analysis were applied for dichotomous outcomes according to the results of heterogeneity tests among individual studies in Review-Manager 4.2 software: the fixed-effects model (Mantel-Haenszel) if Q-statistic $P \geq 0.10$ [25] or the random-effects model (DerSimonian and Laird) if Q-statistic $P < 0.10$ [26].

For the three polymorphisms, the recessive model (C-509T: TT vs. TC + CC, T869C: CC vs. TT + CT, and G915C: CC vs. GG + CG), the allele contrasts (C-509T: T vs. C, T869C: C vs. T, and G915C: C vs. G) and homozygote comparison (C-509T: TT vs. CC, T869C: CC vs. TT, and G915C: CC vs. GG) were also used to assess the association with the risk of asthma. Subgroup analysis was performed by ethnicity for C-509T and T869C polymorphisms. Deviation from Hardy–Weinberg-equilibrium (HWE) ($P < 0.05$) among the control groups within each study was checked by exact test using an online HWE calculator (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>). Publication bias was assessed using funnel plots and Egger's test.

Statistical analysis was performed using the software Stata version 10 (StataCorp LP, College Station, TX, USA), and Review Manager 4.2 (Cochrane Collaboration, <http://www.cc-ims.net/RevMan/relnotes.htm>). All P values were two-tailed, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Eligible studies

A flow chart of the study selection is shown in Fig. 1. Briefly, a total of 62 records relevant to search criteria were identified, and 30 records were excluded for unsuitable study design or not being relevant to TGF- $\beta 1$ polymorphisms and asthma risk. Of the remaining 32 articles, one study was excluded because the numbers of genotype frequency in the cases or controls were not reported and the relevant information could not be obtained from the authors [27]. Five were not case-control studies [28–32], three were a repeat publication [33–35], and one article was excluded due to deviation from HWE in control group [36]. A total of 22 case-control studies met our inclusion criteria. In addition, two studies were excluded, because the ethnicity of the study population was mixed and could not be divided into Asian and Caucasian [37–38]. Finally, 20 studies were included in the current meta-analysis [19–21,39–55]. One of these studies investigated asthma patients and control subjects in both North India and West India and the data were analyzed separately for each group [39]; these data were treated as two independent case-control studies. Another study investigated both Hispanic whites and non-Hispanic whites, with separate analyses of the data, and these were also treated as two independent studies [40]. In addition, genotype distribution in control group of one study for C-509T [41] and two studies for T869C [42–43] significantly deviated from HWE. Finally, 17 studies focused on the C-509T variant, 7 studies on T869C, and 5 studies on G915C (Table 1).

3.2. Association of the TGF- $\beta 1$ C-509T polymorphism with asthma risk

17 studies included 9307 individuals (3694 cases and 5, 613 controls) (Table 2). In all eligible studies, 12 studies were conducted in Asians and five studies were in Caucasians.

For the dominant model, heterogeneity was observed among individual estimates of the ORs ($P_{\text{heterogeneity}} = 0.002$) and the

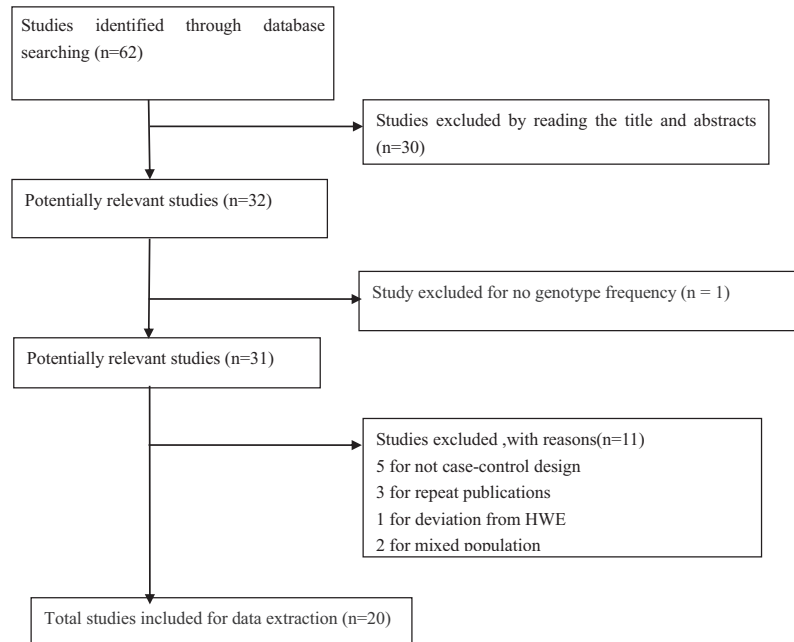


Fig. 1. Flow diagram of papers screening.

Table 1

Characteristics of studies included in a meta-analysis.

First author	Year	Country (ethnicity)	Language	Polymorphisms	Age of population (years)
Daneshmandi S	2012	Iran (Caucasian)	English	T869C	43.03 ± 12.76
Yang XX	2011	China (Asian)	English	C-509T	41.59 ± 15.94
Wisniewski A	2009	Poland (Caucasian)	English	T869C, C-509T, G915C	39.90 ± 16.12
Kumar A	2008	India (Asian)	English	C-509T	–
Salam MT(NH)	2007	USA (Caucasian)	English	C-509T	–
Salam MT(H)	2007	USA (Caucasian)	English	C-509T	–
Mak JCW	2006	China (Asian)	English	T869C, C-509T	41.00 ± 16.10
Heinzmann A	2005	Germany (Caucasian)	English	C-509T, G915C	5–18
Nagpal K(N)	2005	India (Asian)	English	C-509T	28.42 ± 0.97
Nagpal K(W)	2005	India (Asian)	English	C-509T	34.22 ± 1.01
Silverman ES	2004	USA (Caucasian)	English	C-509T	33.7 ± 13.7
Pulleyn LJ	2001	UK (Caucasian)	English	C-509T, G915C	44.8
Li HB	2012	China (Asian)	Chinese	T869C, C-509T	3.1–14.6
Feng XM	2012	China(Asian)	Chinese	T869C	1.8–10.0
Dai H	2012	China (Asian)	Chinese	C-509T	3–12
Liu WD	2008	China(Asian)	Chinese	C-509T	1–13
Xia W	2006	China (Asian)	Chinese	C-509T	15–60
Zhang Q	2008	China (Asian)	Chinese	C-509T	39.8
Liebhart J	2008	Poland (Caucasian)	English	T869C, G915C	51 ± 12.5
Jo MY	2008	Korean (Asian)	English	C-509T	17–74
Movahedi M	2008	Iran (Caucasian)	English	T869C, G915C	–
Kim SH	2007	Korea (Asian)	English	C-509T	42.7 ± 14.1

original data were combined by means of the random effects model. As shown in Fig. 2, the summary OR was 1.33 in overall analysis (TT + TC vs. CC: 95% CI = 1.13–1.56; $P = 0.0006$) by the random effects model. In the subgroup analysis of ethnicity, significant association was observed in Asian population under the random effects models (TT + TC vs. CC: $P = 0.004$, OR = 1.43, 95% CI = 1.12–1.81, $P_{\text{heterogeneity}} = 0.001$) and a small significant association was observed in Caucasian population under the fixed effects model (five comparisons, $P = 0.05$, OR = 1.16, 95% CI = 1.00–1.34, $P_{\text{heterogeneity}} = 0.36$) (Fig. 2, Table 3). The results of other comparative genetic models also indicated a significant association between the C-509T polymorphism and asthma risk in overall, Asian and Caucasian population (Table 3).

3.3. Association of the TGF- $\beta 1$ T869C polymorphism with asthma risk

Seven studies involving the T869C variant included 2207 individuals (1109 cases and 1098 controls) (Table 4). In all eligible studies, four studies were in Asians, and two studies were in Caucasians (Table 4).

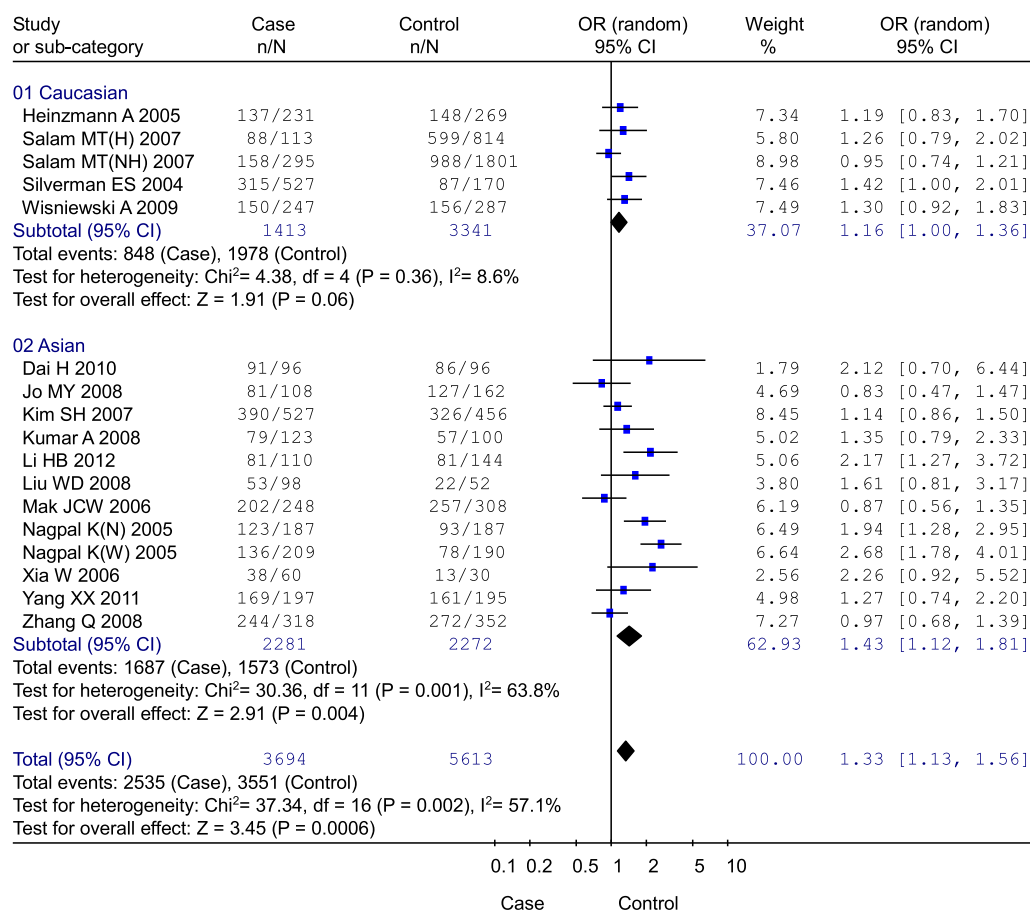
Heterogeneity was not observed among individual estimates of the ORs ($P_{\text{heterogeneity}} = 0.75$) and the original data were combined by using the fixed effects model. As shown in Fig. 3, the summary OR was 1.16 in overall analysis for the dominant model (CC + CT vs. TT: 95% CI: 0.96–1.40, $P = 0.12$). The results of allele contrasts (C vs. T: OR = 1.14, 95% CI: 1.01–1.29, $P = 0.03$) and homozygote comparison (CC vs. TT: OR = 1.29, 95% CI: 1.00–1.65, $P = 0.05$) indicated a

Table 2

The distribution of the C-509T genotype for cases and controls.

Author (reference)	Year	Sample size (Case/Con)	Distribution of genotype			Frequency of allele			
			CC	CT	TT	T (n,%)		C (n,%)	
			Case/Con	Case/Con	Case/Con	Case	Con	Case	Con
Yang XX	2011	197/195	28/34	115/88	54/73	223(56.6)	234(60.0)	171(43.4)	156(40.0)
Wisniewski A	2009	247/287	97/131	118/124	32/32	182(36.8)	188(32.8)	312(63.2)	386(67.2)
Kumar A	2008	123/100	44/43	55/42	24/15	103(41.9)	72(36)	143(58.1)	128(64)
Salam MT(NH)	2007	295/1801	137/813	121/799	37/189	195(33.1)	1177(32.7)	395(66.9)	2425(67.3)
Salam MT(H)	2007	113/814	25/215	60/411	28/188	116(51.3)	787(48.3)	110(48.7)	841(51.7)
Mak JCW	2006	248/308	46/51	109/155	93/102	295(59.5)	359(58.3)	201(40.5)	257(41.7)
Heinzmann A	2005	231/269	94/121	108/111	29/37	166(35.9)	185(34.4)	296(64.1)	353(65.6)
Nagpal K(N)	2005	187/187	64/94	104/77	19/16	142(38.0)	109(29.1)	232(62.0)	265(70.9)
Nagpal K(W)	2005	209/190	73/112	97/63	39/15	175(41.9)	93(24.5)	243(58.1)	287(75.5)
Silverman ES	2004	527/170	212/83	246/76	69/11	384(36.4)	98(28.8)	670(63.6)	242(71.2)
Li HB	2012	110/144	29/63	59/62	22/19	103(46.8)	100(34.7)	117(53.2)	188(65.3)
Dai H	2012	96/96	5/10	77/56	14/30	105(54.7)	116(60.4)	87(45.3)	76(39.6)
Liu WD	2008	98/52	45/30	38/19	15/3	68(34.7)	25(24.0)	128(65.3)	79(78)
Xia W	2006	60/30	22/17	26/11	12/2	50(41.7)	15(25.0)	70(58.3)	45(75.0)
Zhang Q	2008	318/352	74/80	159/172	85/100	329(51.7)	372(52.8)	307(48.3)	332(47.2)
Jo MY	2008	108/162	27/35	45/92	36/35	117(54.2)	162(50.0)	99(45.8)	162(50.0)
Kim SH	2007	527/456	137/130	260/215	130/111	520(49.3)	437(47.9)	534(50.7)	475(52.1)

Case: asthma; Con: Control.

**Fig. 2.** Forest plot for the association between C-509T polymorphism and asthma for 509T allele carriers with 509C allele (TT + TC vs. CC). Each study is shown by the point estimate of the OR and 95%CI for the OR. OR = odds ratio; CI = confidence interval; df = degree of freedom.

small significant association between the T869C polymorphism and asthma risk in overall analysis (Table 5). In the subgroup analysis of ethnicity, the results showed that no significant risks were found among Caucasian population and Asian population for all genetic models (Table 5).

3.4. Association of the TGF- β 1 G915C polymorphism with asthma risk

A total of 1678 subjects were investigated for G915C, made up of 849 cases and 829 controls. All eligible studies were in Caucasians (Table 6). Statistics calculated for each study were

Table 3

Meta-analysis of C-509T polymorphism and asthma risk.

Analysis model	Populations (study no.)	OR(95% CI)	P_{OR}	I^2 (%)	P_H
T vs. C	Total (17)	1.20(1.07–1.35) ^b	0.002	65.0	0.0001
	Caucasian (5)	1.13(1.02–1.26)	0.02	8.3	0.36
	Asian (12)	1.24(1.05–1.48) ^b	0.01	73.3	<0.0001
TT vs. (TC + CC)	Total (17)	1.19(0.97–1.45) ^b	0.09	58.8	0.001
	Caucasian (5)	1.22(0.98–1.50)	0.07	10.4	0.35
	Asian (12)	1.19(0.90–1.57) ^b	0.22	67.5	0.0004
(TT + TC) vs. CC	Total (17)	1.33(1.13–1.56) ^b	0.0006	57.1	0.002
	Caucasian (5)	1.16(1.00–1.34)	0.05	8.6	0.36
	Asian (12)	1.43(1.12–1.81) ^b	0.004	63.8	0.001
TT vs. CC	Total (17)	1.39(1.14–1.71) ^b	0.001	45.7	0.02
	Caucasian (5)	1.31(1.04–1.66)	0.02	10.3	0.35
	Asian (12)	1.47(1.10–1.97) ^b	0.01	56	0.009

 I^2 (%) and P_H value for heterogeneity. P_{OR} The P-value of OR determined by the Z-test.^b Estimates for random effects model.**Table 4**

The distribution of the T869C genotype for cases and controls.

Author (year) (reference)	Year	Sample size (Case/Con)	Distribution of genotype			Frequency of allele			
			TT	TC	CC	C (n,%)		T (n,%)	
			Case/Con	Case/Con	Case/Con	Case	Con	Case	Con
Daneshmandi S	2012	81/124	13/28	38/59	30/37	98(60.5)	133(53.6)	64(39.5)	115(46.3)
Wisniewski A	2009	247/191	76/68	129/90	42/33	213(43.1)	156(40.8)	281(56.9)	226(59.2)
Mak JCW	2006	248/308	49/70	108/151	91/87	290(58.5)	325(52.8)	206(41.5)	291(47.2)
Li HB	2012	110/144	43/51	53/68	14/25	81(36.8)	118(41)	139(63.2)	170(59.0)
Feng XM	2012	100/100	29/31	48/47	23/22	94(47.0)	91(45.5)	106(53.0)	109(54.5)
Liebhart J	2008	110/109	58/49	32/42	20/18	72(32.7)	78(35.8)	148(67.3)	140(64.2)
Pulleyn LJ	2001	213/122	84/48	93/61	36/13	165(38.7)	87(35.7)	261(61.3)	157(64.3)

Case: asthma; Con: Control.

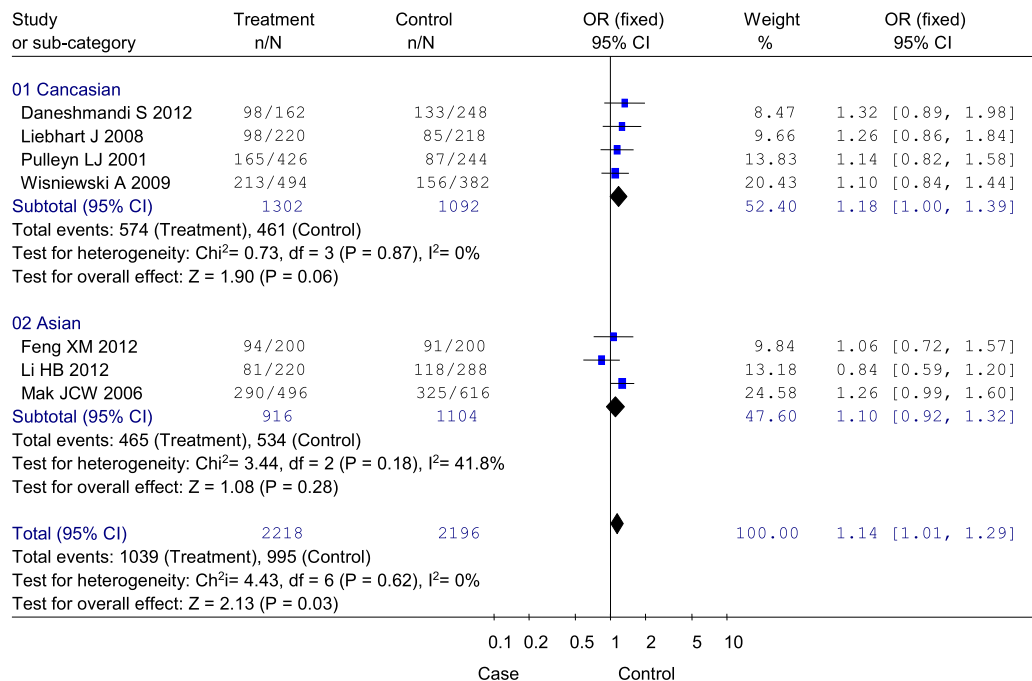
**Fig. 3.** Forest plot for the association between T869C polymorphism and asthma risk for 869C allele carriers with 869T allele (T vs. C). Each study is shown by the point estimate of the OR and 95%CI for the OR. OR = odds ratio; CI = confidence interval; df = degree of freedom.

Table 5
Meta-analysis of T869C polymorphism and asthma risk

Analysis model	Populations (study no.)	OR(95% CI)	P_{OR}	I^2 (%)	P_H
C vs. T	Total (7)	1.14(1.01–1.29)	0.03	0	0.62
	Asian (3)	1.10(0.92–1.32)	0.28	41.8	0.18
	Caucasian (4)	1.18(1.00–1.39)	0.06	0	0.87
CC vs. (TC + TT)	Total (7)	1.22(1.00–1.50)	0.06	0	0.47
	Asian (3)	1.22(0.91–1.62)	0.18	45.6	0.16
	Caucasian (4)	1.23(0.91–1.18)	0.17	0	0.60
(CC + TC) vs. TT	Total (7)	1.16(0.96–1.40)	0.12	0	0.75
	Asian (3)	1.06(0.80–1.41)	0.69	0	0.60
	Caucasian (4)	1.24(0.97–1.59)	0.09	0	0.63
CC vs. TT	Total (7)	1.29(1.00–1.65)	0.05	0	0.61
	Asian (3)	1.18(0.83–1.68)	0.36	36.2	0.21
	Caucasian (4)	1.40(0.99–1.98)	0.06	0	0.82

 I^2 (%) and P_H value for heterogeneity. P_{OR} The P-value of OR determined by the Z-test.**Table 6**
The distribution of the G915C genotype for cases and controls.

Author (reference)	Year	Sample size (Case/Con)	Distribution of genotype			Frequency of allele			
			GG	GC	CC	C (n,%)		G (n,%)	
			Case/Con	Case/Con	Case/Con	Case	Con	Case	Con
Wisniewski S	2009	247/191	214/161	31/28	2/2	35(7.1)	32(8.4)	459(92.9)	350(91.6)
Heinzmann A	2005	231/269	192/230	37/37	2/2	41(8.9)	41(7.6)	421(91.1)	497(92.4)
Pulleyn LJ	2001	213/122	181/95	32/26	0/1	32(6.1)	28(11.5)	394(93.9)	216(88.5)
Liebhart J	2008	220/218	95/91	14/18	1/0	16(7.3)	18(8.3)	204(92.3)	200(91.7)
Movahedi M	2008	48/138	32/119	16/17	0/2	16(16.7)	21(7.6)	80(83.3)	255(92.4)

Case: asthma; Con: Control.

Table 7
Summary ORs and 95% CI of G915C polymorphism and asthma.

Analysis model	Populations (study no.)	OR(95% CI)	P_{OR}	I^2 (%)	P_H
C vs. G	Caucasian (5)	1.03(0.68–1.54) ^b	0.90	61.3	0.03
CC vs. (GC + GG)	Caucasian (5)	0.83(0.29–2.36)	0.73	0	0.81
(CC + GC) vs. GG	Caucasian (5)	0.94(0.69–1.30)	0.72	0	0.66
CC vs. GG	Caucasian (5)	0.85(0.30–2.43)	0.76	0	0.81

 I^2 (%) and P_H value for heterogeneity. P_{OR} The P-value of OR determined by the Z-test.^b Estimates for random effects model.

shown in the forest plot for the dominant model, and no significant risks were found ($P = 0.73$, $OR = 1.21$, $95\%CI = 0.42–3.43$, $P_{heterogeneity} = 0.81$) (Table 6). In addition, no significant risks were found among Caucasian population for all other genetic models (Table 7).

3.5. Publication bias

Under the dominant model, the shape of the funnel plots did not reveal any evidence of obvious asymmetry for three polymorphisms (Fig. 4). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any obvious evidence of small study biases (data not shown).

3.6. Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and most of the corresponding pooled ORs were not materially altered (data not given).

4. Discussion

In the current systematic review, a meta-analysis of 20 case-control studies was performed to assess the association between asthma risk and TGF- $\beta 1$ polymorphisms. The study involved more than 3000 cases and controls for C-509T and T869C polymorphisms, providing strong evidence that C-509T and T869C polymorphisms were associated with an increased risk of asthma. But G915C polymorphisms were not associated with asthma in Asians and Caucasians. As such, homozygous deletion of the C-509T and T869C polymorphisms may be asthma risk factors.

Subgroup analysis by ethnicity also revealed significant association in Asian and Caucasian population for C-509T. But the risk appeared to be more evident in Asians rather than Caucasians, indicating a possible influence of different genetic backgrounds and environmental exposures. For T869C, a small significant association was found in overall analysis, but no significant association was found in Asian and Caucasian population. A possible explanation for this observation was limited sample size after subgrouping. The small sample size may have been underpowered to sufficiently detect minor associations. As such, additional more

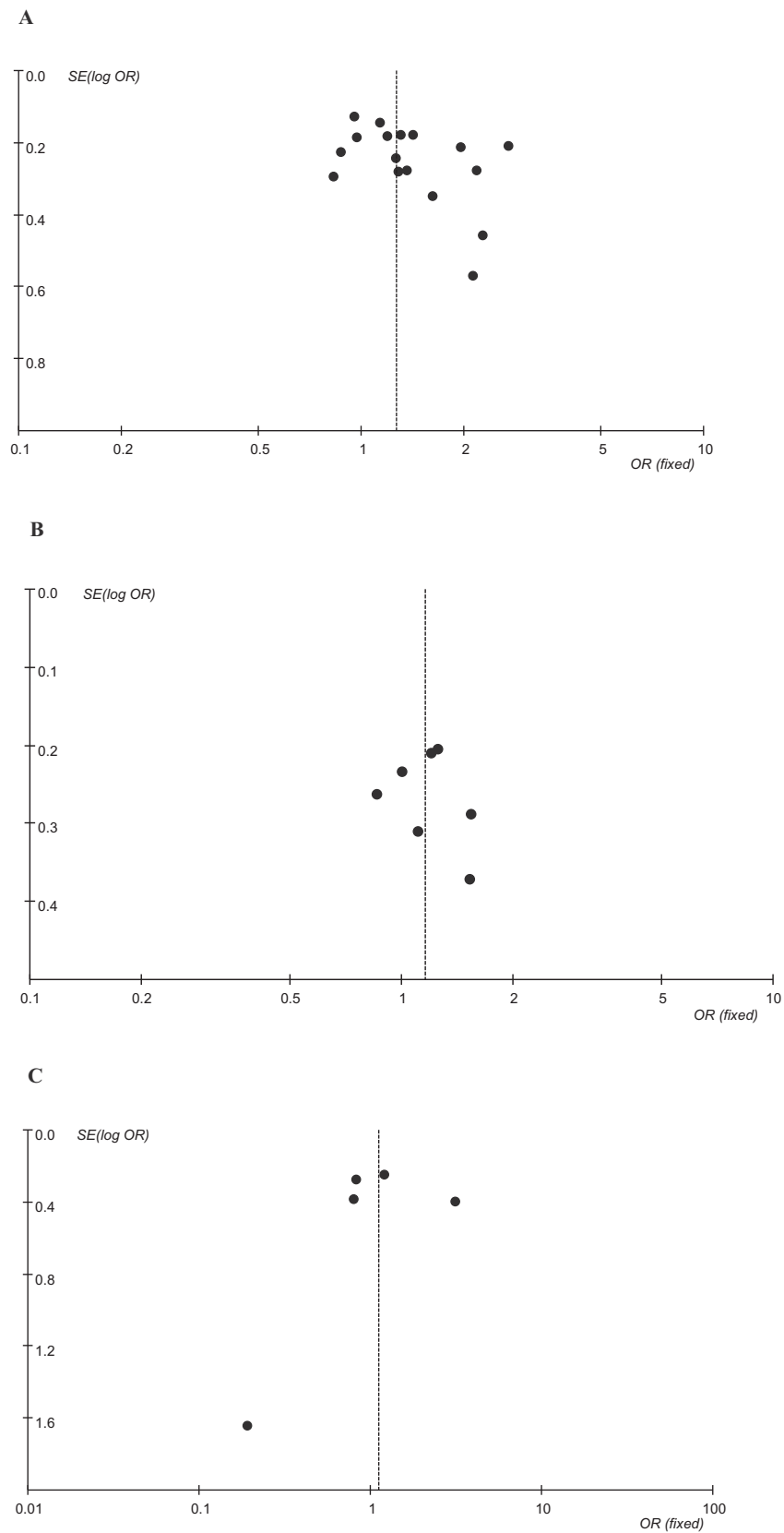


Fig. 4. Funnel plot for publication bias in selection of studies on the TGF- β 1 polymorphisms (A: C-509T; B: T869C; C: G915C).

studies are required, focusing on asthma populations with different ethnic backgrounds.

Several meta-analyses had examined the association between asthma risk and the TGF- β 1 polymorphisms. In 2010, Zhang et al. carried out the first relationship between the two SNPs (TGF- β 1 C-509T and G915C) and the risk of asthma, and reported that TGF- β 1 C-509T might be a risk factor for asthma in Asians but not in Caucasians [17]. This result was inconsistent with the findings of our stratified analysis by ethnicity, in which the-509T allele was associated with a significantly elevated risk of asthma both in Asians and in Caucasians. Che and colleagues conducted a larger systematic review to examine the relationship between asthma risk and TGF- β 1 polymorphisms (C-509T and T869C) [18]. In their study, they found that C-509T and T869C polymorphisms might be risk factors for asthma susceptibility. This conclusion was consistent with the results in the current meta-analysis. It should be noted that Che et al. included a total of 24 studies, two of which were not included in the current meta-analysis because these studies were not in HWE [36,56]. In addition, three articles for C-509T and T869C polymorphisms included in our meta-analysis were not part of the study by Che Y et al. [19–21]. What is more, some studies in their meta-analysis were not in Hardy–Weinberg equation (HWE).

There were numerous possible reasons for the same polymorphism playing a different role in different ethnic populations. Firstly, asthma was a heterogeneous disease which was associated with various genetic and environmental factors, as well as associated with interactions between them. Secondly, clinical heterogeneity might also explain the discrepancy. The potential contribution of differences in patient and control groups (e.g. age and years from onset, disease severity and so on) might lead to different results. Sometimes association could only be found in stratification analysis according to the clinical character. In the present study, this information could not be gotten completely.

Meta-analysis had been recognized as an effective method to solve a wide variety of clinical questions by summarizing and reviewing previously published quantitative research. To some extent, some limitations had affected the objectivity of the conclusions and should be addressed when interpreting the results. (1) Given that only published studies were included in the meta-analysis, publication bias might have occurred, even though it was not found when performing the statistical test. (2) A language bias might have occurred because this meta-analysis only contained Chinese and English language literature. However, some relevant articles in other languages were published in specific journals but were not found in the international journals.

In summary, the current study was the latest meta-analysis assessing the relationship between asthma risk and TGF- β 1 polymorphisms. Our results indicated that TGF- β 1 C-509T and T869C polymorphisms were associated with increased risk of asthma. This finding suggested that some polymorphisms in the TGF- β 1 gene might be high-penetrance susceptibility markers for asthma. Further large-scale investigation is required in different ethnic populations.

Conflict of interest

The authors report no conflicts of interest.

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