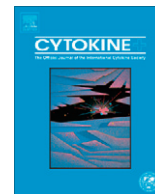


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Interleukin-4 rs2243250 polymorphism is associated with asthma among Caucasians and related to atopic asthma

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ABSTRACT

Published data on the association between interleukin-4 (IL-4) rs2243250 (C-589T) polymorphism and asthma susceptibility are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. A total of 17 studies with 3037 asthma patients and 3032 healthy controls were included. Overall, significantly elevated asthma risk was associated with IL-4 T allele when all studies were pooled into the meta-analysis (CT vs. CC: OR = 1.187, 95% CI = 1.016–1.387; dominant model: OR = 1.213, 95% CI = 1.046–1.405). In the subgroup analysis by ethnicity, significantly increased risk was only found for Caucasians (TT vs. CC: OR = 1.591, 95% CI = 1.032–2.452; dominant model: OR = 1.292, 95% CI = 1.028–1.624). When stratified by asthma type, statistically significantly elevated risk was only found in atopic asthma group (dominant model: OR = 1.313, 95% CI = 1.033–1.667). Despite some limitations, this meta-analysis suggests that T allele at position –589 of the IL-4 gene promoter region is a low-penetrant risk factor for asthma development especially for Caucasians and atopic type.

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1. Introduction

Asthma is one of the most common chronic inflammatory respiratory diseases, and is characterized by bronchial hyper-responsiveness (BHR) with periodic episodes of wheezing, and atopy. Asthma results from the effects of environmental stimuli in genetically-susceptible individuals, with a suggested overall genetic contribution of around 50–60% [1]. Numerous previously published studies have investigated the association between genetic variants of pro-inflammatory genes and asthma predisposition, and the interleukin-4 (IL-4) gene has been extensively studied.

IL-4 is a cytokine secreted by type 2 T helper (Th 2) cells and has a central role in regulation of immunoglobulin E (IgE) production. IL-4 stimulates B-cell proliferation, isotype switching from IgM to IgE production by B lymphocytes and differentiation to the Th 2 phenotype on T cells, thus playing a critical role in the induction and maintenance of allergy. The IL-4 gene has been mapped to the 5q31 locus, which also codes for some other important genes involved in the pathogenesis of asthma and atopy [2,3]. Stimulation of IL-4 can influence mast cell responsiveness to IgE-mediated signaling [4]. IL-4 can also induce airway inflammation by induction of vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells [5]. Furthermore, asthmatic patients have been shown to have increased expression of IL-4 in both peripheral blood and BAL fluid [6,7].

IL-4 gene transcription can be modified by genetic variants in the IL-4 promoter. For IL-4 rs2243250 (C-589T), it was shown that the binding of a transcription factor is increased by the presence of the polymorphic T allele [8]. In the light of previously published association studies, it can be hypothesized that this single nucleotide polymorphism may lead to an overexpression of the IL-4 gene and thus increases the strength of any IL-4-dependent immunological reaction including asthma.

Many studies have evaluated the association of the IL-4-589 C/T variant with asthma [9–30]. Noguchi et al. [31] found that the IL-4 promoter C-589T polymorphism may be associated with the development of asthma in Japanese children. Conversely, in a later report, no association was found between this polymorphism and asthma in Kuwaiti Arabs [11]. A series of related studies were carried out later, however, results were generally inconsistent and inconclusive, probably due to the possible small effect of the polymorphism on asthma risk or the relatively small sample size in each of published studies. Therefore, we conducted this meta-analysis to derive a more precise estimation of these associations.

2. Material and methods

2.1. Publication search

The databases, PubMed, Medline, Embase, Web of Science and China Knowledge Resource Integrated Database (CNKI), were searched (updated to Jan 1, 2012) using the terms: “interleukin-4”, “polymorphism”, “variant”, “genotype” and “asthma”. All the

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searched studies were retrieved, and their references were checked as well for other relevant publications. Review articles were also searched to find additional eligible studies. Only those published in English or Chinese language with full text articles were included. For overlapping studies, only the first published one was selected; for republished studies, only the one with the largest sample numbers was included.

2.2. Eligible studies and data extraction

Selection criteria were: (a) retrospective or prospective case-control asthma studies of IL-4 C-589T or C-590T polymorphism with complete genotypes distribution data; (b) there were at least two comparison groups; for example, asthma versus control (non-asthma or healthy) groups, participants could be of any age; (c) written in English or Chinese; (d) fulfilling Hardy–Weinberg equilibrium (HWE) in the control group ($P > 0.05$ was eligible); (e) the number of case and control was more than 100; and (f) literature quality assessment score >4 . The quality assessment score system of molecular association studies of asthma was recommended by Thakkestian et al. [32] which were based on both traditional epidemiologic considerations and genetic issues [33]. The scale included eight items. Elements were as follows: (1) representativeness of cases, (2) representativeness of controls, (3) ascertainment of asthma, (4) ascertainment of controls, (5) genotyping examination, (6) HWE, (7) association assessment, and (8) response rate. Total scores ranged from 0 (worst) to 15 (best). The studies designed based on family or sibling-pairs were excluded.

The following variables were extracted from each study if available: first author's surname, publication year, country of origin, study design, ethnicity, matching variables (mean or range of age, percentage of female), type of asthma, evaluation method of

Table 1

Main characteristics of studies included in the meta-analysis.

Author	Year	Country	Study design	Ethnicity	Age (years) mean or range	Female	Asthma cases	Evaluation of atopic phenotype	Quality score
<i>Interleukin-4 C-589T</i>									
Takabayashi A	2000	Japan	HB	Asian	<18	Cases: 42.0% Controls: 44.0%	Atopic	Total IgE/specific IgE	6
Hijazi Z	2000	Kuwait	HB	Arabian	NS	NS	Asthma	SPT	6
Sandford AJ	2000	New Zealand	PB	Caucasian	Cases: 34.4 ± 1.4 Controls: 37.7 ± 1.1	Cases: 45.9% Controls: 54.3%	Atopic	SPT	9
Cui TP(2003)	2003	Canada Australia China	PB	Asian	Cases: 43.4 ± 14.1 Controls: 39.4 ± 11.4	Cases: 48.0% Controls: 46.6%	Atopic	Total IgE/specific IgE	8
Lee SG(A)	2004	Korea	HB	Asian	Cases: 11.5 ± 2.60 Controls: 11.3 ± 3.10	Cases: 37.8% Controls: 52.0%	Atopic	SPT/specific IgE	10
Lee SG(NA)	2004	Korea	HB	Asian	Cases: 10.9 ± 2.60 Controls: 11.3 ± 3.10	Cases: 36.7% Controls: 52.0%	Non-atopic	SPT/specific IgE	10
Wang W	2004	China	PB	Uighurs	Cases: 39.0 ± 8.0 Controls: 37.0 ± 10.0	Cases: 53.8% Controls: 51.6%	Asthma	Total IgE/ Specific IgE	8
Adjers K	2005	Finland	PB	Caucasian	Cases: 59.0 ± 11.0 Controls: 60.0 ± 11.0	Cases: 62.0% Controls: 62.7%	Asthma	SPT	9
Donfack J	2005	USA	PB	Caucasian African	NS	NS	Asthma	SPT	7
Cui TP(2005)	2005	China	HB	Asian	Cases: 2–16 Controls: 2–15	Cases: 49.0% Controls: 47.2%	Atopic	Total IgE/specific IgE	9
Zhang WD	2005	Singapore	PB	Asian Malayan Indian	Cases: 51.0 ± 16.0 Controls: 33.0 ± 10.0	Cases: 58.1% Controls: 38.8%	Asthma	Total IgE	6
Gervaziev YV	2006	Russia	HB	Caucasian	Cases: 39.8 ± 13.8 Controls: 43.0 ± 14.9	Cases: 52.3% Controls: 45.6%	Asthma	Total IgE	9
Mak JCW	2007	China	PB	Asian	Cases: 42.4 ± 16.1 Controls: 43.7 ± 16.1	Cases: 56.2% Controls: 43.8%	Asthma	SPT	10
Hosseini-Farahabadi S	2007	Iran	HB	NS	Cases: 34.0 ± 11.0 Controls: 33.0 ± 9.0	Cases: 56.7% Controls: 70.0%	Atopic	SPT	9
Chiang CH	2007	China	PB	Asian	Cases: 46.0 ± 20.0 Controls: 30.0 ± 7.0	Cases: 48.5% Controls: 45.9%	Asthma	Total IgE/specific IgE	10
Kamali-Sarvestani E	2007	Iran	HB	NS	Cases: 15–79 Controls: matched	Cases: 44.8% Controls: 43.4%	Asthma	NS	10
de Faria IC	2008	Brazil	PB	Mixed	Cases: 10.3 ± 2.8 Controls: 34.0 ± 11.3	Cases: 53.0% Controls: NS	Asthma	SPT/specific IgE	7
Amirzargar AA	2009	Iran	PB	Persian	Cases: 1.5–33 controls: matched	Cases: 31.7% controls: matched	Asthma	SPT/total IgE	7
Wu XH	2010	China	HB	Asian	Cases: 8.8 ± 3.2 Controls: 9.2 ± 2.8	Cases: 45.2% Controls: 48.0%	Asthma	Total IgE	10
Bijanzadeh M	2010	India	HB	Indian	Cases: 0.5–80 Controls: NS	Cases: 45.0% Controls: 12.0%	Asthma	NS	9
Huang HR	2010	China	HB	Asian	Cases: 6.6 ± 2.8 Controls: 7.5 ± 2.9	Cases: 49.0% Controls: 42.6%	Asthma	Total IgE	9
Fan CE	2010	China	PB	Asian	Cases: 18–60 Controls: 22–50	Cases: 51.6% Controls: 43.3%	Asthma	Total IgE	7
Daneshmandi S	2011	Iran	NS	NS	Cases: 43.0 ± 12.8 Controls: matched	Cases: 69.1% Controls: matched	Asthma	Total IgE	8

(A): Atopic asthma; (NA): nonatopic asthma; HB: hospital-based study; PB: population-based study; Nest: nested case-control study; NS: not-stated; SPT: skin prick test.

atopic phenotype, quality score, genotyping methods, numbers of cases and controls, and numbers of cases and controls of different genotypes, respectively. Study design was stratified into population-based study, hospital-based study and not-stated. Different ethnicity descents were categorized as Caucasian, Asian, African, Arabian, Indian, Persian, mixed or not-stated. The types of asthma were stratified into atopic asthma and non-atopic asthma. In the subgroup analyses, only the studies with the number of case and control more than 100 were included. Data was extracted independently by two investigators and consensus were reached on all

items. If they could not come to an agreement, a third investigator (Jianwei Liu) adjudicated the disagreements.

2.3. Statistical analysis

Based on the genotype frequencies in cases and controls, crude odds ratios (ORs) as well as their 95% confidence intervals (CIs) were calculated to assess the strength of association between the IL-4 C-589T polymorphism and asthma risk. The pooled ORs were performed with co-dominant model (CT vs. CC, TT vs. CC), domi-

Table 2

Main characteristics of studies included in the meta-analysis.

Author	Method	Cases				F(C) of Cases	Controls				F(C) of Controls	HWE of Controls
		TT	CT	CC	N		TT	CT	CC	N		
Interleukin-4 C-589T												
Takabayashi A	PCR-RFLP	51	43	6	100	28	51	39	10	100	30	Y
Hijazi Z	PCR-RFLP	54	25	5	84	21	60	31	9	100	25	Y
Sandford AJ	AS-PCR/PCR-RFLP	9	78	146	233	79	2	41	100	143	84	Y
Cui TP(2003)	PCR-RFLP	56	37	5	98	24	67	32	4	103	19	Y
Lee SG	PCR-RFLP/DNA sequencing	168	77	9	254	19	68	29	3	100	18	Y
Wang W	PCR-RFLP	22	42	29	93	54	15	26	21	62	55	Y
Adjers K	PCR-RFLP	35	109	99	243	63	48	164	189	401	68	Y
Donfack J(Caucasian)	PCR-DHPLC	7	35	84	126	81	6	55	144	205	84	Y
Donfack J(African)	PCR-DHPLC	98	82	25	205	32	77	82	24	183	36	Y
Cui TP(2005)	PCR-RFLP	85	52	6	143	22	47	20	5	72	21	Y
Zhang WD(Asian)	PCR-RFLP	95	46	4	145	19	109	44	3	156	16	Y
Zhang WD(Malayan)	PCR-RFLP	28	34	11	73	38	37	42	14	93	38	Y
Zhang WD(Indian)	PCR-RFLP	6	31	48	85	75	7	30	62	99	78	Y
Gervaziev YV	PCR-RFLP	18	75	16	109	49	7	43	18	68	58	N
Mak JCW	PCR-RFLP	179	95	15	289	22	186	87	19	292	21	Y
Hosseini-Farahabadi S	PCR-RFLP	5	8	17	30	70	0	12	38	50	88	Y
Chiang CH	PCR-RFLP	147	19	1	167	6	70	34	7	111	22	Y
Kamali-Sarvestani E	PCR-RFLP	4	60	139	203	83	1	18	93	112	91	Y
de Faria IC	PCR-RFLP	9	41	38	88	66	27	108	67	202	60	Y
Amirzargar AA	AS-PCR	0	59	0	59	50	0	129	10	139	54	N
Wu XH	PCR-RFLP	132	84	11	227	23	163	83	6	252	19	Y
Bijanzadeh M	PCR-RFLP	4	4	92	100	94	1	1	48	50	97	N
Huang HR	PCR-RFLP	80	19	1	100	11	75	43	4	122	21	Y
Fan CE	PCR-RFLP	11	13	38	62	72	2	1	27	30	92	N
Daneshmandi S	PCR-RFLP	3	15	63	81	87	4	26	94	124	86	Y

F(C): C allele frequency; PCR-RFLP: polymerase chain reaction and restriction fragment-length polymorphism; AS-PCR: allele-specific PCR; DHPLC: denaturing high performance liquid chromatography; HWE: Hardy–Weinberg equilibrium; Y: Yes; N: No.

Table 3

Information collected according to atopic or non-atopic asthma studies.

Author	Cases				F(C) of Cases	Controls				F(C) of Controls	HWE of Controls
	TT	CT	CC	N		TT	CT	CC	N		
Atopic asthma											
Takabayashi A	51	43	6	100	28	51	39	10	100	30	Y
Hijazi Z(A)	39	18	3	60	20	50	26	7	112	31	Y
Sandford AJ	9	78	146	233	79	2	41	100	143	84	Y
Cui TP(2003)	56	37	5	98	24	67	32	4	103	19	Y
Lee SG(A)	131	58	5	194	18	68	29	3	100	18	Y
Donfack J(Caucasian)(A)	5	23	54	82	80	6	55	144	205	84	Y
Donfack J(African)(A)	77	62	21	160	33	77	82	24	183	36	Y
Cui TP(2005)	85	52	6	143	22	47	20	5	72	21	Y
Zhang WD(Asian)(A)	57	32	4	93	22	46	17	1	64	15	Y
Zhang WD(Malayan)(A)	19	28	10	57	42	19	16	6	41	34	Y
Zhang WD(Indian)(A)	5	27	39	71	74	0	4	24	28	93	Y
Mak JCW(A)	113	57	8	178	21	104	57	9	170	22	Y
Non-atopic asthma											
Hijazi Z(NA)	15	7	2	24	23	50	26	7	83	24	Y
Lee SG(NA)	37	19	4	60	23	68	29	3	100	18	Y
Donfack J(Caucasian)(NA)	2	12	30	44	82	6	55	144	205	84	Y
Donfack J(African)(NA)	21	20	3	44	30	77	82	24	183	36	Y
Zhang WD(Asian)(NA)	38	14	0	52	13	46	17	1	64	15	Y
Zhang WD(Malayan)(NA)	9	6	1	16	25	19	16	6	41	34	Y
Zhang WD(Indian)(NA)	1	4	9	14	79	0	4	24	28	93	Y
Mak JCW(NA)	52	30	6	88	24	104	57	9	170	22	Y

F(C): C allele frequency; HWE: Hardy–Weinberg equilibrium; Y: Yes; N: No (A): atopic asthma; (NA): nonatopic asthma.

nant model (CT + TT vs. CC), and recessive model (TT vs. CC + CT), respectively. Subgroup analyses were performed by ethnicity and type of asthma.

The fixed-effects model (Mantel–Haenszel method), or the random effects (DerSimonian Laird) model, were appropriately used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2 , respectively [34]. In case significant heterogeneity was detected, the random effects model was chosen. Meta-analysis was performed using the 'metan' STATA command.

Sensitivity analysis was performed to assess the stability of the results. 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 [35]. Evidence of publication bias was determined using Egger's [36] formal statistical test and by visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $P < 0.10$. The Egger's test was performed using the 'metabias' STATA command. Analyses were conducted using STATA 10.0 (STATA Corp., College Station, TX, USA).

Table 4

Main results of pooled ORs in the meta-analysis.

Interleukin-4 C-589 T	CT vs. CC		TT vs. CC		Dominant model		Recessive model	
	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h
Total	1.187(1.016–1.387)	0.638	1.221(0.983–1.516)	0.469	1.213(1.046–1.405)	0.267	1.124(0.915–1.380)	0.002
<i>Ethnicity</i>								
Caucasian	1.235(0.971–1.570)	0.856	1.591(1.032–2.452)	0.568	1.292(1.028–1.624)	0.890	1.420(0.942–2.141)	0.494
Asian	1.230(0.829–1.827)	0.701	1.193(0.821–1.733)	0.133	1.227(0.847–1.779)	0.237	1.109(0.783–1.572)	<0.001
<i>Asthma</i>								
Atopic	1.274(0.991–1.637)	0.739	1.287(0.920–1.801)	0.722	1.313(1.033–1.667)	0.594	0.999 (0.836–1.195)	0.386
Non-atopic	1.165(0.738–1.838)	0.793	1.248(0.713–2.186)	0.592	1.219(0.791–1.878)	0.586	1.038(0.778–1.385)	0.865

P_h : P value of Q-test for heterogeneity test.

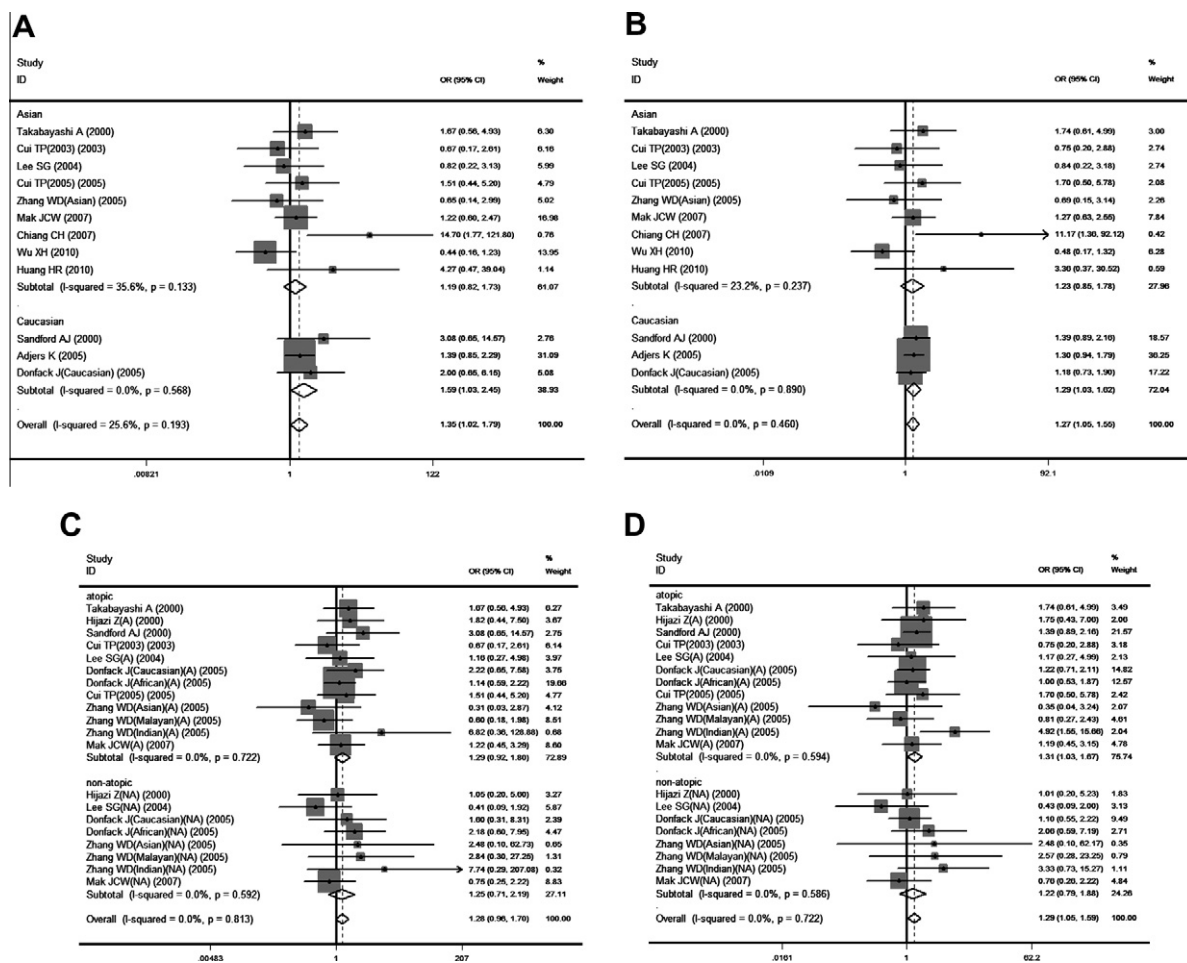


Fig. 1. Selected forest plots for the association between IL-4 rs2243250 (C-589T) polymorphism and asthma risk stratified by ethnicity (a TT vs. CC analysis. b dominant model analysis) and by asthma type (c TT vs. CC analysis. d dominant model analysis). The gray boxes represent the point estimates of ORs, and the size of the boxes are proportional to the weight given to each study in the meta-analysis. Horizontal lines represent the 95% CI. The diamonds and dashed lines represent the summary estimates of ORs across all listed studies (size of the diamond = 95% CI). When a confidence interval exceeds the chosen X-axis limit, it will display an arrow head.

3. Results

3.1. Study characteristics

A total of 17 publications met the inclusion criteria [9–18,20,22–24,26,28,30]. The studies of Gervaziev et al. [19], Amirzargar et al. [25], Bijanzadeh et al. [27], and Fan et al. [29] were excluded because of not fulfilling HWE in the control group. The study of Hosseini-Farahabadi et al. [21] was excluded because the number of case and control was less than 100. All these studies were characterized and listed in Tables 1 and 2, including first author's surname, publication year, country of origin, study design, ethnicity, matching variables (mean or range of age, percentage of female), type of asthma, evaluation method of atopic phenotype, quality score, genotyping methods, numbers of cases and controls, numbers of cases and controls of different genotypes, C allele frequency and HWE. Of the 17 studies, sample sizes ranged from 155 to 644. In studies of Donfack et al. [16] and Zhang et al. [17], the data were collected separately according to the different subgroup of ethnicity. Including the subgroup studies, there were 3 studies of Caucasians, 9 studies of Asians, 1 study of African, 1 study of Arabian, 1 study of Indian, 1 study of Malayan, 1 study of Uighurs, 1 study of mixed populations, and 2 studies of not-stated ethnicity. In these studies, 7 were hospital-based, 12 were population-based, and 1 was not-stated. The information collected according to atopic or non-atopic asthma studies were shown in Table 3. All the control groups used for data collection in the meta-analysis were non-asthmatic or healthy control. What is more, in the subgroup analysis by asthma type, we used non-atopic healthy ones as the control if the numbers were available.

3.2. Main results

Table 4 listed the main results of this meta-analysis.

Overall, significantly elevated asthma risk was associated with IL-4 T allele when all studies were pooled into the meta-analysis (CT vs. CC: OR = 1.187, 95% CI = 1.016–1.387; dominant model: OR = 1.213, 95% CI = 1.046–1.405). In the subgroup analysis by ethnicity, significantly increased risk was only found for Caucasians (TT vs. CC: OR = 1.591, 95% CI = 1.032–2.452; dominant model: OR = 1.292, 95% CI = 1.028–1.624) (Fig. 1). When stratified by asthma type, statistically significantly elevated risk was only found in atopic asthma group (dominant model: OR = 1.313, 95% CI = 1.033–1.667) (Fig. 1).

3.3. Sensitivity analysis and publication bias

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 the corresponding pooled ORs were not materially altered, indicating that our results were statistically robust. Begg's funnel plot and Egger's test were performed to evaluate the publication bias of the literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Supplement figure 1), and the Egger's test suggested the absence of publication bias ($P = 0.854$ for CT vs. CC; $P = 0.269$ for TT vs. CC; $P = 0.787$ with dominant model; and $P = 0.208$ with recessive model; all the P values > 0.05).

4. Discussion

It is well recognized that there is individual susceptibility to asthma even with the same environmental exposure. Host factors, including polymorphisms of genes involved in asthma may have

accounted for this difference. Therefore, genetic susceptibility to asthma has been a research focus in scientific community. Recently, genetic variants of IL-4 gene in the etiology of asthma have drawn increasing attention. Growing number of studies have suggested that T allele at position –589 of the IL-4 gene promoter region was emerging as a low-penetrance susceptibility allele in the development of asthma. However, the results are inconclusive. To better understanding of the association between this polymorphism and asthma, a meta-analysis with a big sample and subgroup analysis performed is necessary.

The results from our meta-analysis involving 3037 cases and 3032 controls confirmed IL-4 promoter C-589T substitution as a low-penetrant risk factor for developing asthma. In the subgroup analysis based on ethnicities, significant association was found in Caucasians but not in Asians under TT vs. CC model and dominant model, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they live in [37]. Moreover, when stratified by asthma type, statistically significantly elevated risk was only found in atopic asthma group. This reason may be that different types of asthma have different mechanism of pathogenesis or this polymorphism may exert varying effects in different asthma types. In addition, it is also likely that the observed differences of ethnicity and asthma type may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate [38]. Considering the relatively limited studies and population numbers included in this meta-analysis, our results should be interpreted with caution.

Several limitations of this meta-analysis should be addressed. Firstly, the sample size was still relatively small for some stratified analyses. Secondly, in our analysis, the controls were not uniformly defined. Although most of the controls were selected mainly from non-asthmatic healthy populations, some had atopic diseases. Therefore, non-differential misclassification bias was possible because these studies may have included the control groups who have different risks of developing asthma. Thirdly, there might exist heterogeneity of the phenotype definition or diagnosis of asthma and atopic cases among different studies. Although the diagnostic criteria of asthma were mainly based on clinical history, physical examination, and pulmonary function tests, there did exist a few differences among studies. In addition, patients were considered as atopic if total IgE, allergen specific IgE or skin prick test results were positive, but different test methods might lead to different diagnoses of asthma types. Finally, our results were based on unadjusted estimates, while a more precise analysis should be conducted if all individual raw data were available, which would allow for the adjustment by other possible co-variants including age, gender, smoking status, obesity, environmental factors, and other lifestyles.

In spite of these limitations, our meta-analysis had several strengths. First, sufficient number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication biases were detected, indicating that the whole pooled results may be unbiased.

In conclusion, our meta-analysis suggests that IL-4 C-589T polymorphism probably contribute to asthma susceptibility especially for Caucasians and for atopic type. However, it is necessary to conduct large sample studies using homogeneous asthmatic patients and well matched controls. Moreover, gene–gene and gene–environment interactions should also be considered in the analysis. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between the IL-4 C-589T polymorphism and asthma risk.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cyto.2012.05.006>.

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