Association of the *IL-4R* Q576R polymorphism and asthma in the Chinese Han population: A meta-analysis

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ABSTRACT. The *IL-4R* Q576R polymorphism has been reported to increase susceptibility to asthma, but the results are controversial. Thus, we performed a meta-analysis to evaluate the association of the *IL-4R* Q576R polymorphism and asthma risk in the Chinese Han population. A total of sixteen eligible case-control studies that evaluated the relationship between the *IL-4R* Q576R polymorphism and asthma in the Chinese Han population were obtained by comprehensive literature search incorporating electronic databases, and included 2077 asthma cases and 1589 controls. Our analysis detected a significant association between the *IL-4R* Q576R polymorphism and the risk of asthma in the Chinese Han population (Allelic model: OR = 1.481, 95%CI = 1.134-1.935, P = 0.004; Dominant model: OR = 1.542, 95%CI = 1.194-1.990, P = 0.001; Recessive model: OR = 1.695, 95%CI = 1.170-2.456, P =

0.005, Additive model: OR = 1.897, 95%CI = 1.299-2.771, P = 0.005). The year of publication and size of total sample might be sources of between-study heterogeneity. Upon subgroup analysis by size of total sample of each study, the significant association only remained in a subgroup with a small sample size. In summary, our meta-analysis suggested that the *IL-4R* Q576R polymorphism is associated with asthma in the Chinese Han population.

Key words: Polymorphism; Single nucleotide polymorphism; Meta-analysis; Asthma

INTRODUCTION

Asthma is one of the most common complex diseases and threatens the health of many people in both developing and developed countries, with prevalence between 10 and 15% in childhood (Berce and Potocnik, 2010). Epidemiological studies have demonstrated that the causes of asthma are related to environmental and genetic risk factors.

Interleukin-4 (IL-4) is a cytokine that induces differentiation of naive helper T cells (Th0 cells) to Th2 cells and plays an important role in the development of allergic inflammation. IL-4 mediates the IgE isotype switch, induces the expression of vascular cell adhesion molecule-1 (VCAM-1), and promotes eosinophil transmigration across the endothelium, mucus secretion, and differentiation of T helper type 2 lymphocytes, leading to cytokine release.

The IL-4 receptor (IL-4R) is a transmembrane protein that consists of two subunits, α and γ chains. A growing body of evidence indicates that IL-4R plays a key role in the pathogenesis of asthma and the modulation of IgE level. When the IL-4 protein binds to IL-4R, the system of tyrosine is activated. Then, the signal transducer and activator of transcription 6 (STAT6) is activated, promoting the expression of IL-4 sensitive genes, such as *CD23*, *MH-CII*, and *IgE* (Nelms et al., 1999).

Previous studies have suggested that the *IL-4R* gene is a candidate gene for asthma. The coding gene for the IL-4Rα subunit has been localized to chromosome 16p12.1 (GenBank Accession No. NM000418). In 1997, Hershey et al. (1997) first identified the *IL-4R* Q576R polymorphism (rs1801275) and found that the *IL-4R* 576R allele was strongly associated with atopy. This polymorphism is located in the exonic region of the *IL-4R* gene, so that allelic variation leads to a glutamine-to-arginine substitution in the cytoplasmic domain of the IL-4Rα protein. *IL-4R* Q576R has been associated with several diseases, including bladder cancer, atopic dermatitis, chronic periodontitis, and bronchiolitis (Oiso et al., 2000; Huang et al., 2010; Reichert et al., 2011; Chu et al., 2012). To date, a number of epidemiological studies have been performed to explore the relationship between the *IL-4R* Q576R polymorphism and asthma risk, but the results have been conflicting (Beghé et al., 2003; Mak et al., 2007; Zhang et al., 2007a; Dmitrieva-Zdorova et al., 2012). Several studies concluded that the *IL-4R* Q576R polymorphism might increase the susceptibility to asthma (Beghé et al., 2003; Dmitrieva-Zdorova et al., 2012), but other studies reported the converse conclusion (Mak et al., 2007; Zhang et al., 2007b). The association between the *IL-4R* Q576R polymorphism and asthma risk has been extensively explored in the Chinese Han population (Cui et al., 2003, 2005; Liu and Zhang, 2005; Deng et al., 2006; Gui et al., 2006; Mak et al., 2007; Zhang et al., 2006, 2007a,b; Dai et al., 2010; Fan et al., 2010; Sun et al., 2005, 2008, 2010; Wu et al.,

2010; Jin et al., 2011). These results were also conflicting, and furthermore, the sample sizes in the studies were relatively small. Therefore, we performed a meta-analysis including 2077 patients with asthma and 1589 control individuals in order to derive a more precise association of the *IL-4R* Q576R polymorphism and risk of asthma in the Chinese Han population.

MATERIAL AND METHODS

Study selection

We searched out the relevant studies for the present meta-analysis from the following databases: PubMed, Foreign Medical Journal Service (FMJS), Wanfang Data (http://www.wanfangdata.com.cn), and China National Knowledge Infrastructure (CNKI); the last search was updated on December 1, 2013. The following terms were adopted in the electronic searches: "Interleukin-4 receptor or IL-4R" and "variant or gene or polymorphism" and "asthma" and "Chinese." Manual research was also performed. The most comprehensive study was adopted if several similar data sets were published from one research center. Studies included in this meta-analysis were required to meet all the following criteria: a) case-control study design; b) evaluation of the relationship between the *IL-4R* Q576R polymorphism and asthma; c) having clear original data of genotypic and allelic frequencies; d) no restriction on the language and sample size; and e) were based upon the Chinese Han population.

Data extraction

Original data were recorded in standard form. All relevant studies were read carefully. The original data was extracted independently by two authors (Z.Y.H. and B.J.C.). Any points of disagreement were resolved by discussion between the two authors. The following data were extracted from each study: first author's name, year of publication, average age, gender, region, numbers of cases and controls, numbers of AA, AG, GG genotypes in cases and controls, diagnosis criteria of asthma, and genotyping methodology.

Data analysis

Hardy-Weinberg equilibrium (HWE) for the control group was determined by the Chi-square test. Pooled odds ratios (ORs) with 95% confidence intervals (CI) were used to evaluate the strength of association between the *IL-4R* Q576R polymorphism and asthma susceptibility. The pooled ORs were calculated by the Allelic (G versus A), Additive (GG versus AA), Recessive (GG versus GA + AA), and Dominant models (GG + GA versus AA).

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2012) was used to evaluate the quality of the eligible studies. The range of the NOS score was 0 (worst) to 9 (best) stars. The stability of the results was checked by recalculating the result following omission of each single study.

A fixed effect model (Mantel-Haenszel method) was adopted to evaluate the pooled results if the heterogeneity was not significant ($I^2 \leq 50\%$, $P > 0.05$), which was checked using the Cochrane Q statistic. Otherwise, a random-effect model (DerSimonian-Laird method) was applied. The sources of heterogeneity among studies were explored by meta-regression analysis. The subgroup analyses were carried out following the study characteristics: region, and

size of total sample. Begg's funnel plots were used to examine the publication bias between studies, and the asymmetry of funnel plots was examined by Egger's test (P < 0.05 was taken as a statistically significant publication bias).

All statistical analyses were performed with STATA version 12.0 (StataCorp LP, College Station, Texas 77845 USA). P value < 0.05 (two-sided) was considered to be statistically significant.

RESULTS

Study characteristics

A total of sixteen eligible case-control studies that evaluated the relationship between the *IL-4R* Q576R polymorphism and asthma in the Chinese Han population were obtained by comprehensive literature search; these included 2077 patients with asthma and 1589 control individuals (Figure 1). The main characteristics of the eligible studies are listed in Table 1. According to the data from all of the pooled studies, the frequency of the G allele was 18.5% for patients and 16.1% for controls, although for the control subjects, the frequency of the G allele ranged from 5.0 to 34.0%. The total sample size of the studies ranged from 85 to 576. The provinces covered in the meta-analysis included Hubei, Hunan, Guangdong, Anhui, Chongqing, Henan, Inner Mongolia, Shanghai, Heilongjiang, Hong Kong, and Liaoning. In one study, the samples were collected from three provinces (Zhang et al., 2007a), but we were unable to obtain the data because the data specific to each province was not extractable. The diagnostic criteria of asthma were appropriate in all of these studies. The controls in two studies deviated from HWE (Sun et al., 2005; Fan et al., 2010). Three genotyping methods were applied in these studies, including polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP), PCR-direct sequencing, and allele-specific PCR. The range of NOS scores was from four to nine stars, in which eleven articles' scores were greater than six stars. Among the eligible studies, six studied adult asthma populations and seven papers studied children.
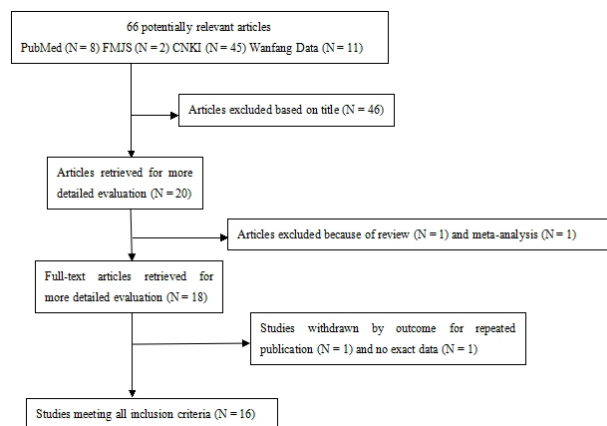
Figure 1. Flow diagram of the article selection process for the *IL-4R* Q576R polymorphism and asthma meta-analysis. FJMS: Foreign Medical Journal Service; CNKI: China National Knowledge Infrastructure.

Table 1. Main characteristics of studies involved in this meta-analysis.

Author	Year	Province	Geography	Phenotype	Type of study	NOS score	Sample size (patient/control)	Patient AA	AG	GG	Control AA	AG	GG	MAF (control)	Genotyping method	HWE Y/N (P)
Cui TP	2003	Hubei	South	Adult	Retrospective	6	98 / 103	52	37	9	75	25	3	0.15	PCR-RFLP	Y (0.61)
Cui TP	2005	Hubei	South	Children	Retrospective	7	143 / 72	77	52	14	55	16	1	0.13	PCR-RFLP	Y (0.89)
Liu LN	2005	Henan	North	Children	Retrospective	8	76 / 60	46	27	3	47	12	1	0.12	PCR-RFLP	Y (0.82)
Sun J	2005	Heilongjiang	North	Children	Retrospective	8	82 / 59	59	19	4	46	10	3	0.14	PCR-RFLP	N (0.03)
Deng RQ	2006	Guangdong	South	Mixed	Retrospective	8	100 / 100	32	42	26	47	38	15	0.34	Allele-specific PCR	Y (0.13)
Gui Q	2006	Chongqing	South	Adult	Retrospective	6	50 / 50	33	15	2	34	14	2	0.18	PCR-RFLP	Y (0.72)
Zhang AM	2006	Hunan	South	Children	Retrospective	7	94 / 68	55	39	0	57	11	0	0.08	PCR-RFLP	Y (0.47)
Mak JC	2007	Hong Kong	South	Adult	Retrospective	8	285 / 291	200	81	4	191	91	9	0.19	PCR-RFLP	Y (0.64)
Zhang HB	2007a	Three provinces	Mixed	Mixed	Retrospective	4	352 / 114	257	87	8	87	27	0	0.12	PCR-direct sequencing	Y (0.15)
Zhang WD	2007b	Guangdong	South	Adult	Retrospective	7	145 / 157	115	30	0	115	38	4	0.15	PCR-RFLP	Y (0.69)
Sun YL	2008	Liaoning	North	Mixed	Retrospective	4	35 / 50	27	7	1	42	8	0	0.08	PCR-RFLP	Y (0.54)
Dai H	2010	Shanghai	South	Children	Retrospective	7	96 / 96	47	48	1	62	33	1	0.18	PCR-RFLP	Y (0.13)
Fan CE	2010	Inner Mongolia	North	Adult	Retrospective	6	62 / 30	48	8	6	25	2	3	0.13	PCR-RFLP	N (<0.01)
Sun J	2010	Heilongjiang	North	Children	Retrospective	7	91 / 42	67	24	0	33	9	0	0.11	PCR-RFLP	Y (0.44)
Wu XH	2010	Hubei	South	Children	Retrospective	9	252 / 227	183	61	8	168	55	4	0.14	PCR-RFLP	Y (0.84)
Jin JW	2011	Anhui	South	Adult	Retrospective	8	116 / 70	87	22	7	63	7	0	0.05	PCR-direct sequencing	Y (0.66)

MAF: main allelic frequency; NOS: Newcastle-Ottawa Scale; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism analysis; HWE: Hardy-Weinberg equilibrium; Y: yes; N: no.

Meta-analysis results

The main results of the present meta-analysis are listed in Table 2. A significant asso-

Table 2. Meta-analysis results of association between the IL-4R Q576R polymorphism and asthma.

	GG + AG vs AA				GG vs AG + AA				G vs A				GG vs AA			
	OR (95%)	POR	PQ	Pm	OR (95%)	POR	PQ	Pm	OR (95%)	POR	PQ	Pm	OR (95%)	POR	PQ	Pm
Total	1.542 (1.194-1.990)	0.001	0.001		1.695 (1.170-2.456)	0.005	0.284		1.481 (1.134-1.935)	0.004	0.001		1.897 (1.299-2.771)	0.001	0.150	
Ratio of case size to control size				0.122				0.587				0.134				0.602
<1	1.144 (0.647-2.022)	0.644	0.008		0.973 (0.464-1.890)	0.855	0.050		1.048 (0.538-2.039)	0.891	0.000		1.031 (0.188-5.642)	0.972	0.023	
≥1	1.708 (1.337-2.181)	0.000	0.102		2.122 (1.355-3.324)	0.001	0.728		1.660 (1.323-2.082)	0.000	0.048		2.168 (1.335-3.521)	0.002	0.651	
Year				0.012				0.254				0.012				0.265
≤2006	2.149 (1.662-2.779)	0.000	0.358		2.257 (1.357-3.753)	0.002	0.596		1.980 (1.513-2.592)	0.000	0.454		2.819 (1.652-4.811)	0.000	0.454	
>2006	1.388 (0.920-1.327)	0.286	0.066		1.186 (0.684-2.059)	0.54	0.226		1.165 (0.844-1.608)	0.353	0.001		1.216 (0.702-2.107)	0.486	0.186	
Geography				0.693				0.939				0.716				0.920
North	1.615 (1.084-2.408)	0.019	0.854		1.308 (0.529-3.234)	0.561	0.766		1.526 (1.075-2.165)	0.018	0.842		1.401 (0.555-3.535)	0.475	0.735	
South	1.599 (1.114-2.294)	0.011	0.000		1.705 (1.128-2.576)	0.011	0.106		1.515 (1.038-2.211)	0.031	0.000		1.808 (0.843-3.876)	0.128	0.043	
Genotyping methods				0.690				0.493				0.682				0.517
PCR-RFLP	1.501 (1.111-2.026)	0.008	0.001		1.360 (0.862-2.145)	0.186	0.277		1.411 (1.030-1.932)	0.032	0.000		1.484 (0.943-2.335)	0.088	0.153	
Others	1.715 (1.055-2.788)	0.030	0.163		2.567 (1.337-4.929)	0.005	0.449		1.764 (1.125-2.766)	0.013	0.113		3.294 (1.612-6.728)	0.001	0.541	
Phenotype				0.000				0.523				0.466				0.549
Adult	1.289 (0.791-2.100)	0.308	0.004		1.116 (0.627-1.988)	0.709	0.095		1.203 (0.694-2.087)	0.510	0.000		1.166 (0.393-3.456)	0.782	0.048	
Children	1.841 (1.285-2.639)	0.001	0.050		2.202 (1.052-4.608)	0.036	0.563		1.762 (1.262-2.459)	0.001	0.032		2.095 (0.961-4.568)	0.063	0.483	
Mixed	1.457 (1.023-2.075)	0.037	0.490		2.289 (1.178-4.450)	0.015	0.709		1.522 (1.141-2.032)	0.004	0.611		1.715 (1.055-2.788)	0.006	0.815	
Size of total sample				0.867				0.164				0.000				0.171
<300	2.029 (1.640-2.510)	0.000	0.615		2.227 (1.411-3.515)	0.001	0.699		1.881 (1.534-2.306)	0.000	0.258		2.714 (1.686-4.367)	0.000	0.607	
≥300	0.924 (0.746-1.145)	0.471	0.397		0.896 (0.457-1.754)	0.748	0.107		0.872 (0.604-1.259)	0.465	0.015		0.878 (0.449-1.720)	0.705	0.094	
NOS score								0.856				0.834				0.834
>6	1.585 (1.134-2.216)	0.007	0.000		1.570 (1.029-2.393)	0.036	0.139		1.505 (1.057-2.143)	0.023	0.000		1.750 (1.299-2.697)	0.011	0.065	
≤6	1.489 (1.087-2.040)	0.013	0.445		2.168 (0.985-4.773)	0.055	0.593		1.502 (1.141-1.977)	0.004	0.419		2.436 (1.100-5.396)	0.028	0.528	

HWE = Hardy-Weinberg equilibrium; POR = P value of odds ratios; PQ = P value of Q statistic; Pm = P value of meta-regression.

ciation between the *IL-4R* Q576R polymorphism and asthma risk in the Chinese Han population was identified (Allelic model: OR = 1.481, 95%CI = 1.134-1.935, P = 0.004; Dominant model: OR = 1.542, 95%CI = 1.194-1.990, P = 0.001; Recessive model: OR = 1.695, 95%CI = 1.170-2.456, P = 0.005, and Additive model: OR = 1.897, 95%CI = 1.299-2.771, P = 0.005) (Figure 2). Because the number of GG genotypes was zero in both patient and control groups, these two studies were omitted in the Additive model and in the Recessive model (Zhang et al., 2006; Sun et al., 2010). Because of the vast natural and cultural discrepancy on the two sides of Huai River-Qinling Mountains, China is divided into North and South (Li et al., 2013). In subgroup analysis stratified by geography, the pooled ORs were not significantly different between South and North China.
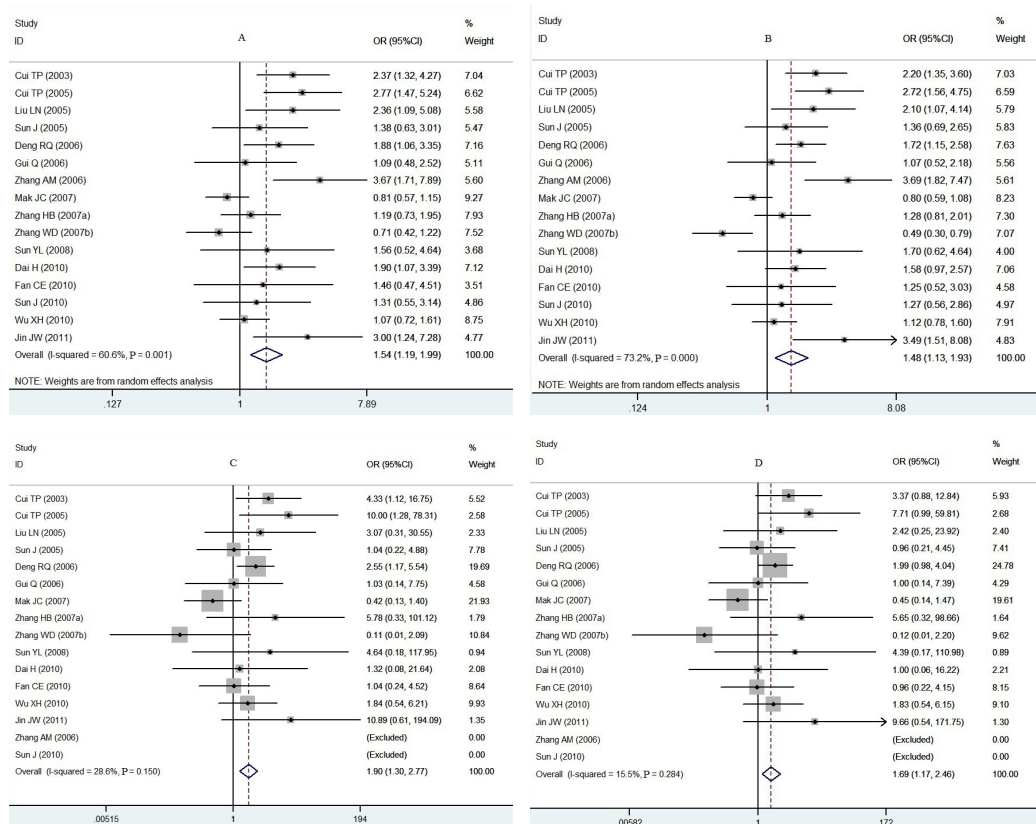
Figure 2. Forest plots of asthma associated with distribution of genotypic frequencies of the *IL-4R* Q576R polymorphism in the overall population. **A.** Dominant model; **B.** Allelic model; **C.** Additive model; **D.** Recessive model. OR: odds ratio; CI: confidence interval; ID: study identification.

Because the between-study heterogeneity was significant (Allelic model: P = 0.001; Dominant model: P = 0.001), meta-regression was performed to explore the sources of heterogeneity. The confounding factors included year of publication, geography, phenotype of study, size of total sample, ratio of patient to control group size, genotyping methods, and NOS score. Year of publication and size of total sample might be sources of between-study hetero-

geneity (year of publication: $P_{\text{meta-regression}}$ = 0.012 for the Dominant model; size of total sample: $P_{\text{meta-regression}}$ = 0.000 for the Dominant model). When the subgroup analysis was carried out by size of total sample of each study, the significant association only remained in a subgroup with small sample size (size of total sample <300) (Figure 3).
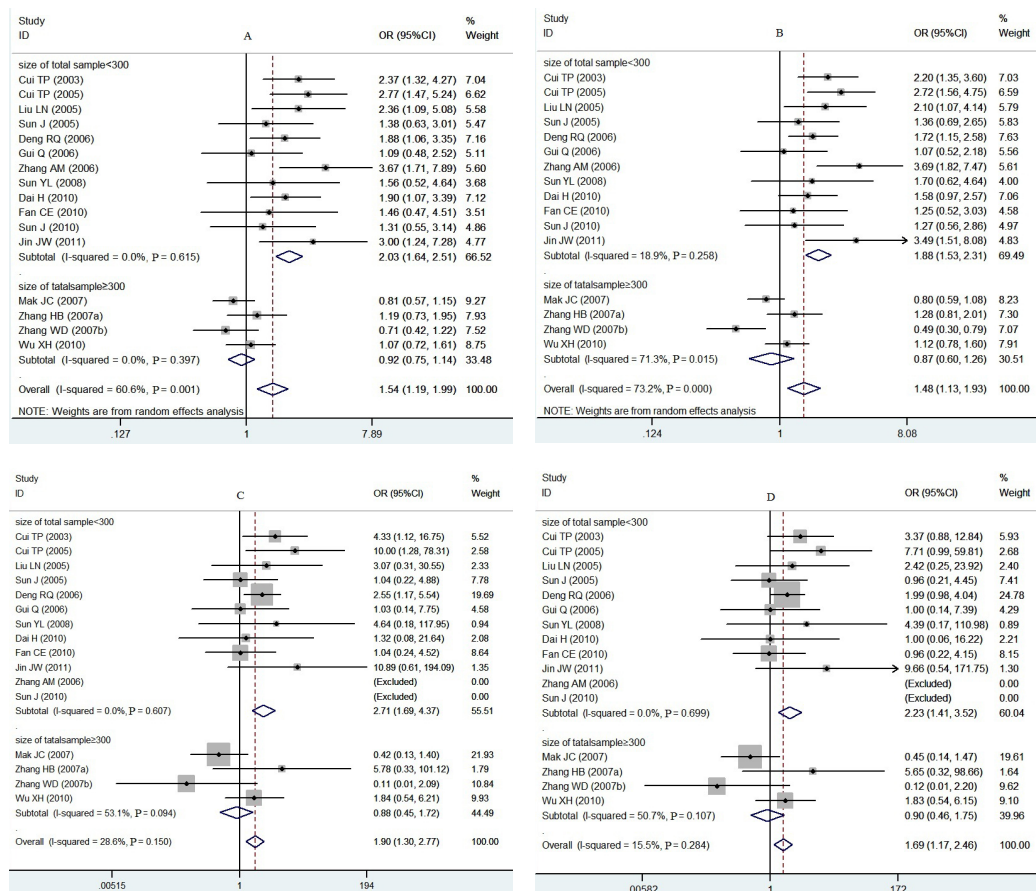

Figure 3. Forest plots of asthma associated with distribution of genotypic frequencies of *IL-4R* Q576R stratified by size of total sample. **A.** Dominant model; **B.** Allelic model; **C.** Additive model; and **D.** Recessive model. OR: odds ratio; CI: confidence interval; ID: study identification.

Sensitivity analysis

The sensitivity of the study was examined by recalculating the results following repeated omission of each individual study (Figure 4); the statistical difference was not changed in any case. We also performed the analysis with omission of two studies, which deviated from HWE. The statistical difference was not altered in any genetic model, which indicated that the results were statistically reliable.
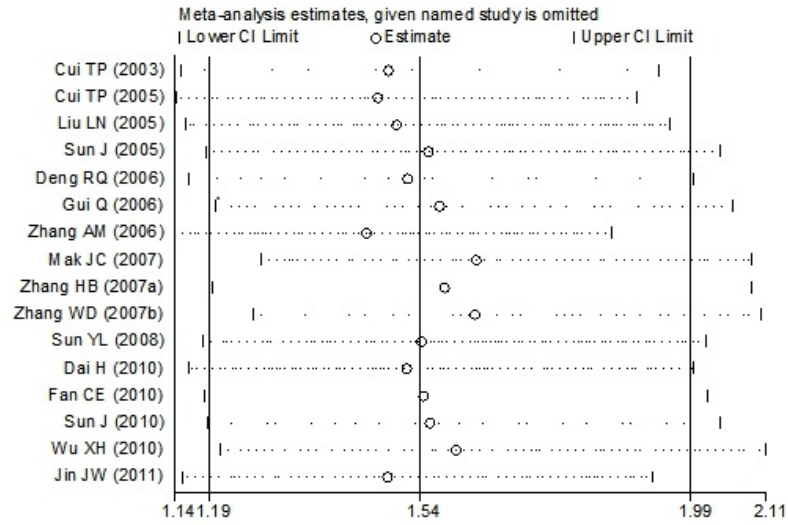
Figure 4. Analysis of the influence of individual studies on the pooled estimate in the Dominant model in the overall population. CI: confidence interval.

Publication bias

The publication bias between studies was examined using Begg's funnel plots. No obvious asymmetry was observed in the funnel plots (Figure 5) and no publication bias was found when the asymmetry of funnel plots was examined by Egger's regression test (Allelic model: P = 0.325; Dominant model: P = 0.164; Recessive model: P = 0.080; and Additive model; P = 0.139).
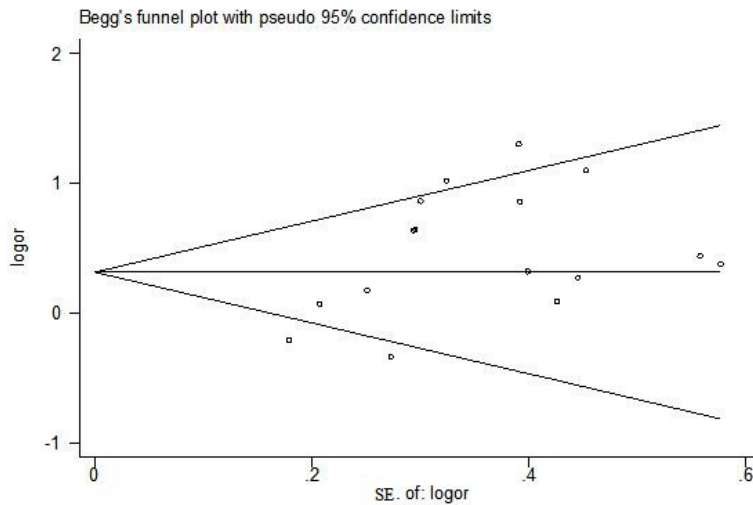
Figure 5. Funnel plot of asthma associated with *IL-4R* Q576R for the Dominant model in the overall study. SE: standard error.

DISCUSSION

To our knowledge, this study represents the first meta-analysis to explore the relationship between the *IL-4R* Q576R polymorphism and asthma in the Chinese Han population. We have found that this variant might be associated with the susceptibility to asthma in the Chinese Han population, and that the carriers of the G allele of the *IL-4R* Q576R polymorphism in this population might be predisposed to asthma.

The *IL-4Rα* gene consists of 12 exons, and the *IL-4R* Q576R polymorphism is located in exon 10. At this site (nucleotide position 1902), the guanine is substituted for adenine, which leads to an amino acid change from glutamine to arginine at position 576 in the cytoplasmic domain of the IL4-Rα protein.

In recent years, many studies have explored the relationship between the *IL-4R* Q576R polymorphism and asthma in different ethnic populations, including Europeans (Beghé et al., 2003; Dmitrieva-Zdorova et al., 2012) and Asians (Mak et al., 2007; Zhang et al., 2007b). The results from these studies, however, have been contradictory. In addition, even within the Chinese population, results from published studies have also been inconsistent. Dai et al. (2010) demonstrated that *IL-4R* Q576R was a single nucleotide polymorphism (SNP) site that increased susceptibility to childhood asthma in the Shanghai region, showing a significant association between the *IL-4R* Q576R heterozygous genotype and asthma. However, Mak et al. (2007) concluded that the *IL-4R* gene Q576R polymorphism was not associated with asthma in Chinese adults from Hong Kong. In 2010, Fan et al. (2010) designed a case-control study involving 62 patients with asthma and 30 controls to explore the relationship between the *IL-4R* gene Q576R polymorphism and bronchial asthma in the Han population of Inner Mongolia. Fan et al. (2010) also concluded that there was no significant difference between this variant and bronchial asthma.

In 2007, Loza and Chang (2007) carried out a meta-analysis of a total of eight studies with 1495 asthma patients and 976 controls to explore the relationship between the *IL-4R* Q576R polymorphism and asthma. They confirmed that the *IL-4R* 576R variant was significantly associated with asthma (OR = 1.38, 95%CI = 1.13-1.70), especially atopic asthma (OR = 1.54, 95%CI = 1.14-2.08). However, only one study in this meta-analysis was performed in the Chinese population, and the sample size was relatively small (241 asthma patients and 175 controls). In 2013, Zhu et al. (2013) also conducted a meta-analysis to explore the relationship between *IL-4* and *IL-4R* gene polymorphisms and asthma. Their study encompassed six SNPs, including rs1801275 (Q576R). A total of 8462 subjects were included in their research, including both Asian and Caucasian populations. They concluded this polymorphism was significantly associated with asthma in Asian population. However, their research had some limitations. Firstly, there were some errors made in data extraction. Secondly, there were significant heterogeneities between studies, but the study did not explore the sources of heterogeneities, which might have had an impact on the conclusions. We therefore performed the current meta-analysis to attempt to demonstrate a more authentic association between the *IL-4R* Q576R polymorphism and asthma through a comprehensive coverage of studies in the Chinese Han population. Sixteen studies including 2077 patients with asthma and 1589 control subjects were included in this meta-analysis. We found that the *IL-4R* Q576R polymorphism was significantly associated with asthma in the overall Chinese Han population (Allelic model: OR = 1.481, 95%CI = 1.134-1.935, P = 0.004; Dominant model: OR = 1.542, 95%CI = 1.194-1.990, P = 0.001; Recessive model: OR = 1.695, 95%CI = 1.170-2.456, P = 0.005, and

Additive model: OR = 1.897, 95%CI = 1.299-2.771, P = 0.005).

Because of the significant heterogeneity between studies included, confounding factors (year of publication, geography, phenotype of study, size of total sample, RR, genotyping methods, and NOS score) were included in the regression analysis. Among these confounding factors, the year of publication and size of total sample could account for the heterogeneities. When the subgroup analysis was carried out using size of total sample, the significant association only remained in the subgroup with small sample size. Accordingly, the false-positive result was not negligible and we should therefore interpret the results from this study cautiously. In the future, the research design should include increased sample size, which could enhance the power of the statistical analysis.

Because of the vast genetic discrepancy on the two sides of the Huai River-Qinling Mountains, we stratified the results for geography. Consequently, we found that the pooled ORs were not significantly different between South and North China.

We acknowledge that our meta-analysis had several inherent limitations. Firstly, the asthma classification included both atopic and nonatopic asthma, as most of the studies included did not subgroup asthma into these categories. This might be relevant, as some previous studies concluded that the *IL-4R* Q576R polymorphism was associated specifically with atopic asthma. Therefore, future study design should include exploration of the relationship between the *IL-4R* Q576R polymorphism and atopic *vs* nonatopic asthma. Secondly, the number of studies included was relatively small and the total sample size in each study ranged from 85 to 576. As the positive result of this meta-analysis was only upheld in the subgroup with small sample size, we should interpret the result cautiously.

Despite the limitations above, the result of this current meta-analysis suggest that the *IL-4R* Q576R polymorphism is associated with asthma in the Chinese Han population. However, because of the relatively small size of the included study populations, we should interpret this result cautiously.

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