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Original Article

Interleukin-17F 7488T/C polymorphism is associated with protection against asthma: a meta-analysis

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Abstract: The association between interleukin-17F (*IL-17F*) 7488T/C polymorphism and asthma risk is conflicting. This study conducted a meta-analysis by pooling all available data to make a more precise estimation of the association. Electronic databases PubMed, EMBASE, and China National Knowledge Infrastructure were searched to identify all eligible studies assessing the association between *IL-17F* 7488T/C polymorphism and asthma risk. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were calculated. A total of five case-control studies with 1445 cases and 1608 controls were included. Overall, the pooled ORs showed that the *IL-17F* 7488T/C polymorphism was inversely associated with risk of asthma (OR=0.29, 95% CI=[0.12, 0.70]) using recessive genetic model. Furthermore, this association was found to be exclusive to Asians (OR=0.31, 95% CI=[0.12, 0.84]). Sensitivity analysis by omission of single study in turn showed similar results. In conclusion, the present meta-analysis suggested that homozygote of *IL-17F* 7488T/C variant could protect against asthma in Asians. However, more studies conducted in different ethnic groups with large sample size are warranted to validate the precise association.

Keywords: Interleukin-17, polymorphism, asthma, meta-analysis

Introduction

Asthma is a common, chronic airway inflammatory disease, affecting 1-18% of the population in different regions worldwide [1]. Recently, interleukin 17 (IL-17) cytokines secreted by Th17 cells were found to be involved in the pathogenesis of asthma [2-5]. IL-17F, a recently discovered member of IL-17 is overexpressed in several types of inflammatory cells such as activated mast cells, basophils, $CD4^+$ T cell and γδT cells [6, 7]. In addition, it helps induce the production of inflammatory mediators including IL-6, IL-8, TGF-β and ICAM-1 [6, 8], which subsequently lead to neutrophil recruitment and airway remodeling [9, 10]. In fact, upregulated *IL-17F* gene expression was found in the lavage fluid from allergen-challenged sites of airways of asthma patients and its expression level was observed to be associated with disease severity [6]. In an asthma mice model, IL-17F amplifies antigen-induced allergic inflammation [11]; and *IL-17F* deficient mice had defective airway neutrophilia in response to an allergen challenge [12]. All these findings indicate that IL-17F plays crucial role in the pathophysiology of asthma.

Structurally, the *IL-17F* gene is located on chromosome 6p, a genomic region linked to asthma and asthma-related phenotypes [13]. The available evidence also suggests that *IL17F* gene is an excellent candidate gene for asthma susceptibility. Several single nucleotide polymorphisms of *IL-17F*, such as 1165T/C, 2367C/T, and 7469G/A, have been investigated in relation to asthma [14]. However, the relationship between *IL-17F* 7488T/C polymorphism (rs763780) and the risk of asthma is conflicting. The rs763780 TC heterozygote was found to be related with development of asthma in Qian's study [15], while the homozygote of rs763780 variant was found to help protect against asthma in Kawaguchi's study [16]. However, no association was found between *IL-17F* 7488T/C polymorphism and asthma risk in other studies [14, 17-19]. Thus the current study conducted a meta-analysis to determine the relationship

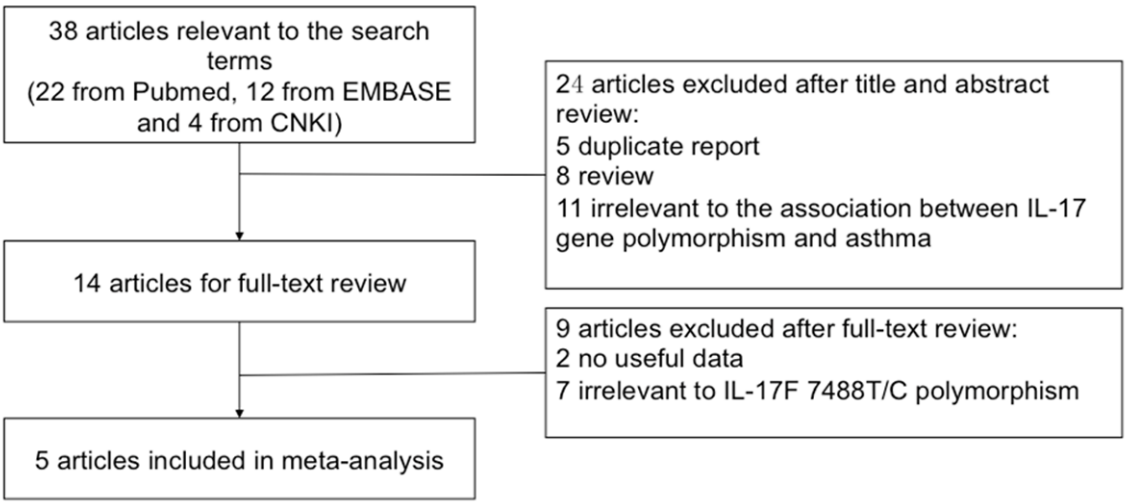

Figure 1. Flow chart of study process.

between *IL-17F* 7488T/C polymorphism and the risk of asthma.

Methods

Search strategy

Literature search was performed using electronic databases PubMed, EMBASE and China National Knowledge Infrastructure (CNKI) until October 22, 2014. The following terms were utilized to identify potential studies from these databases: (asthma or asthmatic) and (interleukin 17 or IL-17 or IL 17) and (polymorphism or mutation or variant). No publication language or initial time restriction was imposed. Further, reference lists of all potential articles were reviewed to identify additional relevant studies. The PRISMA flow diagram (**Figure 1**) was also available.

Data extraction

Two independent reviewers (TW and MZ) extracted the data from the selected studies complied with the following inclusion and exclusion criteria: 1) have evaluated the 7488T/C polymorphism in *IL-17* gene and asthma risk; 2) designed as case-control study; 3) have informed sufficient data for estimating an odds ratio (OR) and 95% confidence interval (CI). Reviews, abstracts, and unpublished date were excluded. If no useful data was reported, we requested details via contacting the authors. For the overlapping studies, the study with largest sample size was selected. In case of disagreement, consensus was reached by discussion with a third author (BML).

Quality assessment

The quality of eligible studies was assessed by the same two reviewers independently according to the methodological quality assessment scale which was modified from previous meta-analysis studies [20, 21]. A higher score indicated a better quality.

Statistical analyses

Whether the observed frequencies of genotypes in controls departed from Hardy-Weinberg equilibrium (HWE) or not was tested by the Chi-square test. Heterogeneity was examined by the *Q* test with $P<0.10$ indicating significant heterogeneity. I-square (I^2) statistic greater than 50% indicated moderate or high heterogeneity. Meta-analysis was conducted with the fixed effects model when there was no significant heterogeneity, otherwise the random-effects model. Pooled ORs with 95% CIs were calculated to assess the relationship between *IL-17F* 7488T/C polymorphism (rs763780) and the risk of asthma. *Z* test was used to analyze the statistical significance of OR. OR1, OR2 and OR3 were calculated for genotypes CC versus TT, CT versus TT, and CC versus CT. These pairwise differences (OR1, OR2 and OR3) were used to indicate the most appropriate genetic model as follows: if OR1=OR3≠1 and OR2=1,

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Asthma definition	Age group	Sample size, n (case/control)	Age, mean ± SD (range)		Gender, n (male/female)		Genotyping	Quality score
							case	control	case	control		
Kawaguchi	2006	Japan	Asian	Physician-diagnosed; had symptoms; and lung function test	Adults	432/435	47 (16-79)	36 (18-72)	197/235	281/154	Allele-specific PCR	7
Bazzi	2011	Saudi Arabia	Arabian	NA	NA	100/102	NA	NA	NA	NA	PCR-Taqman	4
Jin	2011	Korea	Asian	ATS	Adults	424/548	54.8	40.4	210/214	340/208	PCR-HRM	7
Qian	2012	China	Asian	GINA	Adults	318/352	39.8±14.23	38.26±13.31	135/183	152/200	GenomeLab SNPstream	7
Maalmi	2014	Tunisia	Arabian	GINA	Children	171/171	9.2 (4-16)	9.5 (5-16)	105/66	106/65	PCR-RFLP	8

ATS, American Thoracic Society; GINA, Global Initiative for Asthma; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NA, not available.

Table 2. Distribution of *IL-17F* 7488T/C genotype among patients and controls

Author	Year	Ethnicity	Case			Control			HWE, *P*
			CC	CT	TT	CC	CT	TT	
Kawaguchi	2006	Asian	0	100	332	9	79	347	0.082
Bazzi	2011	Arabian	0	7	93	1	8	93	0.109
Jin	2011	Asian	1	77	346	8	112	428	0.828
Qian	2012	Asian	3	71	244	0	57	295	0.098
Maalmi	2014	Arabian	0	16	155	3	23	145	0.081

then a recessive model was suggested; if OR1=OR2≠1 and OR3=1, then a dominant model was suggested; if OR2=1/OR3≠1 and OR1=1, then a complete overdominant model was suggested; if OR1>OR2>1 and OR1>OR3 >1 (or OR1<OR2<1 and OR1<OR3<1), then a codominant model was suggested. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except a codominant model) and to pool the results again. Subgroup analysis was performed by ethnicity. Sensitivity analyses were conducted by omitting each study one by one. Harbord test was used to evaluate potential publication bias for binary outcome. Power calculations were conducted using the Power and Sample Size Calculations (PS) program, version 3.1.2. [22]. All analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA). *P* value less than 0.05 was considered statistically significant.

Results

Study characteristics

The primary search strategy initially yielded a total of 38 articles relevant to the search terms. After screening and carefully reviewing, five studies [15-19] with 1445 asthmatic cases and 1608 controls studied on the relationship between *IL-17F* 7488T/C polymorphism and asthma risk were identified eligible for meta-analysis (**Figure 1**). The characteristics of the studies included in the meta-analysis are presented in **Table 1**. Of the five studies, three were carried out in Asian population [15, 16, 19], while the rest two were carried out in Arabian population [17, 18]. All of them had a high quality (quality score ranged from 7-8) except one reported by Bazzi *et al.* [18] Distribution of each genotype and HWE test results are presented in **Table 2**.

Quantitative data synthesis

The estimated OR1, OR2 and OR3 were 0.29, 1.07, and 0.27 respectively, indicating that recessive genetic model (CC vs. CT+TT) was the most suitable one. Using a recessive genetic model, pooled effect size (OR=0.29, 95% CI=[0.12, 0.70]) showed an association of *IL-17F* 7488T/C polymorphism with the protection against asthma with less heterogeneity (I^2=40.2%, *P*=0.15), which indicated individuals with CC genotype had lower risk for asthma than those with CT or TT genotypes. In the subgroup analysis by ethnicity, significant associations were found among Asians (OR=0.31, 95% CI=[0.12, 0.84]) but not Arabians (OR=0.20, 95% CI=[0.02, 1.71]) (**Figure 2**). Summary of meta-analyses results is presented in **Table 3**.

Sensitivity analysis

Sensitivity analyses were conducted repeatedly by omitting each study in turn. After exclusion of individual study, the pooled ORs ranged from 0.12 to 0.47. As shown in **Figure 3**, after exclusion of Qian's study, the pooled effect size closed to the lower limits of the CI of overall estimate extremely, suggesting this study had a potential to influence the robustness of the meta-analysis. A meta-analysis was performed with the other four studies for CC vs. CT+TT comparison. The result showed a similar pattern that *IL-17F* 7488T/C variant help protect against asthma (OR=0.12, 95% CI=[0.03, 0.45]), with the overall heterogeneity dropped to zero (**Figure 4**). Subgroup analysis conducted on these four studies by ethnicity also found significant association among Asians (OR=0.10, 95% CI=[0.02, 0.51]) but not Arabians. Similarly, in the subgroup analysis with high quality studies, significant association was also observed for CC vs. CT+TT (OR=0.11, 95% CI=[0.03, 0.45]) (**Table 3**).

Publication bias

No publication bias was detected with Harbord test (P=0.64).

Discussion

IL-17F, an important member of IL-17 cytokine family, contributes to the development of asth-

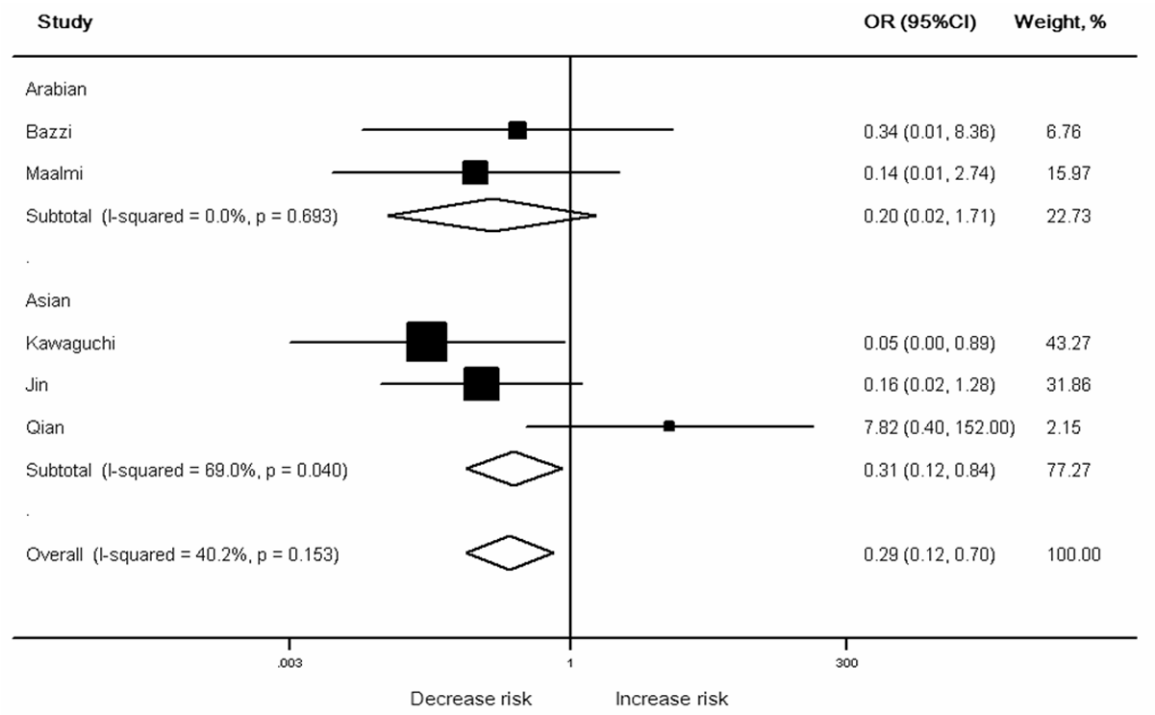

Figure 2. The association of *IL-17F* 7488T/C polymorphism and asthma risk in CC vs. CT+TT (n=5).

Table 3. Meta-analyses of the genetic effect of *IL-17F* 7488T/C polymorphism on asthma

Group	Comparison	Study	Test of association		Heterogeneity		Model	Statistical power
			OR (95% CI)	*P*	I^2 (%)	*P*		
Overall	CC vs. TT	Overall (n=5) [15-19]	0.29 (0.12, 0.72)	0.01	42	0.14	F	0.79
	CT vs. TT	Overall (n=5) [15-19]	1.07 (0.79, 1.45)	0.68	53.7	0.07	R	0.11
	CC vs. CT	Overall (n=5) [15-19]	0.27 (0.11, 0.68)	0.01	31.4	0.21	F	0.82
	CC vs. CT+TT	Overall (n=5) [15-19]	0.29 (0.12, 0.70)	0.01	40.2	0.15	F	0.79
	CC vs. TT	Sensitivity analysis (n=4) [16-19]	0.12 (0.03, 0.45)	<0.01	0.0	0.87	F	0.96
	CT vs. TT	Sensitivity analysis (n=4) [16-19]	1.00 (0.81, 1.23)	0.98	43.6	0.15	F	0.05
	CC vs. CT	Sensitivity analysis (n=4) [16-19]	0.13 (0.03, 0.47)	<0.01	0.0	0.75	F	0.95
	CC vs. CT+TT	Sensitivity analysis (n=4) [16-19]	0.12 (0.03, 0.45)	<0.01	0.0	0.85	F	0.96
High quality	CC vs. TT	Overall (n=4) [15-17, 19]	0.29 (0.04, 2.24)	0.24	56.4	0.08	R	0.76
	CT vs. TT	Overall (n=4) [15-17, 19]	1.08 (0.77, 1.51)	0.66	64.5	0.04	R	0.13
	CC vs. CT	Overall (n=4) [15-17, 19]	0.26 (0.10, 0.69)	<0.01	48.2	0.12	F	0.82
	CC vs. CT+TT	Overall (n=4) [15-17, 19]	0.29 (0.04, 2.14)	0.22	55.1	0.08	R	0.77
	CC vs. TT	Sensitivity analysis (n=3) [16, 17, 19]	0.11 (0.03, 0.45)	<0.01	0.0	0.84	F	0.96
	CT vs. TT	Sensitivity analysis (n=3) [16, 17, 19]	0.96 (0.65, 1.41)	0.83	62.0	0.07	R	0.07
	CC vs. CT	Sensitivity analysis (n=3) [16, 17, 19]	0.11 (0.03, 0.47)	<0.01	0.0	0.66	F	0.96
	CC vs. CT+TT	Sensitivity analysis (n=3) [16, 17, 19]	0.11 (0.03, 0.45)	<0.01	0.0	0.81	F	0.96

ma. As neutrophils play a pathogenic role in severe asthma [23], cytokines including IL-17F involved in the accumulation of neutrophils caught researcher's eyes recently [24]. IL-17F level was found to be correlated with asthma severity [25] and treatment targeted IL-17 pathway could help improve asthma control in patients with high bronchodilator reversibility [26]. Recently, association of *IL-17F* 7488T/C polymorphism with asthma risk caught more attention because of its role in regulation of IL-17F ability. The current meta-analysis demonstrates that homozygote of the *IL-17F* 7488T/C variant, a coding-region sequence variant, is inversely associated with asthma risk.

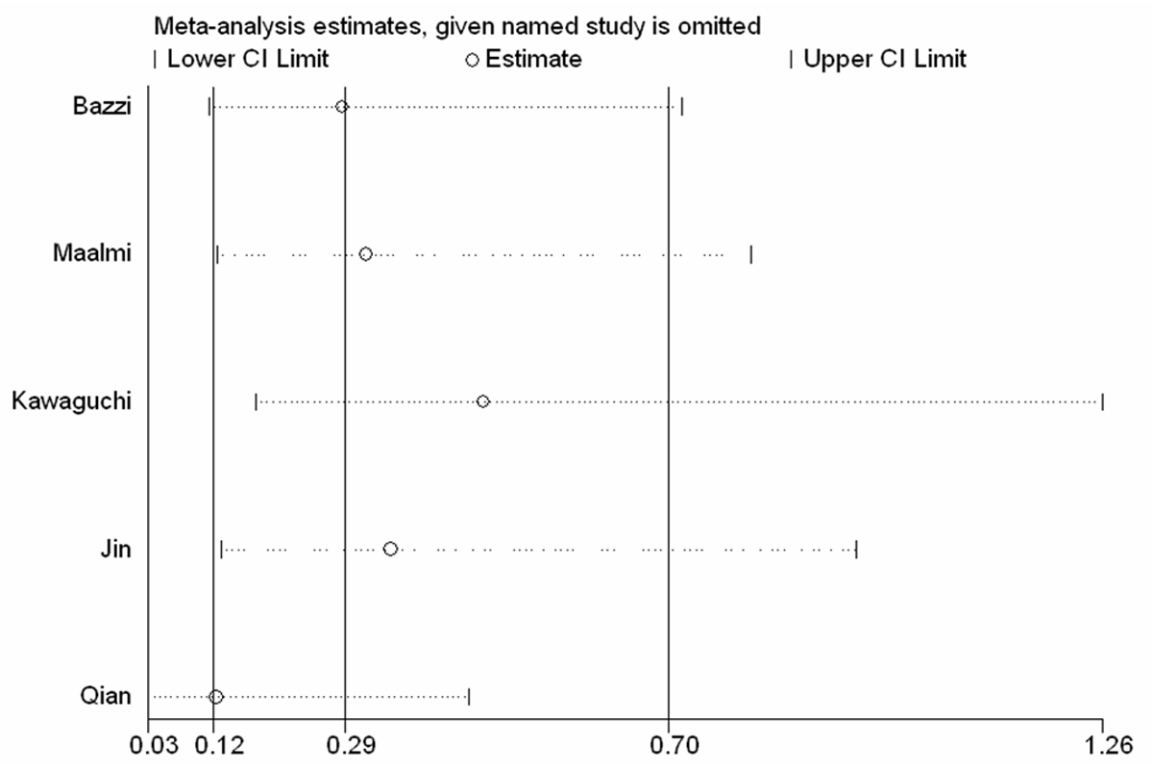

Figure 3. Sensitivity analysis for the *IL-17F* 7488T/C polymorphism with asthma risk.

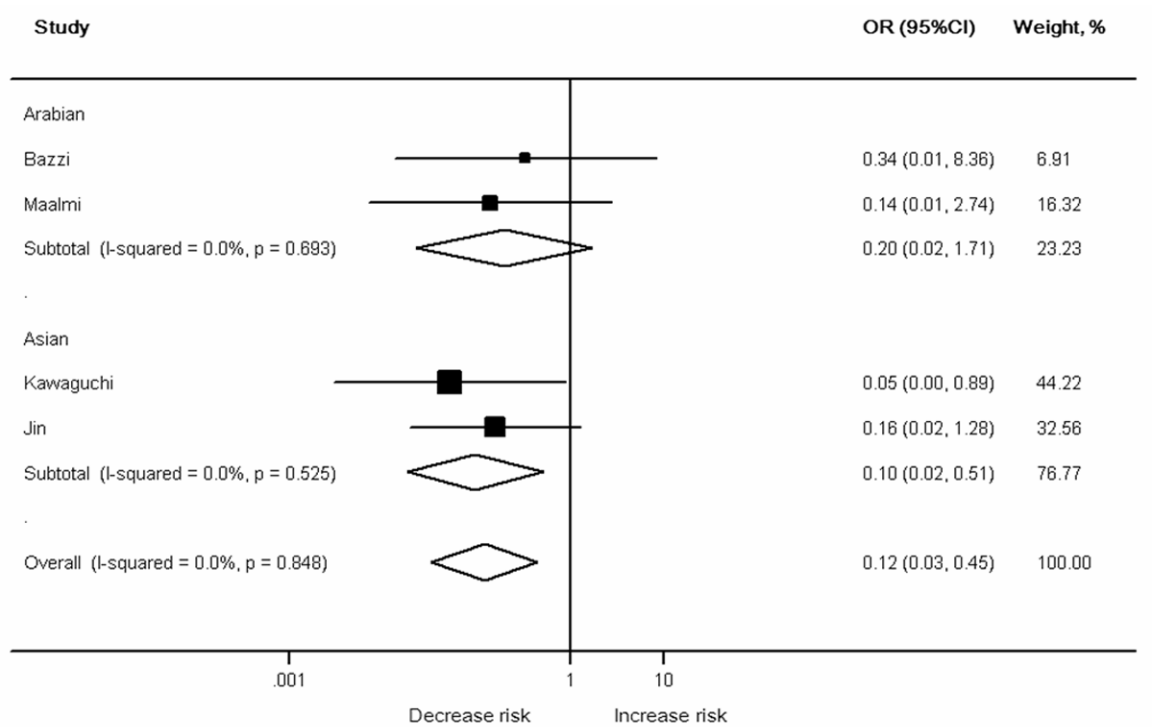

Figure 4. The association of *IL-17F* 7488T/C polymorphism and asthma risk in CC vs. CT+TT (n=4).

The present study, including a total of 1445 cases and 1608 controls, suggested that *IL-17F* 7488T/C polymorphism is inversely associated with development of asthma in a recessive

genetic model, indicating individuals with CC genotype had a lower risk for asthma than those with CT or TT genotype. *IL-17F* sequence variant rs763780 (7488T/C) could cause a His-to-Arg substitution at amino acid 161 (also named H161R), which leads to loss of the ability of IL-17F to induce expression of certain cytokines and chemokines in bronchial epithelial cells.[16] In addition, the muIL-17F protein (Arg161 variant) was found to act as a naturally occurring antagonist of wtIL-17F and could inhibit wtIL-17F-induced IL-8 production in a dose-dependent manner. It could not active Raf-1, MEK1/2, or ERK1/2 in bronchial epithelial cells, either. These findings suggested that homozygote of the *IL-17F* 7488T/C variant might protect against development of asthma through blocking activation of the mitogen-activated protein kinase pathway, certain cytokine production and chemokine production, and counteracting the pro-inflammatory capacity of IL-17F.

Subgroup analysis by ethnicity exhibited significant association between *IL-17F* 7488T/C polymorphism in Asians but not Arabians, which is consistent with the view that the association of gene and disease varies between ethnic groups. This might be the genetic heterogeneity and differences between living environments. Sensitivity analysis was carried out to assess the robustness of this meta-analysis. Removal of each study did not alter the result of decreased asthma risk, though exclusion of Qian's study brought the estimate close to the lower limit of 95% CI of overall effect size. In addition, removal of Qian's study reduced I^2 value effectively, which indicative of that this study might be the major source of the overall heterogeneity. Moreover, no publication bias across the studies was found in the present meta-analysis.

Some limitations must be noted in the current meta-analysis. First, lake of enough studies conducted in each ethnicity limited our further analysis of subgroups. However, the pooled statistical power is 0.79 for the overall analysis. Second, although asthma is a multifactorial disease, both genetic and environmental factors is associated with its development, no sufficient data was available to evaluate the potential interactions between *IL-17F* 7488T/C polymorphism and other SNPs, other susceptible genes, or environmental factors. Third, lake of original data to adjust the pooled estimates by covariant which might influence asthma risk.

In conclusion, the current study suggested that homozygote of *IL-17F* 7488T/C variant could protect against asthma in Asians. However, further studies with standardized defined asthma cased and matched controls, and large sample size is needed to validate these findings in different populations. Moreover, the exact mechanism that could account for the relationship between *IL-17F* 7488T/C polymorphism and the pathogenesis of asthma is needed to be further elucidated.

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Disclosure of conflict of interest

None.

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