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*Original Article*

# Association between *IL-17F* rs763780 polymorphism and susceptibility of asthma: a meta-analysis

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**Abstract:** Published data on the association between interleukin-17F (*IL-17F*) rs763780 polymorphism and asthma susceptibility are inconclusive. To derive a more precise estimation of this association, a meta-analysis was performed. A literature search was conducted in PubMed, Web of Science, Elsevier, Wanfang, and China National Knowledge Infrastructure (CNKI) databases to identify eligible studies. The pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to calculate the strength of association. Sensitivity analysis was performed to evaluate the influence of individual studies on the overall effect estimates and funnel plots were inspected for indication of publication bias. Seven studies with a total of 4200 subjects were finally identified. Overall, we found no significant association between *IL-17F* rs763780 polymorphism and asthma susceptibility (G vs. A: OR = 1.08, 95% CI = 0.81-1.44, *P* = 0.62; GA vs. AA: OR = 1.11, 95% CI = 0.84-1.47, *P* = 0.47; GG + GA vs. AA: OR = 1.07, 95% CI = 0.79-1.44, *P* = 0.65). After categorizing studies into different subgroups on the basis of ethnicity and age, there remained no significant association (all *P* > 0.05). Sensitivity analysis demonstrated the stability of our results and publication bias was not evident. The present meta-analysis, combining all currently available data, suggests that *IL-17F* rs763780 polymorphism is not associated with the susceptibility of asthma.

**Keywords:** *IL-17F*, single nucleotide polymorphism, asthma, meta-analysis

## Introduction

Asthma is a chronic respiratory inflammation disease characterized by airway hyperresponsiveness (AHR) and reversible airway obstruction [1]. It is believed to be a multifactorial disorder with a strong genetic component in its pathogenesis [2, 3]. So far, considerable efforts have been made to evaluate the association between genetic variants and asthma susceptibility, and numerous genes have been identified as asthma susceptible genes [4-6].

Interleukin-17F (*IL-17F*) is a novel proinflammatory cytokine produced by activated mast cells, $CD4^+$ T cells, and basophils cells, in response to infectious and antigenic stimuli [7, 8]. *IL-17F* has a number of biological activities through induction of various cytokines, chemokines and mediators including IL-6, IL-8, transforming growth factor-β (TGF-β), monocyte chemoattractant protein-1 (MCP-1), intracellular adhesion molecule-1 (ICAM-1) and granulocyte macrophage-colony forming factor (GM-CSF) [9, 10]. These molecules play crucial roles in neutrophil recruitment and activation [11, 12]. Furthermore, the expression of *IL-17F* is increased in the sputum and bronchoalveolar lavage (BAL) fluid of asthmatics [13, 14], and its level is correlated with the degree of disease severity [15, 16]. These accumulated data support the idea that *IL-17F* plays an important role in asthma pathogenesis and the *IL-17F* gene may be a susceptibility gene of asthma.

Up to now, a lot of studies of genetic epidemiology have assessed the association of *IL-17F* gene polymorphisms and susceptibility of asthma in different populations [17-23]. Most of them focused on rs763780 (also referred to as -7488A/G). However, these results were inconclusive and inconsistent. Therefore, we performed a meta-analysis of all eligible studies to obtain more precise estimation of the association of *IL-17F* rs763780 polymorphism with asthma susceptibility.

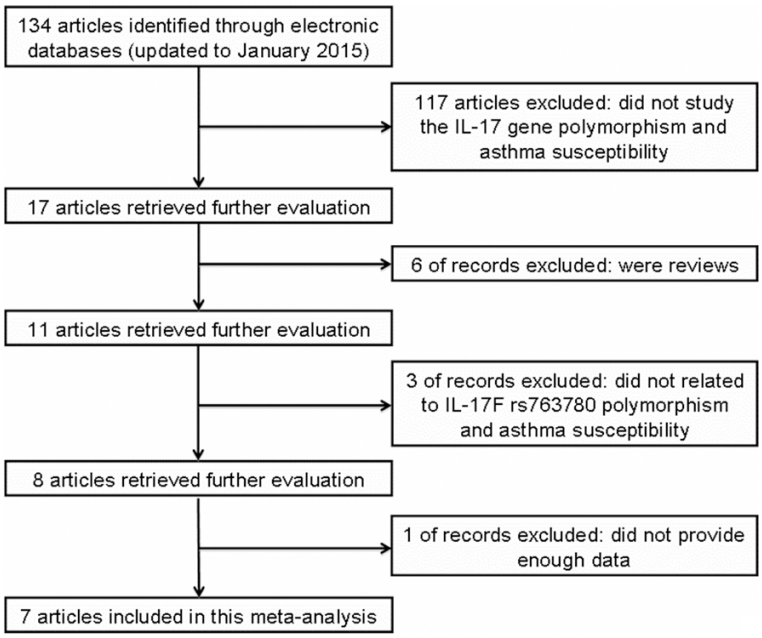



**Figure 1.** Flow diagram of studies included and excluded in the present meta-analysis.

## Methods

### *Publication search*

We conducted an elaborate search for studies that examined the association of *IL-17F* polymorphisms with asthma. Two independent reviewers (Xinming Xie and Xiaofan Su) searched PubMed, Web of Science, Elsevier, Wanfang, and China National Knowledge Infrastructure (CNKI) databases to identify available studies published up to January 2015. The search terms used were "asthma or asthmatic or respiratory hypersensitivity" and "interleukin-17 or IL-17" and "polymorphism or mutation or variant or genotype or SNP". Additional studies were also identified by searching of reference lists from original studies or reviews on this topic. There was no limit on language, sample size, or population for minimizing potential publication bias. Unpublished data were not considered.

### *Selection criteria*

Studies included had to meet all the following criteria: (1) evaluation of the association between *IL-17F* rs763780 polymorphism and asthma susceptibility; (2) a case-control design; (3) sufficient data for calculating the odds ratio (OR) with a 95% confidence interval (CI). The exclusion criteria of the meta-analysis were: (1) non-case-control studies; (2) not relevant to *IL-17F* rs763780 polymorphism or asthma; (3) genotype frequencies or numbers were not offered; (4) editorials, reviews, abstracts and duplication of literatures.

### *Data extraction*

Data were extracted from eligible studies independently by two reviewers (Yang Song and Lan Yang). Discrepancy was resolved by consensus or a third reviewer (Rui Ke). The following information was collected from each study: the first author's name, year of publication, original country, ethnicity, age group, gender, the number of cases and controls, genotype and allele frequency information, and evidence of the Hardy-Weinberg equilibrium (HWE) in controls. We verified accuracy of data by comparing collection forms from each investigator.

### *Quality score assessment*

The quality of studies was assessed by two reviewers (Yang Song and Lan Yang) independently. The quality scoring system is based on both traditional epidemiological considerations and asthma genetic issues recommended by Thakkinstian et al. [24]. Total scores ranged from 0 (worst) to 15 (best). Any disagreement was adjudicated by a third reviewer (Rui Ke). Studies with quality scores < 4 were considered as low quality studies and excluded from our study [25].

### *Statistical analysis*

The summary ORs and corresponding 95% CIs were used to assess the strength of association between *IL-17F* rs763780 polymorphism and asthma susceptibility. The statistical significance of summary ORs was evaluated with the Z test. Heterogeneity among studies was assessed by using chi-square based Cochrane Q-test and $I^2$ index. A fixed effects model was adopted when heterogeneity between studies

**Table 1.** Characteristics of the case-control studies included in meta-analysis

| Author | Year | Country | Ethnicity | Age group | Gender | Case (n) | Control (n) | Quality score |
|---|---|---|---|---|---|---|---|---|
| Ramsey | 2005 | European | Caucasian | Adult | Female | 511 | 516 | 11 |
| Kawaguchi | 2006 | Japan | Asian | Adult | Mix | 432 | 435 | 12 |
| Bazzi | 2011 | Arabia | Caucasian | NA | NA | 100 | 102 | 8 |
| Jin | 2011 | Korean | Asian | Adult | Mix | 424 | 548 | 12 |
| Qian | 2012 | China | Asian | Adult | Mix | 318 | 352 | 13 |
| Maalmi | 2014 | Tunisia | Caucasian | Child | Mix | 171 | 171 | 13 |
| Zhao | 2014 | China | Asian | Child | Mix | 60 | 60 | 9 |

NA, not available.

**Table 2.** Distribution of *IL-17F* genotype among cases and controls

| Studies | Case | | | Control | | | HWE |
|---|---|---|---|---|---|---|---|
| | AA | AG | GG | AA | AG | GG | *P* value |
| Ramsey | 467 | 41 | 3 | 469 | 47 | 0 | 0.2784 |
| Kawaguchi | 332 | 100 | 0 | 347 | 79 | 9 | 0.0821 |
| Bazzi | 93 | 7 | 0 | 93 | 8 | 1 | 0.1088 |
| Jin | 346 | 77 | 1 | 428 | 112 | 8 | 0.8277 |
| Qian | 244 | 71 | 3 | 295 | 57 | 0 | 0.0984 |
| Maalmi | 155 | 16 | 0 | 145 | 23 | 3 | 0.0811 |
| Zhao | 36 | 24 | 0 | 48 | 12 | 0 | 0.3894 |

HWE, Hardy-Weinberg equilibrium.

was not significant. Otherwise, a random effects model was used. Subgroup analyses were performed by ethnicity and age to assess the effect of possible clinical heterogeneity on the summary ORs. Sensitivity analysis was carried out by sequentially excluding individual study. Publication bias was assessed through visual inspection of funnel plots, as well as the Begg's rank correlation test and Egger's linear regression test. Departure from HWE in control group was evaluated by the chi-square test. A *P* value of less than 0.05 was considered statistically significant, except for tests of heterogeneity, where a level of 0.10 was used. All statistical analyses were conducted using Stata 11.0 software (Stata Corporation, College Station, TX, USA).

## Results

### *Study characteristics*

The flow diagram in **Figure 1** summarized the selection process of this literature review. A total of 134 studies were relevant to the search terms. After reviewing the titles, abstracts and articles, 127 studies were excluded. Eventually, we identified seven case-control publications, including 2,016 asthma patients and 2,184 controls, to evaluate the association of *IL-17F* rs763780 polymorphism with asthma susceptibility [17-23]. There were three studies performed in Caucasians [17, 19, 22] and four studies in Asians [18, 20, 21, 23]. Two studies were carried out in children alone [22, 23] and four studies in adults [17, 18, 20, 21]. Polymorphisms in control subjects were in agreement with HWE in all studies ($P > 0.05$). The characteristics of these studies are shown in **Table 1**. The detailed genotype and allele frequencies and HWE examination are listed in **Table 2**.

### *Quantitative synthesis*

A summary of the meta-analysis findings concerning association between *IL-17F* rs763780 polymorphism and asthma susceptibility was provided in **Figure 2** and **Table 3**. Overall, no significant association was observed under the following allele and genotype models (Allele model, G vs. A: OR = 1.08, 95% CI = 0.81-1.44, $P = 0.62$. $I^2 = 66\%$, $P = 0.007$; Heterogeneous model, GA vs. AA: OR = 1.11, 95% CI = 0.84-1.47, $P = 0.47$. $I^2 = 58\%$, $P = 0.03$; Dominant model, GG + GA vs. AA: OR = 1.07, 95% CI = 0.79-1.44, $P = 0.65$. $I^2 = 63\%$, $P = 0.01$). After categorizing studies into different subgroups on the basis of ethnicity and age, the results remained not significant (**Table 3**). The association was not examined using homozygous model (GG vs. AA) and recessive model (GG vs. GA + AA) due to the low frequency of the GG genotype in cases and controls [26].

### *Sensitivity and publication bias analysis*

In order to assess the stability of our results, we performed a sensitivity analysis by omitting

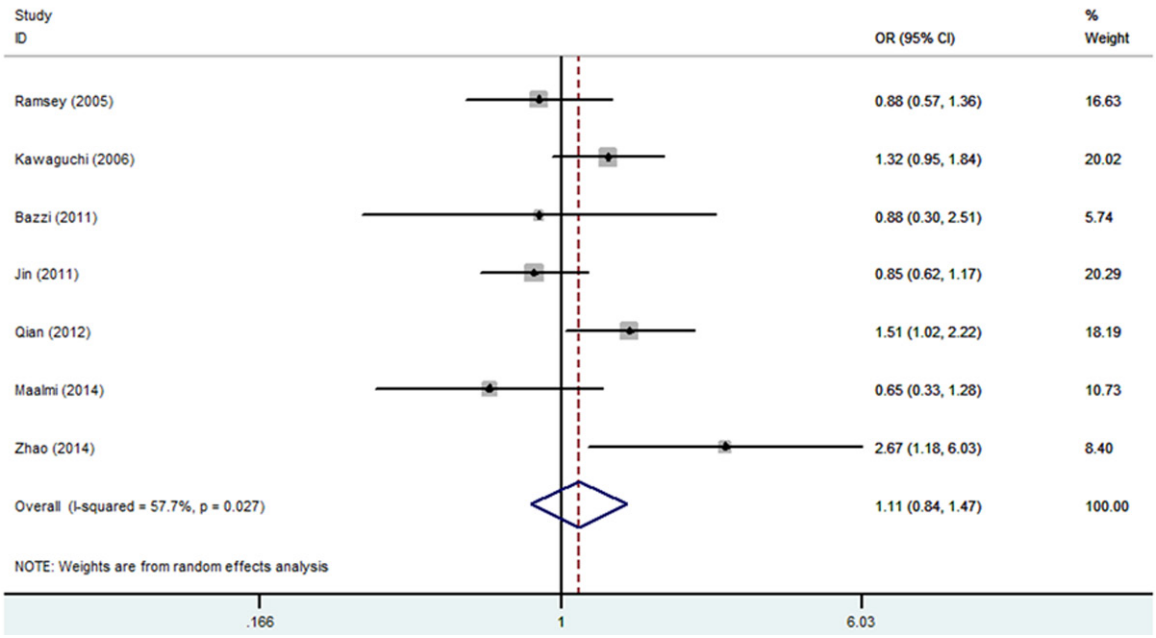



**Figure 2.** Forest plot for the overall association between *IL-17F* rs763780 polymorphism and asthma susceptibility under the GA vs. AA contrast model.

**Table 3.** Summary ORs and 95% CIs of *IL-17F* rs763780 polymorphism and asthma susceptibility

| Genetic comparisons | Population | N | Heterogeneity | | Statistical | Association | |
|---|---|---|---|---|---|---|---|
| | | | $I^2$ (%) | $P_{Het}$ | Model* | OR (95% CI) | $P_{Eff}$ |
| G vs. A | Overall | 7 | 66% | 0.007 | R | 1.08 (0.81-1.44) | 0.62 |
| | Asian | 4 | 76% | 0.01 | R | 1.20 (0.81-1.77) | 0.36 |
| | Caucasian | 3 | 54% | 0.12 | R | 0.90 (0.54-1.50) | 0.67 |
| | Adult | 4 | 65% | 0.03 | R | 1.05 (0.79-1.40) | 0.72 |
| | Child | 2 | 88% | 0.004 | R | 1.08 (0.26-4.44) | 0.92 |
| GA vs. AA | Overall | 7 | 58% | 0.03 | R | 1.11 (0.84-1.47) | 0.47 |
| | Asian | 4 | 69% | 0.02 | R | 1.32 (0.91-1.92) | 0.14 |
| | Caucasian | 3 | 0% | 0.76 | F | 0.81 (0.57-1.15) | 0.23 |
| | Adult | 4 | 58% | 0.07 | R | 1.11 (0.83-1.47) | 0.49 |
| | Child | 2 | 85% | 0.01 | R | 1.29 (0.33-5.15) | 0.72 |
| GG+GA vs. AA | Overall | 7 | 63% | 0.01 | R | 1.07 (0.79-1.44) | 0.65 |
| | Asian | 4 | 74% | 0.01 | R | 1.28 (0.86-1.91) | 0.22 |
| | Caucasian | 3 | 0% | 0.48 | F | 0.81 (0.57-1.13) | 0.22 |
| | Adult | 4 | 61% | 0.05 | R | 1.08 (0.81-1.45) | 0.58 |
| | Child | 2 | 88% | 0.004 | R | 1.22 (0.27-5.46) | 0.80 |

R, random effect model; F, fixed effect model; OR, odds ratio; CI, confidential interval; $P_{Het}$, *P* value of heterogeneity test; $P_{Eff}$, *P* value of pooled effect. *Random effects model was used when $P_{Het} < 0.1$; otherwise, fixed effects model was used.

one study at a time. Statistically similar results were obtained after sequentially excluding each study (**Figure 3**), suggesting the reliability of our meta-analysis. The publication bias in our studies was estimated by Begg's funnel plots and Egger's linear regression test. The Begg's test was used to measure the asymmetry of the funnel plot (**Figure 4**). The results indicated a lack of publication bias for all the genetic models.

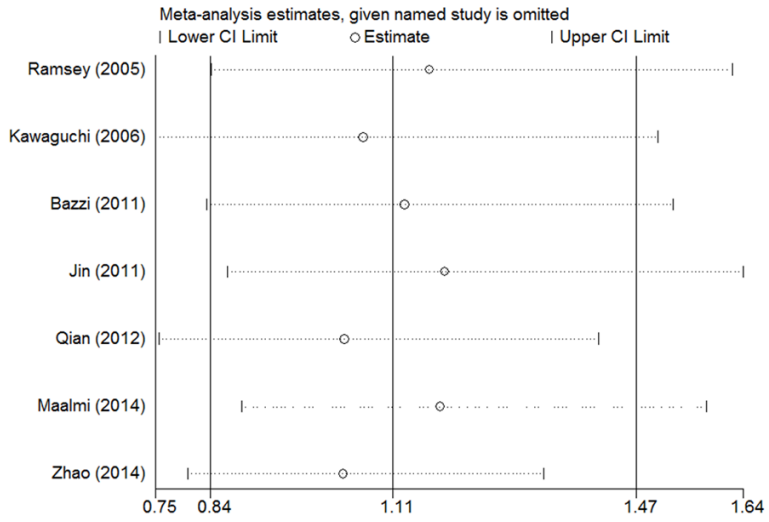



**Figure 3.** One-way sensitivity analysis for the *IL-17F* rs763780 polymorphism with asthma susceptibility under the GA vs. AA contrast model.

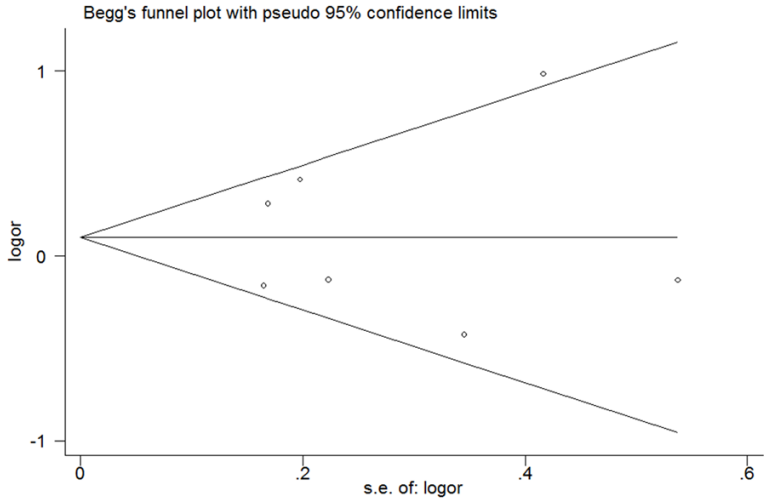



**Figure 4.** Begg's funnel plot for publication bias on asthma susceptibility and the *IL-17F* rs763780 polymorphism under the GA vs. AA contrast model.

## Discussion

To the best of our knowledge, this is the first meta-analysis to assess the association between *IL-17F* gene polymorphism and susceptibility of asthma. Our results indicated that there was no significant effect of *IL-17F* rs763780 polymorphism on asthma susceptibility in overall analyses and subgroup analyses.

Human *IL-17F* gene is present on chromosome 6p and contains three exons [27, 28]. The rs763780 polymorphism located at the third exon of *IL-17F* gene causes a His-to-Arg substitution at amino acid 161 [18]. Functionally, this variant fails to induce cytokines and chemokines, and is able to antagonize the activity of wild-type *IL-17F* [18]. The rs763780 polymorphism of *IL-17F* has been reported to be associated with risk of gastric cancer [29], rheumatoid arthritis [30] and inflammatory bowel disease [31]. Recently, increasing number of studies explored the association of *IL-17F* rs763780 polymorphisms with susceptibility to asthma. Ramsey et al. [17] firstly published their negative findings regarding this issue, and their results were subsequently supported by other researchers, including Jin et al. [20] and Maalmi et al. [22]. In contrast, Bazzi et al. [19] showed that the *IL-17F* rs763780 polymorphism was strongly associated with the risk of asthma, which was consistent with the results of Qian et al. [21] and Zhao et al. [23]. Our meta-analysis provided a more precise estimation based on larger sample size compared with the individual study. The pooled results demonstrated that the *IL-17F* rs763780 polymorphism is not associated with the susceptibility of asthma. There are some feasible explanations for lack of the functional association. As *IL-17F* is a relatively newly discovered cytokine, its role in the inflammatory diseases has not been fully elucidated. The mutant allele in *IL-17F* may have small effects, but tightly linked to other possibly functional polymorphisms within *IL-17F* or other genes involving in the inflammatory response which play more fundamental roles in asthma. In addition, there may be different inflammatory pathways involved in the pathogenesis of atopic and nonatopic asthma [17]. Previous studies have found that *IL-17F* is expressed in cells from the BAL fluid of asthmatics after allergen stimulation, but not from saline-challenged sites [8]. Thus, *IL-17F*

may influence the pathogenesis of atopic asthma, but not nonatopic asthma. However, we did not have complete information on the atopic status of cases and controls to test this hypothesis.

There was significant heterogeneity for *IL-17F* rs763780 polymorphism and susceptibility of asthma among seven studies. After subgroup by ethnicity and age, the heterogeneity was dramatically reduced or disappeared from Caucasian group, and the results remained not significant. Although significant heterogeneity was detected, results from one-way sensitivity analysis suggested high stability and reliability of our results. Moreover, funnel plots and Egger's tests indicated that there was no publication bias in our study.

Several limitations should be taken into account when interpreting our results. First, despite a comprehensive search, the number of studies that qualified for inclusion was modest, and the results might be exposed to interference factors such as random error. Second, only published data was included, leading to possible publication bias in this meta-analysis, despite no statistically significant publication bias was identified. Third, there was significant heterogeneity across study, which might influence the interpretation of the results. Finally, our results were on the basis of unadjusted estimates. The assessment of the gene-gene and gene-environment interactions for asthma might be imprecise on account of failing to get the original data of the eligible studies.

In conclusion, the current meta-analysis indicates that *IL-17F* rs763780 polymorphism is not an independent risk factor for asthma susceptibility. Further large-scale studies are still required to confirm the results.

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## Disclosure of conflict of interest

None.

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