Association between interleukin-17a gene polymorphisms and asthma risk: a meta-analysis

Min Zhu, Ting Wang, Renzhi Chen, Chengdi Wang, Shouzhi Liu and Yulin Ji

Summary

Background: **Interleukin-17A (IL-17A), a proinflammatory cytokine, plays an important role in the pathogenesis of asthma. Considerable research has assessed the association between IL-17A polymorphisms and asthma risk, but the results are inconsistent.**

Objective: **This meta-analysis was carried out to make a more precise estimation of the relationship between IL-17A polymorphisms and asthma risk.**

Methods: **The PUBMED, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure and Wan Fang databases were searched systemically on December 12, 2014 and data were extracted from eligible studies by two independent reviewers. Meta-analysis, sub-group analysis, sensitivity analysis and publication bias assessments were all done using Stata 12.1 software.**

Results: **The IL-17A -737C/T polymorphism and IL-17A -197G/A polymorphism were included in the analysis with seven case-control studies. Asthma patients (n = 2882) and healthy controls (n = 2093) were included. The IL17A -737C/T polymorphism was found to have a significantly protective effect on asthma in the allele model (OR = 0.86, 95% CI 0.78-0.96, *P* = 0.007), dominant model (OR = 0.76, 95% CI 0.65-0.88, *P* <0.001) and heterozygous model (OR = 0.75, 95% CI 0.64-0.88, *P* < 0.001) in the overall analysis. Stratified by ethnicity and age, the effects were also significant in the Asian population and in children. However, for IL-17A -197G/A, no significant association was revealed either in the overall analysis in the ethnicity-special subgroup analysis.**

Conclusions: **The IL-17A -737C/T polymorphism is likely to contribute to protection against asthma, while the IL-17A -197G/A polymorphism may not be associated with asthma susceptibility.** ***(Asian Pac J Allergy Immunol 2016;34:115-23)***

Keywords: *asthma, interleukin-17, genetics, polymorphism, single nucleotide, meta-analysis*

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Introduction

Asthma is a disorder characterized by chronic lower airway inflammation, airway hyperresponsiveness and airway wall remodeling. It leads to recurrent episodes of wheezing, chest tightness, breathlessness and coughing. Around 300 million people in the world suffer from asthma. Furthermore, the incidence is still increasing.[1,2] Asthma is a multifactorial disease triggered by the dynamic interplay of genetic factors and environmental exposure.[3] So far, its exact etiology remains uncertain.

CD4+ T cells have been found to facilitate the initiation and propagation of asthma. The various subgroups (such as Th1, Th2, Th9, Th17 and Treg) secrete different cytokines to join different segments of the immune-inflammation reaction. As an emerging subset of CD4+ T cells, Th17 cells that secrete IL-17 cytokines have recently been found to be associated with asthma.[4]

IL-17A, also known as IL-17, is the hallmark IL-17 family member, first discovered in 1995.[5] IL-17A is increased in the blood, sputum and bronchoalveolar lavage fluid of asthma patients, and positively correlates with asthma severity.[6,7] IL-17A can increase the expression level of proinflammatory cytokines and induce the release of chemokines to promote neutrophil infiltration into the airways.[8] It can also facilitate airway hyperresponsiveness and airway remodeling.[7] Moreover, IL-17A could modulate the activation and proliferation of B cells, thus enhancing IgE production.[9] Collectively, IL-17A plays a role in the pathogenesis of asthma.

Single nucleotide substitutions (SNPs) of cytokine genes are known for having an impact on

the production of cytokines and affecting susceptibility to inflammatory diseases. Whether or not IL-17A gene polymorphisms influence the immune and inflammatory response in asthma is unclear. Thus, unveiling the contribution of IL-17A variants to asthma is required. IL-17A gene is located on chromosome 6p12.1,[10] and carries the polymorphisms rs2275913, rs8193036, rs3819024 and rs4711998. To date, substantial efforts have been made to explore IL-17A polymorphisms and asthma risk. However, these studies have failed to provide sufficient power to yield reliable and consistent results. Meta-analysis, i.e. pooling the collected data from individual studies, is the optimal approach to increase statistical power. Hence, we performed a meta-analysis to explore the association between IL-17A variants and asthma risk.

Methods

Publication search

Two independent reviewers (Z.M. and W.T.) conducted a methodical search on PUBMED, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure (CNKI) and Wan Fang databases to identify potentially eligible studies published before December 12, 2014. Any discordance between the reviewers was resolved by consensus. The search strategy was as follows: ("Interleukin-17" OR "Interleukin17" OR "IL17" OR "IL-17" OR "IL-17A" OR "IL17A") AND ("single nucleotide polymorphism" OR "polymorphism*" OR "genetic polymorphism*" OR "SNP*" OR "mutation*" OR "variant*" OR "genotype*" OR "allele*") AND ("asthma*" OR "allergic asthma*" OR "bronchial asthma*" OR "allergic airway inflammation"). Additionally, reviews and the reference lists of selected articles were perused manually to find further studies. No restrictions with regard to language, publication date, publication status, ethnicity or geographic area were imposed.

Selection criteria and exclusion criteria

All eligible studies were required to comply with the following inclusion criteria: (1) studies that evaluated the correlation between IL-17A polymorphisms and asthma susceptibility; (2) sufficient data on the distribution of genotypes and the frequencies of alleles allowing the calculation of odds ratios (ORs) with corresponding 95% confidence intervals (CIs); (3) the genotype distribution of each control group should be consistent with Hardy-Weinberg equilibrium (HWE); (4) case-control design; (5) the minimum number of studies for each polymorphism was more than three.

Studies meeting any of the following exclusion criteria were excluded: (1) repeated publication; (2) non-clinical studies; (3) reviews; (4) a methodological quality score less than 5. For overlapping or duplicate studies, the most recent and complete one was included. If primary data were not offered in the publication, we contacted the corresponding author for details.

Data extraction

Using a predesigned data collection table, the data were systematically extracted by the two reviewers mentioned above. The data collection form contained the following items: name of the first author, publication year, country and ethnicity of the study population, sample size, age, atopic status, genotyping method, asthma definition, the source of controls, genotype frequency information and evidence of HWE in the controls.

Quality assessment

The methodological qualities of all selection studies were judged by predefined criteria, based on a previous publication (described in detail in Supplementary Table 1.).[11] The quality score ranged from 0 (worst) to 10 (best). The cut-off of 5 classified studies into two levels: low quality studies (≤ 5) and moderate-high quality studies (≥ 6).

Statistical analysis

The HWE in controls was evaluated by the chi-square test. The heterogeneity of studies was evaluated using the Cochrane Q-test, which was considered statistically significant at $P < 0.10$, and was quantified by the inconsistency index (I^2). If the heterogeneity was significant and $I^2 > 50\%$, the random-effect model (DerSimonian and Laird method) was adopted; otherwise, the fixed-effect model (Mantel-Haenszel method) was used.

The ORs and their corresponding 95% CIs were pooled to judge the strength of the association between IL-17A polymorphisms and asthma susceptibility under five genetic models: allelic genetic model (T vs. C), dominant genetic model (CT+TT vs. CC), recessive genetic model (TT vs. CC+CT), homozygous genetic model (TT vs. CC) and heterozygous genetic model (TC vs. CC). The C allele represented the wild type allele and the T allele was the mutant allele in rs8193036. To explore the underlying sources of heterogeneity, stratified analyses were conducted in terms of ethnicity and age. Sensitivity analysis was

Table 1. Characteristics of included case-control studies

First author	Year	country	Ethnicity	Case (n)	Control (n)	Age group	Genotyping method	Asthma definition	SNP type	*P*HWE
Wang1[12]	2009	China	Asian	481	546	child	Taqman	ISAAC	rs8193036 rs2275913	0.62
Wang2[12]	2009	China	Asian	729	202	child	Taqman	ISAAC	rs8193036	0.62
Chen[13]	2010	China	Asian	168	205	child	PCR sequencing	published protocols	rs2275913	0.41
Wang[14]	2011	China	Asian	287	217	child	PCR-LDR	GINA	rs8193036 rs2275913	0.79
Kohyama[15]	2011	Japan	Asian	395	100	adult	SSTEC	GINA	rs8193036	0.39
Schieck[16]	2014	German	Caucasian	651	652	child	MALDI	ISAAC	rs8193036 rs2275913	0.32
Maalmi[17]	2014	Tunisia	African	171	171	child	PCR-PFLP	GINA	rs2275913	0.78
Beloglazov[18]	2014	Ukraine	Caucasian	61	83	adult	PCR	GINA	rs2275913	0.44

GINA: The Global Initiative for Asthma; ISAAC: International Study of Asthma and Allergy in Childhood

MALDI: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

PCR: polymerase chain reaction; PCR-LDR: polymerase chain reaction-ligation detection reaction

PCR-PFLP: polymerase chain reaction-restriction fragment length polymorphism;

SSTEC: sequence-specific thermal-elution chromatography.

performed by excluding each study sequentially to evaluate the influence of an individual study on the combined result. Publication bias was assessed by asymmetry in Begg's funnel plots and Egger's test. All statistical tests were performed using Stata software version 12.1 (Stata Corporation, College Station, TX, USA). A P value < 0.05 for any test or model was considered to be statistically significant unless otherwise specified.

Results

Study characteristics

The selection process is outlined in the flow chart in Figure 1. The inter-rater agreement on studies selection was assessed by the kappa statistic ($\kappa = 0.91$, $P < 0.001$). Only the rs2275913 (IL-17A -197G/A) and rs8193036 (IL-17A -737C/T) polymorphisms were chosen for analysis, and other polymorphisms were excluded for limited study number. After the initial search, seven articles were selected.[12-18] The methodological quality score of Beloglazov's study was only 3, so we excluded it.[18] Furthermore, Wang's 2009 study contained two cohorts, and each cohort was regarded as a case-control study.[12] Ultimately, seven case-control studies, with five studies on IL-17A -197G/A[12-14,16,17] and five on IL-17A -737C/T[12,14-16] were included. A total of 2882 asthma patients and 2093 healthy controls were enrolled. The publication period was from 2009 to 2014. Out of the seven included studies, five were performed in Asian subjects,[12-15] one was conducted in Caucasian subjects [16] and the last one was conducted in African subjects.[17] Only one study on the IL-17A -737C/T polymorphism was performed in adults;[15] the rest were performed in children.[12-14,16,17] Six studies contained both atopic and non-atopic asthmatics.[12,13,15-17] The genotype distributions of controls were all consistent with HWE. The detailed characteristics of the included case-control studies and genotypes with frequencies are listed in Tables 1 and 2, respectively.

The association between the IL-17A -737C/T polymorphism and asthma risk

The association between the IL-17A -737C/T polymorphism and asthma risk was assessed in five studies (2543 asthma patients and 1717 healthy controls). The pooled ORs were conducted in a fixed-effect model with no significant heterogeneity among studies. The analysis of the allele model,

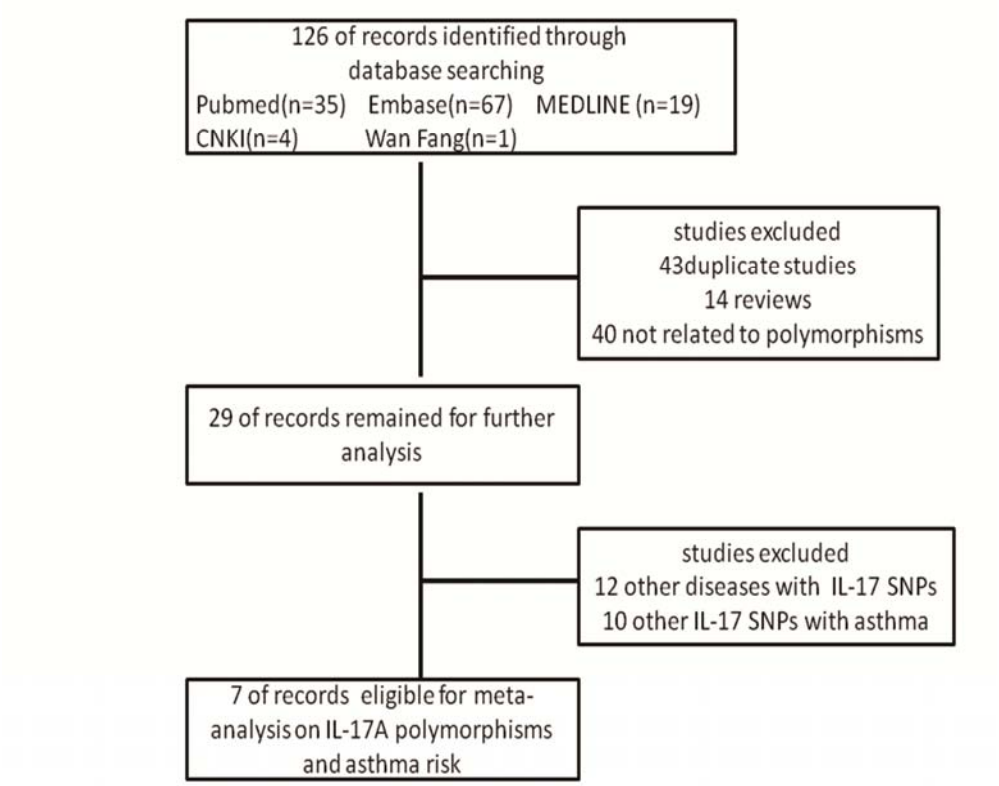

Figure 1. Flow chart of study selection

Table 2. Distribution of IL-17A genotype among asthma patients and controls.

Study	Genotype						Allele			
	Case			Control			Case		Control	
rs2275913	**GG**	**AG**	**AA**	**GG**	**AG**	**AA**	**G**	**A**	**G**	**A**
Wang1[12]	129	234	110	141	251	122	492	454	533	495
Chen[13]	53	65	50	68	105	32	171	165	241	169
Wang[14]	71	151	59	53	110	53	293	269	216	216
Schieck[16]	251	315	85	286	283	83	817	485	855	449
Maalmi[17]	132	39	0	110	55	6	303	39	275	67
rs8193036	**CC**	**CT**	**TT**	**CC**	**CT**	**TT**	**C**	**T**	**C**	**T**
Wang1[12]	285	151	36	273	220	43	721	223	766	306
Wang2[12]	455	238	36	107	78	17	1148	310	292	112
Wang[14]	156	103	25	114	90	13	415	153	318	116
Kohyama[15]	154	198	43	39	50	11	506	284	128	72
Schieck[16]	26	220	405	20	221	411	272	1030	261	1043

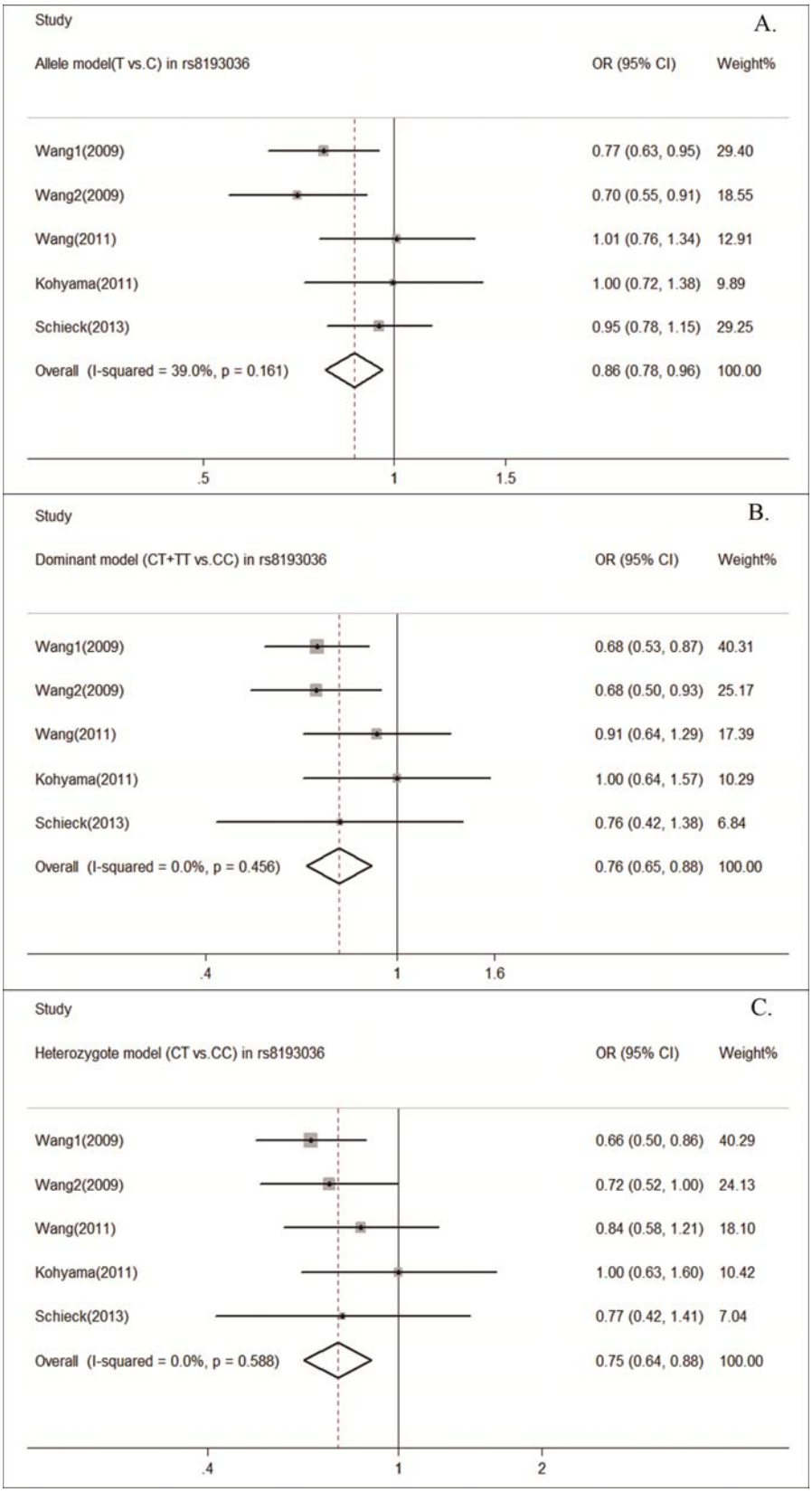

Figure 2. Results of meta-analysis of associations between IL-17A -737C/T (rs8193036) polymorphism and asthma risk. Forest plots for rs8193036 under fixed-effect model in allele model (A.), dominant model (B.), and heterozygote model (C.), respectively.

dominant model and heterozygous model indicated that the IL-17A -737C/T polymorphism reduces asthma risk (T vs. C: OR = 0.86, 95% CI 0.78-0.96, P = 0.007, I^2 = 39%; TT+TC vs. CC: OR = 0.76, 95% CI 0.65-0.88, P < 0.001, I^2 = 0.0%; TC vs. CC: OR = 0.75, 95% CI 0.64-0.88, P < 0.001, I^2 = 0.0%). Similarly, stratification by ethnicity showed the same results in Asian subjects (T vs. C: OR = 0.83, 95% CI 0.73-0.94, P =0.004, I^2 = 42.6%; TT+TC vs. CC: OR = 0.76, 95% CI 0.65-0.89, P = 0.001, I^2 = 17.7%; TC vs. CC: OR = 0.75, 95% CI 0.63-0.88, P = 0.001, I^2 = 0.0%). When stratified by age, the correlation still appeared in children (T vs. C: OR = 0.85, 95% CI 0.76-0.95, P = 0.004, I^2 = 47.3%; TT+TC vs. CC: OR = 0.73, 95% CI 0.62-0.86, P < 0.001, I^2 = 0.0%; TC vs. CC: OR = 0.72, 95% CI 0.60-0.85, P < 0.001, I^2 = 0.0%). Since there was only one study in Caucasians and one in adults, the ethnicity-specific and age-specific analysis were performed only for Asian and juvenile subjects. A summary of these results is shown in Table 3 and Figure 2.

The association between IL-17A -197G/A polymorphism and asthma risk

Overall, 5 studies (1758 asthma patients and 1791 healthy controls) were involved in the evaluation of correlation between IL-17A -197G/A polymorphism and asthma susceptibility. A significant heterogeneity was found among the studies, so random-effect model was adopted. However, there was no significant association between IL-17A -197G/A polymorphism with asthma risk in any genetic model comparisons in the overall population. In the subgroup analysis by ethnicity, no association was observed either. Summary of the results were shown in Table 3 and Supplement Figure 1.

Sensitivity analysis

Sensitivity analysis was conducted to check the stability of the pooled ORs and the contributor to heterogeneity by sequentially deleting individual studies in each SNP genetic model. Consistently, statistically similar results remained when any study was omitted.

Table 3. Summary of the pooled analysis for the association between IL-17A polymorphisms and asthma risk

SNP		IL-17A -737C/T (rs8193036)		IL-17A -197G/A(rs2275913)	
Genetic model	Study	OR (95 % CI), *P*	Heterogeneity (I^2, *P*)	OR (95 % CI), *P*	Heterogeneity (I^2, *P*)
allele model	Overall	0.86(0.78-0.96), 0.007	39%, 0.161	0.99(0.80-1.22), 0.903	74.1%, 0.004
allele model	Asian	0.83(0.73-0.94), 0.004	42.6%, 0.156	1.06(0.86-1.31), 0.590	58.1%, 0.092
allele model	Child	0.85(0.76-0.95), 0.004	47.3%, 0.128		
dominant model	Overall	0.76(0.65-0.88), <0.001	0%, 0.456	0.97(0.76-1.24), 0.817	61.5%, 0.034
dominant model	Asian	0.76(0.65-0.89), 0.001	17.7%, 0.303	1.01(0.82-1.24), 0.917	0%, 0.933
dominant model	Child	0.73(0.62-0.86), <0.001	0%, 0.576		
recessive model	Overall	0.95(0.80-1.14), 0.596	14%, 0.325	1.09(0.74-1.60), 0.675	71.7%, 0.007
recessive model	Asian	0.93(0.69-1.25), 0.637	34.5%, 0.205	1.19(0.70-2.04), 0.522	81.4%, 0.005
recessive model	Child	0.95(0.80-1.14), 0.590	35.3%, 0.201		
homozygote model	Overall	0.82(0.62-1.07), 0.143	20.7%, 0.283	1.10(0.77-1.58), 0.606	58.5%, 0.047
homozygote model	Asian	0.83(0.62-1.13), 0.239	40%, 0.172	1.15(0.72-1.82), 0.563	65.3%, 0.056
homozygote model	Child	0.79(0.59-1.06), 0.119	36.3%, 0.194		
heterozygote model	Overall	0.75(0.64-0.88), <0.001	0%, 0.588	0.96(0.75-1.23), 0.737	57.1%, 0.054
heterozygote model	Asian	0.75(0.63-0.88), 0.001	0%, 0.421	0.97(0.78-1.20), 0.771	0%, 0.654
heterozygote model	Child	0.72(0.60-0.85), <0.001	0%, 0.774		

CI, confidence interval; OR, odds ratio; *P < 0.05.

Publication bias

With such a limited number of studies, we did not choose Begg's funnel plot to detect publication bias. Egger's linear regression test was chosen and showed no publication bias for the association between asthma risk and the IL-17A -737C/T polymorphism or the IL-17A -197G/A polymorphism in any genetic model except for the heterozygous model of IL-17A -197G/A (Egger's Test: t = -3.61, *P* = 0.036).

Discussion

Asthma is a chronic inflammatory disorder, and cytokines provide important contributions to asthma pathogenesis. In this study, we performed a meta-analysis to explore the correlation between IL-17A polymorphisms and asthma risk. The results demonstrate that the IL-17A -737C/T polymorphism has a significantly protective effect on asthma in the allele model, dominant model and heterozygous model in the overall analysis. That is to say, individuals carrying the minor allele T (TT or TC) of the IL-17A -737C/T polymorphism are less likely to suffer from asthma. In the stratified analysis by ethnicity and age, the results in Asian and juvenile subjects were consistent with those of the overall analysis. However, no association was indicated between the IL-17A -197G/A polymorphism and asthma risk.

As a bona fide cytokine, IL-17A has vital effects on the progression of infections, allergic disorders, autoimmune diseases as well as tumors.[19-21] Both IL-17RA and IL-17RC are receptors of IL-17A. However, IL-17A preferentially binds to IL-17RA to IL-17RC.[22] IL-17R transmits biological signaling to subsequent downstream responses via p38 mitogen-activated protein kinases (MAPK), NF-κB and the extracellular signal–regulated kinase (ERK1 and ERK2) signaling pathways, evoking the releasing of proinflammatory cytokines, chemokines, matrix metalloproteinases and other mediators.[10] Then, these proinflammatory cytokines (including IL-1, IL-6 and TNF-α) and chemokines (including CXCL1, ENA-78, CXCL8, MCP-1, and MCP-3) secreted from the airway epithelium, endothelial cells and fibroblasts can activate and recruit neutrophils into the airways.[7] IL-17A also participates in driving airway remodeling by promoting human airway smooth muscle cell proliferation, slackening its apoptosis and enhancing its migration via the p38 MAPK pathway.[23,24] Furthermore, IL-17A not only up-regulates the expression of α-smooth muscle actin gene but also enhances the contractility of smooth muscle in the remodeled airway.[25,26] The increasing secretion of mucus, one hallmark of chronic allergic airway inflammation, as a consequence of increased mucin gene expression, is regulated by IL-1β, IL-6 and IL-17A through the ERK and NF-κB signaling pathways.[27,28] IL-17A thus both initiates and aggravates asthma.

The human IL-17A gene is located on chromosome 6p12.1 with three exons and two introns covering 4,252 bases. The IL-17A -737C/T polymorphism is located at a site -737 bp from the start codon and -692 bp from the start of the IL-17A promoter.[12] Promoter polymorphisms seem to be associated with alterations in transcription factor binding sites and affect the production of coding genes.[29] Although the mechanisms underlying the association between the IL-17A -737C/T polymorphism and asthma have not yet been elucidated, mutation of the IL-17A -737C/T polymorphism in asthmatics may influence the binding affinity of transcription factors controlling the mRNA and protein expression of IL-17A.[30] It is possible that the T allele in the IL-17A -737C/T polymorphism may be associated with a decreased level of IL-17A. As a linked SNP, the IL-17A -197G/A polymorphism may contribute little to the function of IL-17A in asthma patients,[31] although it has been reported in association with other autoimmune disease like rheumatoid arthritis.[32]

Heterogeneity is a vital issue in meta-analysis. When the IL-17A -197G/A polymorphism was under consideration, significant heterogeneity was found in the different models in the overall analysis. After subgroup analysis by ethnicity, heterogeneity was lost from Asian subjects in the dominant model and heterozygous model. Still, no association remained. This shows that ethnicity may account for the source of heterogeneity in certain genetic models. Significant heterogeneity was still observed in the other genetic models under stratified analyses. Asthma is a disorder characterized by heterogeneity and is affected by the interaction of genetic factors and environmental factors. Multiple factors should be taken into account in asthma risk analysis. However, the primary studies did not supply sufficient data for further comprehensive analysis. So, it is probable that potential factors that affect asthma risk may be the true sources of heterogeneity. It should also be considered that heterogeneity can distort results. Based on the

sensitivity analysis presented, the results were found to be stable and robust without influences from heterogeneity.

Egger's test indicated that publication bias was in the heterozygous model of the IL-17A -197G/A polymorphism, but there was no evidence of publication bias regarding the IL-17A -737C/T polymorphism and the IL-17A -197G/A polymorphism in any other genetic model. Meta-analyses are susceptible to potential publication bias since the analysis cannot include unpublished studies; studies that yielded null results are less likely to be reported. As publication bias could affect the results of a meta-analysis, it is necessary to interpret the results of the IL-17A -197G/A polymorphism with caution.

Several inevitable limitations should be taken into account. Firstly, the number of included studies was comparatively small. Secondly, the majority of the included studies were only conducted in Asian and juvenile subjects, with a paucity of data from other ethnicities and ages. Thirdly, the lack of a detailed description of asthma features (such as atopic status, age of onset and disease severity) constrained further subgroup analysis.

In brief, this meta-analysis suggests that the IL-17A -737C/T polymorphism provides protection against asthma susceptibility, while the IL-17A -197G/A polymorphism does not contribute to the risk of asthma. In view of the limitations mentioned above, these results should be verified by more thorough studies with a larger sample size, various ethnicities and adjustments for potentially confounding factors (atopic status, disease severity, smoking, environment, etc.).

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