

Association of interleukin-17a rs2275913 gene polymorphism and asthma risk: a meta-analysis

Cui Zhai, Shaojun Li, Wei Feng, Wenhua Shi, Jian Wang, Qingting Wang, Limin Chai, Qianqian Zhang, Xin Yan, Manxiang Li

Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, China

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Corresponding author:

Prof. Manxiang Li
Department of Respiratory
and Critical Care Medicine
The First Affiliated Hospital
of Xi'an Jiaotong University
277 West Yanta Road
710061 Xi'an, Shaanxi, China
Phone: +86 029 85324053
Fax: +86 029 85324053
E-mail: manxiangli@hotmail.com

Abstract

Introduction: Interleukin-17A (IL-17A), a pro-inflammatory cytokine, plays an important role in the pathogenesis of asthma. A number of studies have investigated the relationship between IL-17A rs2275913 polymorphism and risk of asthma. However, the results obtained are inconclusive. The aim of this meta-analysis is to clarify the relationship between IL-17A rs2275913 polymorphism and asthma risk.

Material and methods: Searches were conducted in PubMed, Web of Science, Elsevier, Google Scholar, Wanfang and Chinese National Knowledge Infrastructure (CNKI) databases, and data were extracted from eligible studies by two independent reviewers. The pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Publication bias, heterogeneity and sensitivity analysis were also assessed.

Results: Ten studies with a total of 5016 subjects were included. Overall, the results indicated a significant association between the IL-17A rs2275913 polymorphism and the risk of asthma (G vs. A: OR = 0.866, 95% CI: 0.789–0.951, $p = 0.003$; GG+GA vs. AA: OR = 0.752, 95% CI: 0.633–0.895, $p = 0.001$). In subgroup analysis by age and ethnicity, the G allele of rs2275913 in IL-17A was significantly associated with a reduced risk of asthma in children and Asians.

Conclusions: The results of this meta-analysis indicate that the G allele of rs2275913 in IL-17A is a protective factor for the development of asthma.

Key words: interleukin-17a, polymorphism, asthma, risk, meta-analysis.

Introduction

Asthma is one of the chronic airway inflammatory diseases in children and adults, characterized by airway hyper-responsiveness (ARH), reversible airflow obstruction, airway remodeling and recurrent symptoms of wheezing, chest tightness and cough [1]. Human asthma is heterogeneous in terms of genetics, severity and in all likelihood pathophysiology [2]. An increasing number of studies have demonstrated a significant relationship between genetic polymorphisms of cytokines and asthma susceptibility [3–6].

Interleukin-17A (IL-17A) is produced by some types of inflammatory cell, including T helper type-17 (Th17), activated mast cells, NK cells, eosinophils cells, neutrophils cells and basophils cells [7–9]. Accumulated studies suggest that IL-17A plays a crucial role in the pathogenesis of asthma. The

levels of IL-17 mRNA and/or proteins are found to be elevated in the lungs, sputum and bronchoalveolar lavage fluids from patients with asthma [10, 11]. The elevation of plasma IL-17A level has been further shown to be associated with asthma severity [11]. A recent study have demonstrated that IL-17A promotes asthma progression by inducing inflammatory cell migration/infiltration and production of other pro-inflammatory cytokines [12].

A number of studies have investigated the association of IL-17A polymorphisms with susceptibility to asthma. Several studies have reported the relationship between IL-17A rs2275913 polymorphism and asthma risk [12–20]. Maalmi *et al.* have shown that the G allele of rs2275913 in IL-17A is associated with an increased risk of asthma [12]. However, Wang *et al.* failed to find an association between IL-17A rs2275913 polymorphism and asthma risk [16]. Due to the contradictory and inconclusive results, we performed this meta-analysis to clarify the correlation between IL-17A rs2275913 polymorphism and asthma risk.

Material and methods

Identification and eligibility of relevant studies

Searches were conducted in PubMed, Web of Science, Elsevier, Google Scholar, Wanfang and Chinese National Knowledge Infrastructure (CNKI) databases to identify available studies published until August 2016. The search terms were: (“interleukin-17” OR “IL-17”) AND (“gene” OR “polymorphism” OR “genetic variant”) AND (“asthma” OR “asthmatic” OR “bronchial asthma”). Furthermore, the reference lists of the eligible studies were identified. No restrictions were placed on language, population, sample size or publication date.

Inclusion and exclusion criteria

Studies included in this meta-analysis were screened according to the following criteria: (1) a case-control study design, (2) evaluation of the association between IL-17A rs2275913 polymorphism and asthma risk, (3) offered sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). The main exclusion criteria of the study were: (1) no usable data offered, (2) non-case-control studies, (3) duplicate papers.

Data extraction

Two reviewers reviewed all eligible studies independently. The following information was collected: first author, year of publication, country, ethnicity, age, numbers of eligible cases and controls, and genotype and allele frequency information. Disagreements were resolved by discussion and consensus.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) in controls was measured using the χ^2 test. The strength of the association between IL-17A rs2275913 polymorphism and asthma risk was assessed by ORs and 95% CIs in an allele model (G vs. A), a codominant model (GG vs. AA, GG vs. GA), a dominant model (GG+GA vs. AA) and a recessive model (GG vs. GA+AA) respectively. The statistical significance of the combined ORs was determined by the Z-test. The χ^2 based Cochrane Q-test and I^2 index were used for the assessment of significant heterogeneity between studies ($p < 0.10$). A random-effects model was performed when heterogeneity was observed in studies. Stratified analyses were adopted by age and ethnicity. Potential publication bias was assessed through Begg's rank correlation test and Egger's linear regression test. The value of $p < 0.05$ was considered statistically significant, except for tests of heterogeneity ($p < 0.10$). All statistical analyses were performed with Stata (version 12.0, Stata Corporation, College Station, TX).

Results

Study characteristics

The detailed process of selection is shown in Figure 1. In total, 1,386 studies met the search criteria in the initial search of databases. Following screening, ten case-control studies [12–21] with 2,510 asthma cases and 2,506 controls were included. As for ethnicity, seven studies investigated Asian populations [13–16, 18–20], two studies investigated African populations [12, 21], and one study investigated a Caucasian population [17]. As for age, seven studies investigated children [12–17, 19], and three studies investigated adults [18, 20, 21]. The genotype frequencies of IL-17A rs2275913 polymorphism in each study are shown in Tables I and II.

Quantitative synthesis

The main results of the relationship between IL-17A rs2275913 polymorphism and asthma risk are listed in Table III. Overall, the results indicated a significant association between IL-17A rs2275913 and asthma (G vs. A: OR = 0.866, 95% CI: 0.789–0.951, $p = 0.003$; GG+GA vs. AA: OR = 0.752, 95% CI: 0.633–0.895, $p = 0.001$). However, no significant association was found in the recessive model (GG vs. GA+AA: OR = 0.879, 95% CI: 0.766–1.008, $p = 0.065$) (Figures 2 and 3).

In addition, subgroup analysis by age showed that the G allele of rs2275913 in IL-17A was associated with a reduced risk of asthma in children (G vs. A: OR = 0.859, 95% CI: 0.692–1.066, $p =$

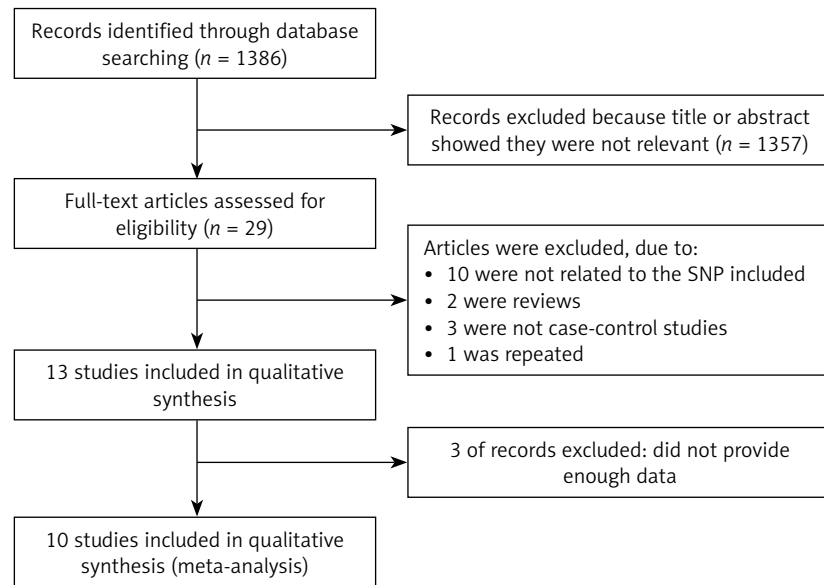


Figure 1. Flowchart showing the process of study selection

Table I. Characteristics of case-control studies included in meta-analysis

Author	Year	Country	Ethnicity	Age group	Gender	Case (n)	Control (n)	Genotyping method
Wang	2009	China	Asian	Child	Mix	931	1027	PCR-RFLP
Chen	2010	China	Asian	Child	Mix	168	205	PCR-RFLP
Wei	2011	China	Asian	Child	Mix	186	198	PCR-RFLP
Wang	2011	China	Asian	Child	Mix	287	217	PCR-LDR
Luo	2013	China	Asian	Adult	Mix	103	48	RT-PCR
Maalmi	2014	Tunisia	African	Child	Mix	171	171	PCR-RFLP
Narbutt	2014	Poland	Caucasian	Child	Mix	166	166	PCR-RFLP
Zeng	2015	China	Asian	Child	Mix	224	150	PCR-RFLP
Du	2016	China	Asian	Adult	Mix	125	132	PCR-RFLP
Resende	2016	Portugal	African	Adult	Mix	192	149	RT-PCR

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

Studies	Case			Control			HWE P-value
	GG	GA	AA	GG	GA	AA	
Wang	129	234	110	141	251	122	0.6178
Chen	53	65	50	68	105	32	0.4145
Wei	53	78	55	62	107	29	0.1160
Wang	71	151	59	53	110	33	0.0602
Luo	29	45	29	14	24	10	0.9614
Maalmi	132	39	0	110	55	6	0.7847
Narbutt	28	43	12	69	74	10	0.0918
Zeng	56	120	48	51	82	17	0.0617
Du	70	60	2	94	21	10	< 0.0001
Resende	69	71	8	94	81	17	0.9397

Table III. Summary ORs and 95% CIs for IL-17F rs2275913 polymorphism and asthma risk

Genetic comparisons	Population	Type of model	Heterogeneity			Test of association	
			I ² (%)	P-value	OR	95% CI	P-value
G vs. A	Overall	Random	66.9	0.001	0.866	0.789–0.951	0.003
	Child	Random	74.8	0.001	0.859	0.692–1.066	0.167
	Adult	Random	41.0	0.183	0.831	0.692–1.133	0.241
	Asian	Random	43.8	0.099	0.794	0.685–0.921	0.002
	African	Random	79.6	0.027	1.373	0.755–2.498	0.299
GG+GA vs. AA	Overall	Random	72.3	< 0.001	0.752	0.633–0.895	0.001
	Child	Random	72.1	0.001	0.607	0.403–0.913	0.016
	Adult	Random	68.8	0.040	1.594	0.552–4.603	0.389
	Asian	Random	74.1	0.001	0.681	0.452–1.026	0.066
	African	Random	48.5	0.164	3.068	0.461–20.410	0.246

0.167; GG+GA vs. AA: OR = 0.607, 95% CI: 0.403–0.913, *p* = 0.016), but not in adults (G vs. A: OR = 0.831, 95% CI: 0.692–1.133, *p* = 0.241; GG+GA vs. AA: OR = 1.594, 95% CI: 0.552–4.603, *p* = 0.389) (Figures 4 and 5).

Furthermore, subgroup analysis by ethnicity revealed that the G allele of rs2275913 in IL-17A was associated with a reduced risk of asthma in Asians (G vs. A: OR = 0.794, 95% CI: 0.685–0.921, *p* = 0.002; GG+GA vs. AA: OR = 0.681, 95% CI: 0.452–1.026, *p* = 0.066). However, no association was found in Africans (G vs. A: OR = 1.373, 95% CI: 0.755–2.498, *p* = 0.299; GG+GA vs. AA: OR = 3.068, 95% CI: 0.461–20.410, *p* = 0.246) (Figures 6 and 7).

Heterogeneity, sensitivity and publication bias analysis

Among the four genetic models, significant heterogeneity was observed in the allele model (G allele vs. A allele) and dominant model (GG+GA vs.

AA) with a *p* < 0.10. After stratifying by age and ethnicity, heterogeneity was still significant in adults, children, Asians and Africans (Table III). Sensitivity analysis was conducted to assess the stability of the results. No material alterations were detected, suggesting the reliability of our results. Furthermore, no significant publication bias was detected by Begg’s test or Egger’s test (all *p* > 0.05).

Discussion

To the best of our knowledge, this is the first meta-analysis to assess the effect of IL-17A rs2275913 polymorphism on risk of asthma. In the present study, ten studies with a total of 5,016 participants (2,510 asthma cases and 2,506 controls) were ultimately identified. The results of this meta-analysis indicate that the G allele of rs2275913 in IL-17A is a protective factor for the development of asthma.

In subgroup analysis by age and ethnicity, the G allele of rs2275913 in IL-17A is significantly as-

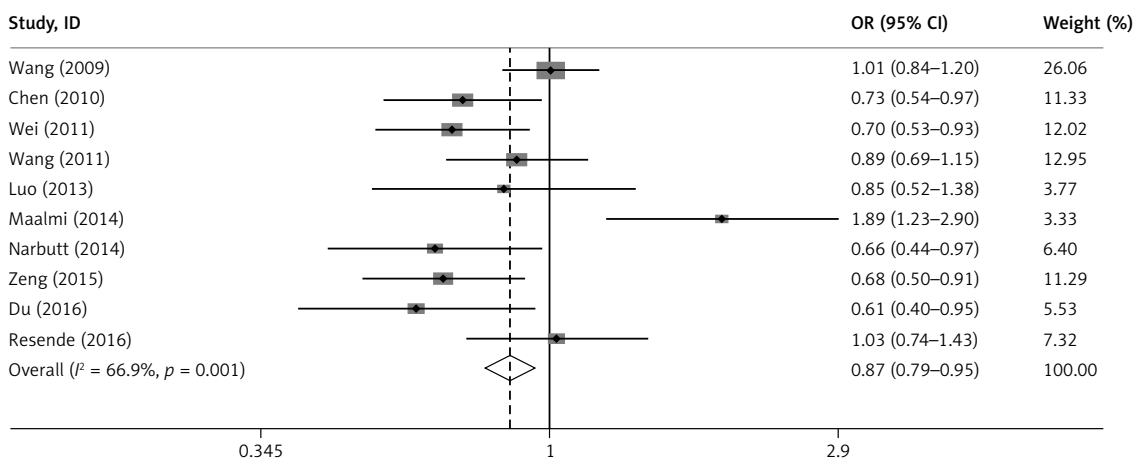


Figure 2. Forest plot for the overall association between IL-17A rs2275913 polymorphism and asthma risk under the G vs. A contrast model

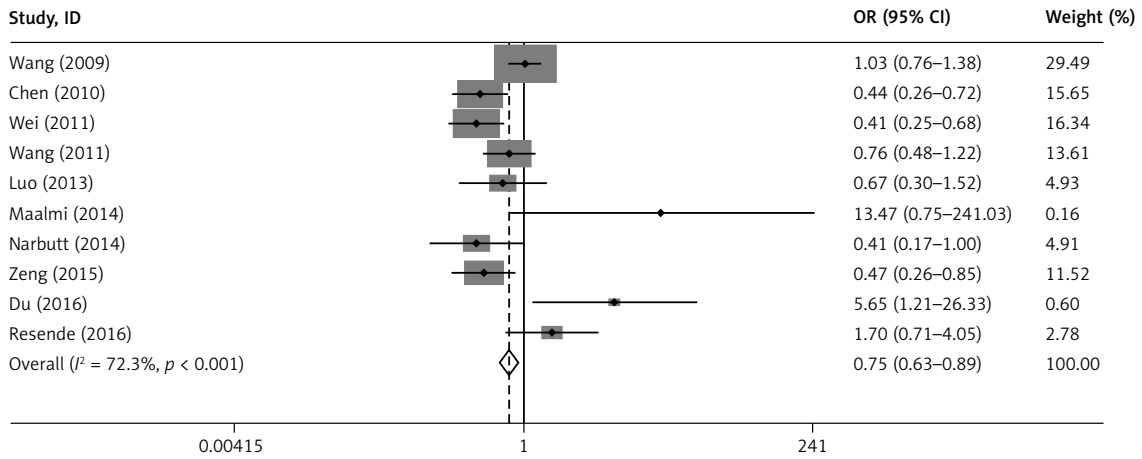


Figure 3. Forest plot for the overall association between IL-17A rs2275913 polymorphism and asthma risk under the GG+GA vs. AA contrast model

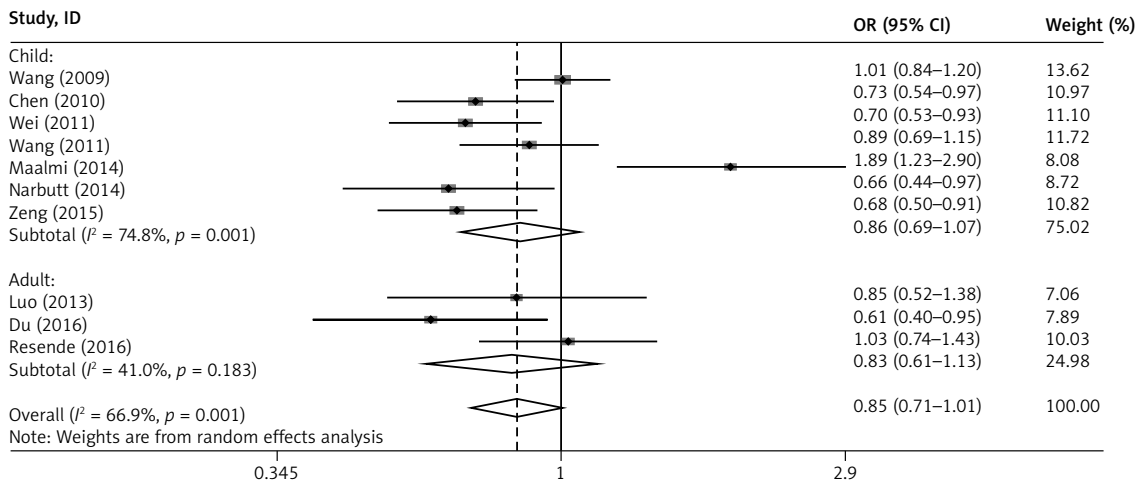


Figure 4. Forest plot of the association between IL-17A rs2275913 polymorphism and asthma risk stratified by age under the G vs. A contrast model

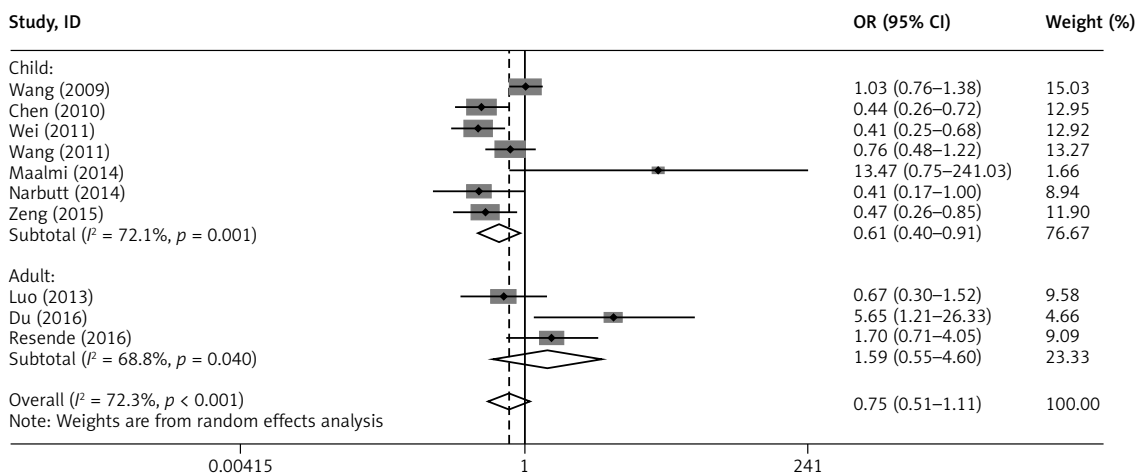


Figure 5. Forest plot of the association between IL-17A rs2275913 polymorphism and asthma risk stratified by age under the GG+GA vs. AA contrast model

sociated with a reduced risk of asthma in children and Asians.

Numerous studies have indicated that IL-17A plays an important role in the development of

infections, autoimmune diseases, tumors and allergic disorders, including asthma [22-24]. It has been shown that IL-17A stimulates the production of a variety of inflammatory mediators,

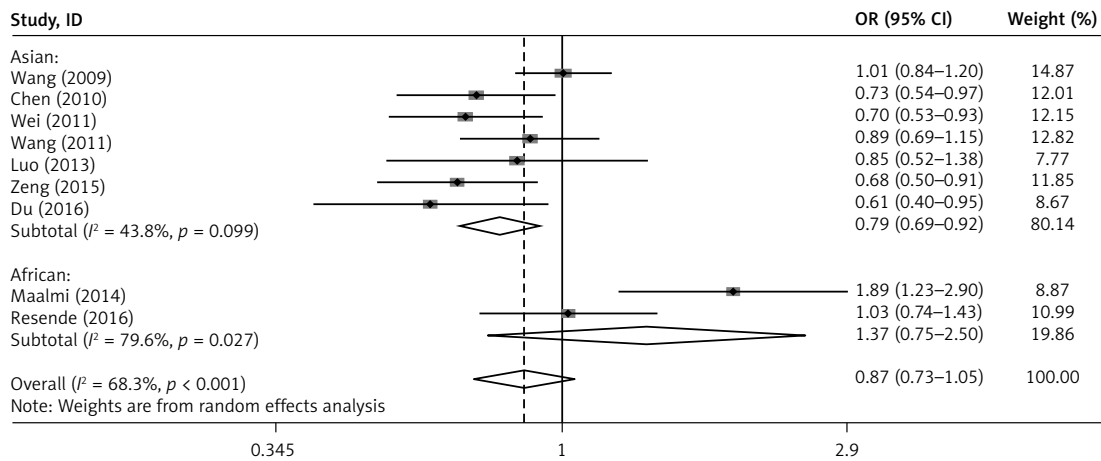


Figure 6. Forest plot of the association between IL-17A rs2275913 polymorphism and asthma risk stratified by ethnicity under the G vs. A contrast model

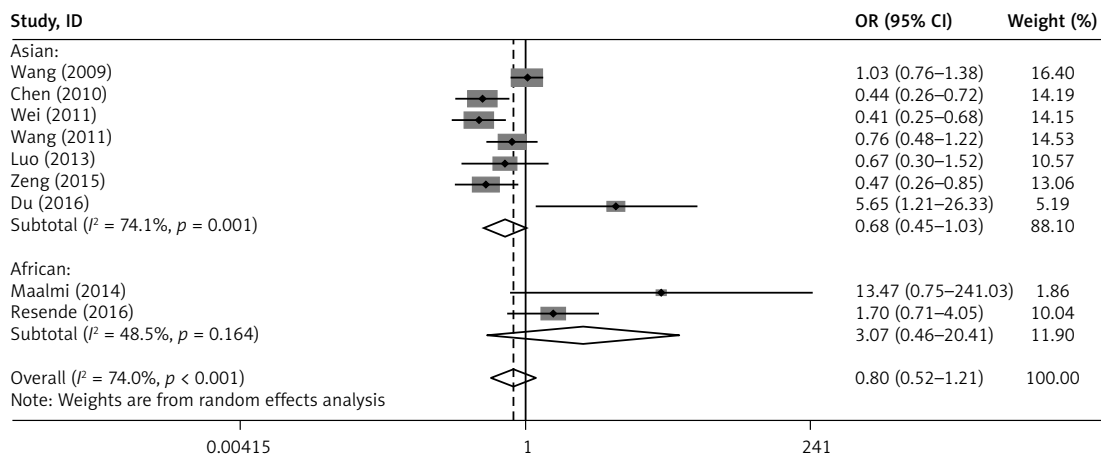


Figure 7. Forest plot of the association between IL-17A rs2275913 polymorphism and asthma risk stratified by ethnicity under the GG+GA vs. AA contrast model

including cytokines, chemokines and adhesion molecules, by bronchial epithelial cells and endothelial cells [25]. Meanwhile, IL-17A induces accumulation of multiple inflammatory cells in the airway mucosa and submucosa to promote asthma development [26, 27]. In addition, IL-17A has been demonstrated to be a potent factor causing airway remodeling by inducing the release of remodeling-associated cytokines (including IL-6, IL-8, IL-11, GM-CSF and VEGF) from airway epithelial cells, endothelial cells and fibroblasts, which promote secretion of mucins by goblet cells, enhance migration/proliferation of airway smooth muscle (ASM) cell and inhibit apoptosis of ASM cells [28–33]. Taken together, IL-17A both initiates and aggravates the pathological process of asthma.

The human IL-17A gene is located on chromosome 6p12.1 [34]. The a allele of rs2275913 in the promoter region of the IL-17 gene has been reported to be associated with risk of ulcerative colitis [35], gastric cancer [36] and atopic dermati-

tis [17]. The a allele of rs2275913 enhances IL-17A promoter activity and promotes its transcription, leading to enhanced inflammation in the airway [37]. However, conflicting research results have been reported on the association between IL-17A rs2275913 polymorphism and IL-17A production. Maalmi *et al.* [12] have found that patients with GG genotype demonstrate mild-to-moderate asthma and low IL-17 levels. Chen *et al.* [14] have shown that IL-17A rs2275913 polymorphism does not affect IL-17A expression level in peripheral blood mononuclear cells (PBMCs).

In this meta-analysis, a more precise conclusion was provided by combining all eligible case-control studies. The results showed that the G allele of rs2275913 in IL-17A was significantly associated with a reduced risk of asthma. Furthermore, subgroup analysis by age showed that the G allele of rs2275913 in IL-17A was associated with a reduced risk of asthma in children, but not in adults. Asthma is believed to be a multifactorial disorder affected not only by genetic predisposition but

also by environmental factors [38, 39]. The discrepancy between children and adults may be caused by the different duration of exposure of asthma patients to environmental risk factors (including contacting allergens and stimulating factors, air pollution, smoking, and occupational exposure) [40]. Subgroup analysis by ethnicity revealed that the G allele of rs2275913 in IL-17A was a protective factor against asthma in Asians, and no association was found in Africans, suggesting that ethnicity affects asthma susceptibility by cytokine polymorphisms, such as IL-17A rs2275913 polymorphism.

Several potential limitations in this meta-analysis should be considered. Firstly, the limited number of studies that qualified for inclusion may lead to relatively insufficient power. Secondly, the majority of the included studies were conducted in Asians and children, with a lack of data from other ethnicities and adults. Thirdly, significant heterogeneity was found between studies. After subgroup analysis by age and ethnicity, the heterogeneity was dramatically reduced for adults, suggesting that a number of factors including differences in age, gender, environment and lifestyle factors affected heterogeneity.

In conclusion, this meta-analysis indicates that the G allele of rs2275913 in IL-17A acts as a protective factor for the development of asthma. Further large-scale and well-designed studies are still needed to confirm our findings.

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Conflict of interest

The authors declare no conflict of interest.

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