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Single-Nucleotide Polymorphisms of *IL-17* Gene Are Associated with Asthma Susceptibility in an Asian Population

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to examine the associations between the single-nucleotide polymorphisms (SNPs) of *interleukin-17* (*IL-17*), including rs763780 (7488A/G), rs2275913 (–197G/A), and rs8193036 (–737C/T), and asthma susceptibility in an Asian population.

Material/Methods: From Oct 2013 to Dec 2014, 125 asthma patients enrolled in our hospital were selected as the case group. Another 132 healthy controls undergoing physical examinations in our hospital were enrolled as the control group. The genotype frequencies of *IL-17* rs763780, rs2275913 and rs8193036 SNPs were detected using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Comprehensive Meta-analysis 2.0 (CMA 2.0) software was applied for meta-analysis.

Results: Our results demonstrated that asthma patients presented with higher frequencies of GA genotype in rs2275913 and TT genotype in rs8193036 of *IL-17* than healthy controls (both $P<0.001$). The genotype frequencies of *IL-17* rs763780 between the asthma patients and healthy controls exhibited no significant differences ($P>0.05$). The comparisons on the rs2275913 and rs8193036 frequencies between the asthma patients and healthy controls were statistically significant in both allele and addictive models (all $P<0.05$). The frequency of *IL-17* rs763780 between the asthma patients and healthy controls were statistically different in allele models ($P<0.05$), but not in addictive models ($P>0.05$). The overall results of our case-control study were further confirmed by meta-analysis.

Conclusions: Our results revealed that, in an Asian population, *IL-17* rs763780, rs2275913, and rs8193036 SNPs may be associated with asthma susceptibility, and GA genotype in rs2275913 and TT genotype in rs8193036 of *IL-17* may contribute to increased risk of asthma in Asians.

MeSH Keywords: Disease Susceptibility • Interleukin-17 • Polymorphism, Single Nucleotide

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Background

Asthma is a complex and common disorder that is characterized by chronic inflammation of the respiratory system, airflow obstruction, and airway hyper-reactivity induced by certain stimulants, such as exercise, infection, allergens, and occupational exposures [1]. As one of the most prevalent chronic diseases, asthma affects more than 30 million people globally, especially children and young adults [2]. In the United State alone, asthma affects more than 23 million adults, and women are more likely to be diagnosed with asthma that imposes greater morbidity than in men [3]. Symptoms of asthma are multifaceted and include wheezing, coughing, hyperpnea, and feeling of suppression in the chest [4]. Previously published evidence suggested that both environmental components and genetic variations may contribute to asthma susceptibility [5]. Recently, the associations between asthma and gene polymorphisms have become an intensive area of research that has generated important insights into the pathogenesis of asthma [6].

Interleukin-17 (IL-17) is a novel pro-inflammatory cytokine family containing 6 distinct isoforms (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F) and 5 receptors (L-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RSEF) [7]. Produced by the T helper 17 (Th17) subsets of CD4+ T cells, IL-17 plays an important role in the development and progression of inflammatory and autoimmune diseases [8]. IL-17 can induce the production of pro-inflammatory cytokines and recruit neutrophils and monocytes, together resulting in an immune-mediated inflammatory reaction through the expression of IL-17 receptors [9]. From a genetic perspective, *IL17* gene is located on human chromosome 6p12.1 [10]. The polymorphisms of *IL-17* are shown to be associated with various autoimmune diseases, including asthma, rheumatoid arthritis and inflammatory bowel disease [11,12]. An increasing number of studies have demonstrated a close relationship between IL-17 and neutrophilic inflammation, implicating *IL-17* as a potential candidate gene in predicting asthma susceptibility [13,14]. Interestingly, an analysis using the Tagger software implemented in the Haploview software according to the Han-Chinese Beijing data set revealed that rs763780 (7488A/G), rs2275913 (-197G/A) and rs8193036 (-737C/T) were found to be commonly associated with asthma [15, 16]. However, conflicting evidence has also been uncovered indicating that not all 3 SNPs were associated with asthma susceptibility [17]. Therefore, we carried out the current case-control study supplemented with a meta-analysis to definitively evaluate the impact of rs763780, rs2275913, and rs8193036 of *IL-17* gene on clinical outcomes in asthma patients.

Material and Methods

Ethical statements

The study design was reviewed and approved by the ethics committee of Huaihe Hospital of Henan University. Written informed consents were obtained from all subjects prior to the study. All procedures in this study were in compliance with the Declaration of Helsinki [18].

Subjects

Form Oct. 2013 to Dec. 2014, 125 asthma patients, comprising 64 males and 61 females in Huaihe Hospital of Henan University, were enrolled as the case group. The mean age for the case group was 39.49±8.61 years (ranging from 25 to 55 years). All asthma patients met the standards of asthma diagnosis as established by the Chinese Thoracic Society, which include: (1) daytime paroxysmal cough or chronic persistent cough; (2) postnasal drip syndrome or pharyngeal mucus; (3) any history of rhinitis, sinusitis, nasal polyps, or chronic laryngopharyngitis; (4) examinations revealed pharyngeal mucus in the posterior pharyngeal wall with formed cobble stone; and (5) the cough was relieved after specific treatments [19]. The inclusion criteria were: (1) age: 24~55 years old; (2) ethnicity: Han; (3) pulmonary function test: positive in bronchial dilation test; and (4) no wheezing, dyspnea, chest distress, or cough symptoms caused by other diseases. The exclusion criteria were: (1) patients with severe complications; (2) patients with heart diseases or complications with liver disease and nephropathy; (3) patients with diseases of the hematopoietic system complicated with tumor diseases; and (4) pregnant or lactating women. In addition, 132 healthy controls (67 males and 65 females) who underwent physical examinations in our hospital were randomly selected as the control group. The age of the control group ranged from 24 to 52 years with a mean age of 38.23±8.45 years.

Sample collection

Ten mL of venous blood were extracted from all subjects after fasting for more than 12 h. The blood samples (4 mL) were anticoagulated with ethylenediaminetetraacetic acid (EDTA) and stored at –70°C. Then the samples were incubated in an upright position for 1 h, followed by centrifuging at 3000 rpm for 10 min at room temperature to isolate the peripheral blood mononuclear cells. Afterwards, the genomic DNA was isolated using a DNA extraction kit (Cat no.: DP318-03, Tiangen Biotech Beijing Co. Ltd., Beijing, China) according to the manufacturer's instructions. The remaining 6 mL blood samples were incubated in an upright position for 1 h and were centrifuged at 3000 rpm for 10 min at room temperature. Subsequently, serum were extracted and stored at –70°C until used.

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Table 1. The PCR primer sequences for *IL-17* single nucleotide polymorphisms.

Gene	SNP	Primer sequences	Length (bp)	Annealing temperature (°C)	Circles
IL-17F	7488 A/G (rs763780)	F: 5'-GTGTAGGAACTTGGGCTGCATCAAT-3' R: 5'-AGCTGGGAATGCAAACAAAC-3'	470	58	30
IL-17A	–197 G/A (rs2275913)	F: 5'-CAGAAGACCTACATGTTACT-3' R: 5'-GTAGCGCTATCGTCTCTCT-3'	344	58	30
IL-17A	–737 C/T (rs8193036)	F: 5'-CCCCCATCATGTCTCCTCTCC-3' R: 5'-CCAAGCAACTTGGTGTTTTGAGG-3'	288	58	30

IL-17 – interleukin-17; PCR – polymerase chain reaction; F – forward; R – reverse; SNP – single nucleotide polymorphism; bp – base pairs.

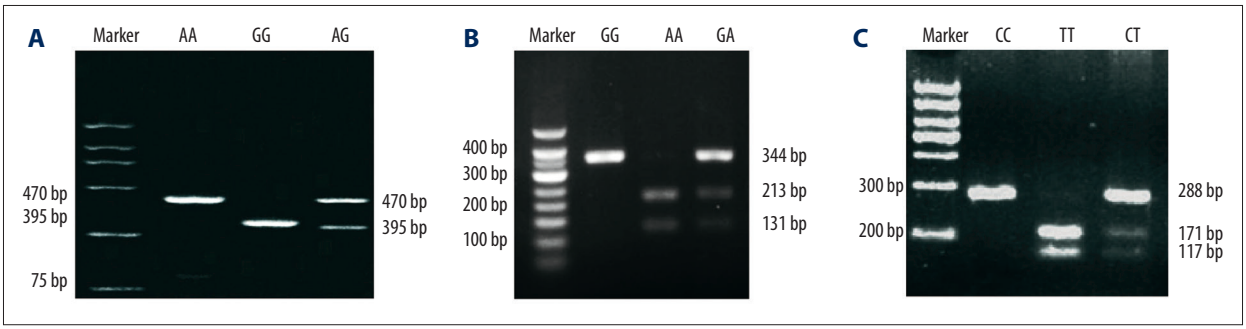

Figure 1. Electropherograms of enzyme digestion for *IL-17* rs763780 (7488A/G), rs2275913 (–197G/A) and rs8193036 (–737C/T) single-nucleotide polymorphisms (**A**: rs763780; **B**: rs2275913; **C**: rs8193036).

SNP detection

Three SNP sites, *IL-17* rs763780, rs2275913, and rs8193036, were selected to conduct the current research. Restriction fragment length polymorphism polymerase chain reaction (PCR-RFLP) was used to analyze the genotype and allele frequency in 3 sites between the case and control groups. The PCR primers were designed using Primer Premier 5.0 software and synthesized by Shanghai Chemical Company (China). The amplification sites, primer sequences, fragment length, annealing temperature, and cycle number for the PCR-RFLP are presented in Table 1. The total volume of PCR reaction included 20 μl: 2 μl of 10×PCR reaction buffer, 2 μl of deoxy-ribonucleoside triphosphate (dNTP) (2.5 mmol/L for each), 0.5 μl of each forward and reverse primer (10 pmol/μl), 2.5 U of Platinum Taq DNA polymerase (Invitrogen, Shanghai, China), and 50 ng of genomic DNA. DNA was amplified during 30 cycles with 5 min predegeneration at 95°C, 30 s denaturation at 95°C, 30 s annealing at 58°C, and 40 s extension at 72°C. Then the DNA was further extended for 5 min at 72°C and stored at 4°C. A total of 20 μl PCR production was extracted to construct the enzyme reaction system. Then the PCR products were digested with restricted enzyme RsaI and XmnI (New England Biolabs LTD., Beijing). After incubation at 21°C overnight, the PCR products were placed in a water bath at 4°C for 15 min to terminate the reaction. Then the enzyme-digested products were electrophoresis-separated by 2% agarose gel (containing ethidium bromide). The gel imaging system (Bio-Rad, USA) was used for genotyping interpretation. The electropherograms of enzyme digestion for *IL-17* rs763780, rs2275913, and rs8193036 SNPs are presented in Figure 1.

Statistical analysis

Statistical analysis was conducted using SPSS 18.0 software (IBM Corporation, Somers, NY, USA). Continuous data are expressed as $\bar{\chi}\pm$ standard deviation (SD), using *t* test or variance analysis for comparisons. Categorical data was presented with percentages and chi-square test was applied for comparisons between groups. Chi-square test was also used to verify whether the genotype distribution of the 3 SNPs met Hardy-Weinberg (HW) equilibrium. The genotype frequency and allele frequency between the case and control were calculated by OR (odds ratio) with 95%CI (confidence interval). All tests were 2-sided and differences were considered statistically significant at $P<0.05$.

Comprehensive Meta-analysis 2.0 (Biostat Inc., Englewood, New Jersey, USA) was used for statistical analysis. The association between *IL-17* SNPs and asthma was assessed using OR with 95%CI under a fixed-effects model or a random-effects model. The Z-test was utilized to determine the significance

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Table 2. Comparisons on the clinical characteristics between case group and control group.

Characteristics	Case group (n=125)	Control group (n=132)	*P*
Age	39.49±8.61	38.23±8.45	0.238
Sex (n,%)			
Male	64 (51.2%)	67 (50.8%)	0.944
Female	61 (48.8%)	65 (49.2%)	
Smoking history (n,%)			
Yes	45 (36.0%)	33 (25.0%)	0.055
No	80 (64.0%)	99 (75.0%)	
Family history of cancers (n,%)			
Yes	37 (29.6%)	26 (19.7%)	0.065
No	88 (70.4%)	106 (80.3%)	
Alcohol history (n,%)			
Yes	51 (40.8%)	39 (29.5%)	0.059
No	74 (59.2%)	93 (70.5%)	
FEV1	65.92±15.67	95.81±16.40	<0.001

FEV1 – forced expiratory volume in the first second of expiration.

of the pooled ORs. Forest plots were drawn to reflect the comparisons among groups.

Results

Comparisons on baseline characteristics

The clinical characteristics of the study participants are summarized in Table 2. No significant difference was found between the asthma patients and healthy controls in terms of age and sex (both $P>0.05$). The case group had elevated percentages of patients with a smoking history, a family history of cancers, and a history of alcohol consumption compared with the control group, although no statistical significance was achieved (all $P>0.05$). However, the FEV1 was significantly lower in the case group than the control group ($P<0.001$).

Genotype distribution

The genotype frequencies and allele frequencies of *IL-17* 7488A/G (rs763780), –197G/A (rs2275913) and –737C/T (rs8193036) are presented in Table 3. The genotypes constructed from the genotype frequencies and allele frequencies met Hardy-Weinberg equilibrium and were representative of the case that emerged. Our results revealed that the asthma patients presented with higher frequencies of the GA genotype in rs2275913 and the TT genotype in rs8193036 of *IL-17* compared to healthy controls (both $P<0.001$); however, the genotype frequency of *IL-17* rs763780 between the asthma patients and healthy controls failed to achieve statistical significance ($P>0.05$). The comparisons of the rs2275913 and rs8193036 frequencies between the asthma patients and healthy controls were statistically significant in both allele and additive models (all $P<0.05$). The frequency of *IL-17* rs763780 between the asthma patients and healthy controls were statistically different in the allele model ($P<0.05$), but not in the additive model ($P>0.05$).

Meta-analysis results

The present meta-analysis enrolled 12 eligible case and control studies [13,14,17,20–28], including 3575 asthma patients and 3671 healthy controls. A total of 6 studies investigated the association between the *IL-17* 7488A/G (rs763780) SNP and asthma, which demonstrated that *IL-17* 7488A/G (rs763780) SNP may increase asthma risk in allele models (OR=0.667, 95%CI=0.489-0.908, $P=0.010$), but not additive models (OR=0.693, 95%CI=0.453-1.060, $P=0.091$) (Figure 2). The association between *IL-17*–197G/A(rs2275913) SNP and asthma was investigated in 4 studies, which revealed that the *IL-17*–197G/A (rs2275913) polymorphism may elevate the risk of asthma in both allele and additive models (allele model: OR=0.764, 95%CI=0.607-0.961, $P=0.021$; additive model: OR=0.639, 95%CI=0.436-0.937, $P=0.022$) (Figure 3). A total of 4 studies explored the association between *IL-17*–737C/T (rs8193036) SNP and asthma susceptibility. The results in allele and additive model suggested that *IL-17*–737C/T (rs8193036) SNP may enhance the risk of asthma (allele model: OR=0.807, 95%CI=0.722–0.903, $P<0.001$; additive model: OR=0.751, 95%CI=0.648–0.870, $P<0.001$) (Figure 4).

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Table 3. Comparisons on the gene frequencies among the three site of *IL-17* single nucleotide polymorphism.

SNP	Control group (n=132)		Case group (n=125)		*P*	OR	95% CI
rs763780 (A>G)							
AA	111	(84.1%)	114	(91.2%)	Ref		
AG	19	(14.4%)	11	(8.8%)	0.15	1.774	0.807~3.899
GG	2	(1.5%)	0	(0.0%)	0.154	5.135	0.244~1.082
AA+AG	130	(98.5%)	125	(100.0%)	Ref		
GG	2	(1.5%)	0	(0.0%)	0.167	0.208	0.010~4.378
A	241	(91.3%)	239	(95.6%)	Ref		
G	23	(8.7%)	11	(4.4%)	0.049	0.482	0.230~0.911
rs2275913 (G>A)							
GG	70	(53.0%)	94	(75.2%)	Ref		
GA	60	(45.5%)	21	(16.8%)	< 0.001	3.837	2.136~6.891
AA	2	(1.5%)	10	(8.0%)	0.077	0.269	0.057~1.265
GG + GA	130	(98.5%)	115	(92.0%)	Ref		
AA	2	(1.5%)	10	(8.0%)	0.014	5.652	1.213~26.340
G	200	(75.8%)	209	(83.6%)	Ref		
A	64	(24.2%)	41	(16.4%)	0.028	0.613	0.396~0.950
rs8193036 (C>T)							
CC	55	(41.7%)	44	(35.2%)	Ref		
CT	75	(56.8%)	65	(52.0%)	0.762	0.923	0.550~1.548
TT	2	(1.5%)	16	(12.8%)	< 0.001	10.00	2.181~45.85
CC + CT	130	(98.5%)	109	(87.2%)	Ref		
TT	2	(1.5%)	16	(12.8%)	< 0.001	9.541	2.146~42.430
C	185	(70.1%)	153	(61.2%)	Ref		
T	79	(29.9%)	97	(38.8%)	0.034	1.485	1.029~2.141

IL-17 – interleukin-17; SNP – single nucleotide polymorphism; *P* – *P* value; OR – odds ratio; CI – confidence interval; Ref – reference.

Discussion

Our study interrogated the associations between rs763780, rs2275913 and rs8193036 SNPs in *IL-17* gene and asthma susceptibility in an Asian population. Asthma is an inflammatory and immune disease mediated by aberrant Th2 immune responses induced by excessive stimulation of exogenous factors, which engages the IgE receptor to elicit the secretion of pro-inflammatory cytokines, including IL-17, TNF-α, IL-1β, and IL-6 [29]. Emerging evidence supports that IL-17 is closely involved in the pathologies of the airway asthmatics. Indeed, functional analysis demonstrated that overexpression of IL-17F in a mouse model with increased numbers of neutrophils in the airways resulted in antigen-induced allergic inflammatory responses, whereas IL-17F-deficient mice had defective airway neutrophilia responding to allergen challenge [24]. The ability of IL-17A and IL-17F to induce neutrophils migration suggests that they are involved in severe asthma, in which accumulation of neutrophils in the airways is a major defining hallmark [16]. This is consistent with the role of IL-17 in enhancing the activation of bronchial fibroblasts, epithelial cells, and smooth muscle cells and in inducing the secretion of cytokines and chemokines, which in concert leads to the accumulation of neutrophils with proteolytic enzymes that may burden the airway [30].

The most important finding in our study was that rs763780, rs2275913 and rs8193036 SNPs were closely associated with

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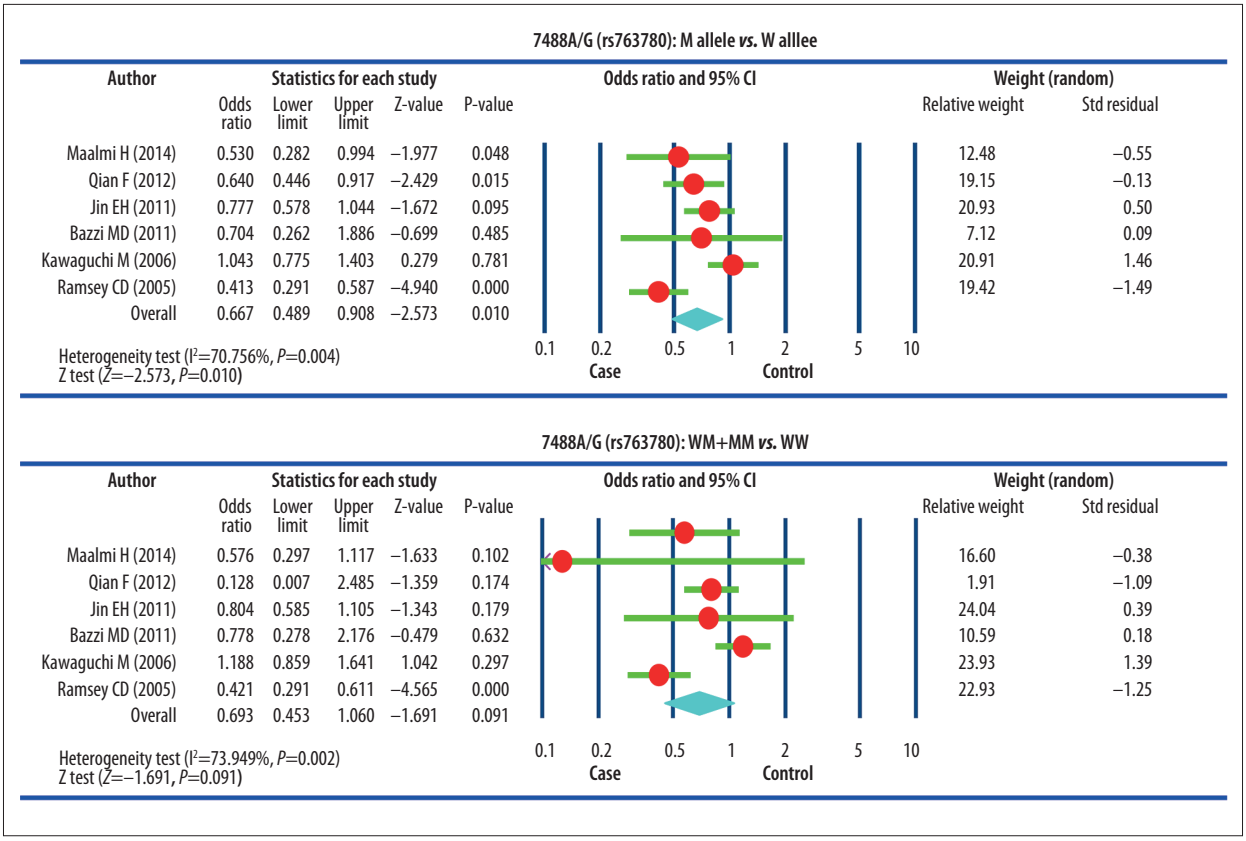

Figure 2. Forest plots investigating the association between *IL-17* rs763780 (7488A/G) single-nucleotide polymorphism and asthma susceptibility. M stands for G and W stands for A.

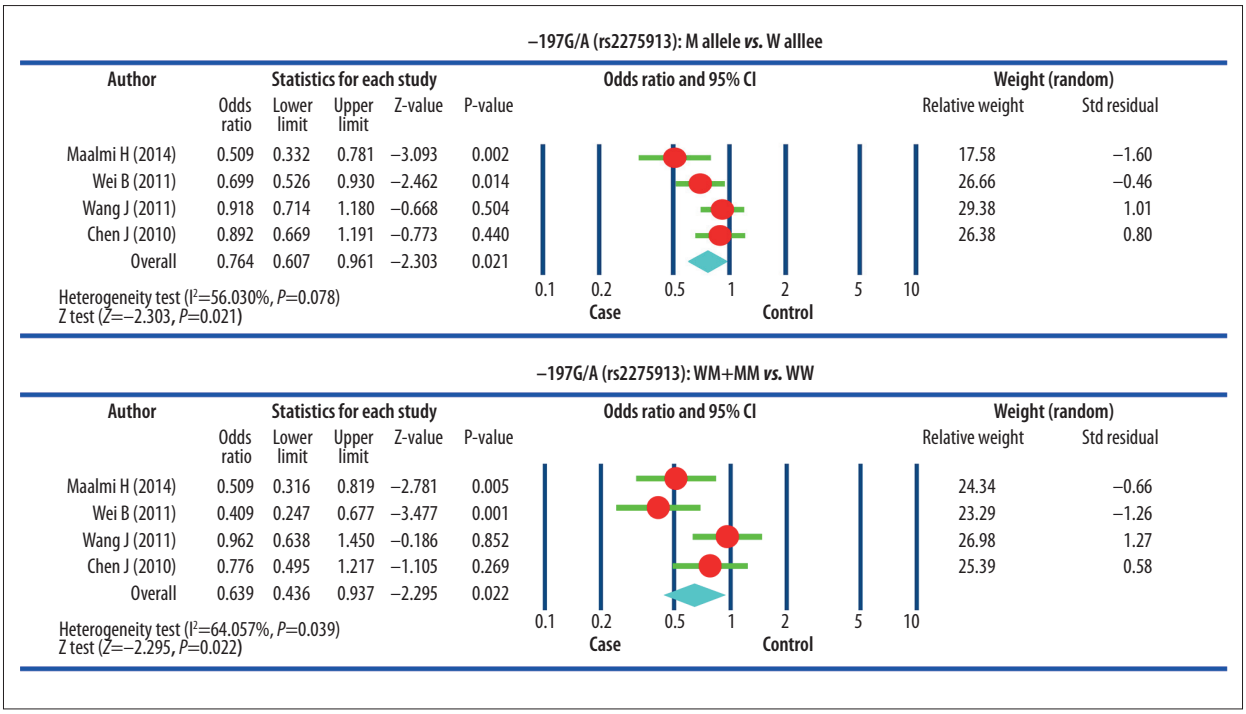

Figure 3. Forest plots investigating the association between *IL-17* rs2275913 (−197G/A) single-nucleotide polymorphism and asthma susceptibility. M stands for A and W stands for G.

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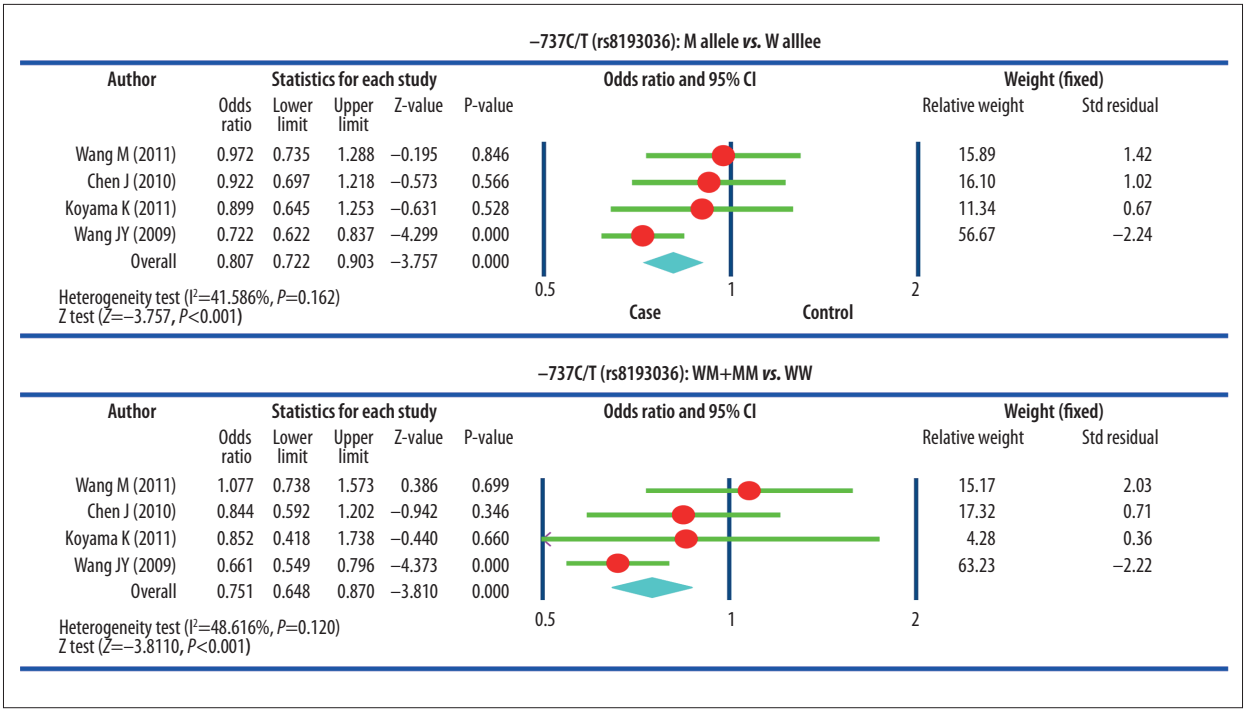

Figure 4. Forest plots investigating the association between *IL-17* rs8193036 (–737C/T) single-nucleotide polymorphism and asthma susceptibility. M stands for T and W stands for C.

asthma susceptibility. Consistent with our results, Kenya Kohyama et al. conducted a genetic analysis investigating the association between asthma and common variants *IL-17* and *IL-13*, indicating that *IL-17* may play a role in the etiology of asthma because the *IL-17A* rs8193036 sequence variations significantly influence the risk of asthma [13]. A close association between rs8193036 in the *IL17A* promoter region and pediatric bronchial asthma was also reported in a Taiwanese population [27]. The SNP rs2275913, located at position 152 bp upstream of the starting site of IL-17 mRNA, has been reported to influence the susceptibility and pathophysiological features of ulcerative colitis [31]. In addition, Chen et al. demonstrated that *IL-17* SNP rs2275913 was implicated in several asthma-related traits that confer genetic susceptibility to childhood asthma [21]. Our study also found that the frequencies of *IL-17* rs763780 in the asthma patients and healthy controls were statistically different in allele models. Intriguingly, a study conducted in Saudi Arabia suggested no significant association between *IL17F* SNPs and asthma risk, except for the AG heterozygotes of rs17880588 in *IL17A* [20]. However, Qian F et al. indicated that the C allele of rs763780 in *IL17* was associated with an increased risk of asthma [24]. This discrepancy may be explained by the different genetic backgrounds and distinct environmental exposures.

Conclusions

Our study provides compelling evidence that *IL-17* SNPs (rs763780, rs2275913, and rs8193036) may be associated with asthma susceptibility. Our study combined a carefully designed case-control study with a large sample size and carried out a meta-analysis using data from previously published studies. However, our results must be interpreted with caution because more prospective studies with larger sample size and diverse populations are needed to validate the association between *IL-17* SNPs and the development of asthma.

Acknowledgement

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Declaration of interest

The authors declare no conflicts of interest.

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