



Short Communication

Association of *interleukin-13* SNP rs1800925 with allergic rhinitis risk: A meta-analysis based on 1,411 cases and 3169 controls

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ABSTRACT

Studies investigating the association between *interleukin-13* (*IL-13*) single nucleotide polymorphism (SNP) rs1800925 and allergic rhinitis risk have reported conflicting results. The aim of the present study was to conduct a meta-analysis assessing the possible association of *IL-13* SNP rs1800925 with allergic rhinitis risk. The relevant studies were identified through a search of PubMed, Embase, ISI Web of Knowledge and Chinese National Knowledge Infrastructure until December 2011 and selected on the basis of the established inclusion criteria for publications. Five studies were included in the present meta-analysis (1411 cases and 3169 controls). The combined results based on all studies showed that *IL-13* SNP rs1800925 was not associated with increased allergic rhinitis risk (T versus C: odds ratio (OR) = 1.06, 95% confidence interval (CI) = 0.94–1.20; C/T versus C/C: OR = 1.12, 95% CI = 0.97–1.29; T/T versus C/C: OR = 1.00, 95% CI = 0.69–1.44; C/T + T/T versus C/C: OR = 1.10, 95% CI = 0.96–1.27; T/T versus C/C + C/T: OR = 0.91, 95% CI = 0.64–1.31). This meta-analysis supported that *IL-13* SNP rs1800925 was not associated with allergic rhinitis.

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1. Introduction

Allergic rhinitis (AR) is an atopic disease, which is characterized by high serum levels of immunoglobulin E (IgE), overproduction of T helper type 2 (Th2) cytokines, and selective eosinophil accumulation in the nasal mucosa (Kay, 2001). The development of AR generally entails the complex interaction between genetic predisposition and environmental exposure to different factors, of which the most important is the implicated allergen (Davila et al., 2009). Despite environmental exposures play important roles in the development of atopy, there is a strong inherited susceptibility in the etiology and pathogenesis of AR. Accumulating evidence indicates that genetic polymorphisms have also been extensively investigated to identify inherited genetic risk for AR (Wang, 2011).

Interleukins-13 (*IL-13*), which is a critical immunoregulatory cytokines produced by activated Th2 cells and can switch B cells to produce IgE, plays a pivotal role in the development of AR (Gelfand, 2004). With respect to the *IL-13* gene located on chromosome 5q31, numerous single nucleotide polymorphisms (SNPs) have been identified. Among these SNPs, *IL-13* SNP rs1800925 is a common SNP in the promoter region, which caused C to T transition at position –1112/1024/1055 (Cameron et al., 2006). Interindividual variation in the

IL-13 SNP rs1800925 has been investigated in relation to AR in ethnically diverse groups.

Many studies have evaluated the potential role of *IL-13* SNP rs1800925 in the development of AR. The first study (Wang et al., 2003) conducted by Wang et al. suggested that the *IL-13* SNP rs1800925 was not associated with a risk to develop AR. Conversely, the study (Llanes et al., 2009) conducted by Llanes et al. demonstrated that the risk of AR was associated with the *IL-13* SNP rs1800925. A series of related studies were carried out later, however, results were generally inconsistent and inconclusive. Concerning the *IL-13* SNP rs1800925 in AR, a recent meta-analysis (Bunyavanich et al., 2011) have reported that the T allele of *IL-13* SNP rs1800925 was not related to the risk of AR. Careful examination of the meta-analysis revealed that two otherwise eligible case–control studies had not been taken into account, on the other hand, only allele analysis was performed, without concerning genotype analyses. Therefore, we conducted this updated meta-analysis that might increase statistical power to address the possible associations of *IL-13* SNP rs1800925 with AR risk.

2. Materials and methods

2.1. Literature search strategy

Eligible studies published up to December 2011, were identified by a search of PubMed, Embase, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure, with a combination of the following keywords: “*IL-13*,” “*interleukin-13*,” “polymorphism,” “SNP,” “*IL-13* SNP rs1800925,” and “allergic rhinitis.” The search was done

Abbreviations: *IL-13*, *interleukin-13*; AR, allergic rhinitis; OR, Odds ratio; CI, Confidence interval.

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Table 1Characteristics of all studies included in the meta-analysis *IL-13* SNP rs1800925.

Author (year)	Ethnicity (country)	Cases	Controls	Cases					Controls					HWE of controls
				CC	CT	TT	C	T	CC	CT	TT	C	T	
Wang et al., 2003	Asian China	188	87	127	57	4	311	65	62	22	3	146	28	0.565
Llanes et al., 2009	Caucasian Spain	37	50	13	18	6	44	30	17	14	19	48	52	0.002
Lu et al., 2011	Asian China	264	273	183	75	6	441	87	197	71	5	465	81	0.622
Black et al., 2009	Caucasian, UK	629	1992	407	199	23	1013	245	1357	571	64	3285	699	0.680
Miyake et al., 2011	Asian Japan	293	767	201	84	8	486	100	516	230	21	1262	272	0.434

HWE, Hardy–Weinberg equilibrium.

without restriction on language, and was conducted on human subject. All searched papers were retrieved, and their references were checked as well for other relevant publications. Review articles were also searched to find additional eligible studies. For papers on the same population or with overlapping data, only the most recent or the ones with the largest group of subject data-set were included in this analysis. To identify potentially eligible papers, the title and abstract of each paper identified by the literature search were assessed independently by two authors. Disagreements were resolved by discussion.

2.2. Inclusion and exclusion criteria

All papers involving studies that investigated *IL-13* SNP rs1800925 and AR risk were included. The following inclusion criteria were used for the paper selection: 1) the association of AR with *IL-13* SNP rs1800925 was clearly evaluated; 2) the paper clearly described the diagnoses of AR; 3) enough information about the number of AR cases and controls studied with the different *IL-13* genotype was offered. Accordingly, the following exclusion criteria were also used: 1) studies without controls; 2) not offering the number of cases and controls and other essential information; 3) reviews and repeated literature were also excluded.

2.3. Data extraction

From each of the eligible papers, the following data were extracted: first author's surname, publication year, country of origin, ethnicity, genotype and allele frequency, and number of cases and controls, respectively. Data were extracted independently by the same authors previously mentioned, and consensus were reached on all items. Discrepancies were resolved by discussion.

2.4. Statistical analysis

The strength of the associations between AR and the *IL-13* SNP rs1800925 was estimated by odds ratio (OR) and 95% confidence interval (CI), based on the genotype or allele frequencies in cases and controls. The pooled ORs were performed with allele contrast (T versus C), heterozygous comparison (C/T versus C/C), homozygous comparison (T/T versus C/C), dominant model (C/T + T/T versus C/C) and recessive model (T/T versus C/T + C/C), respectively. To calculate the pooled OR, the fixed-effect model and the random-effect model were appropriately used. The significance of the pooled OR was determined by the Z-test and $P < 0.05$ was considered as statistically significant. Heterogeneity was tested by the I^2 statistic (Higgins et al., 2003).

Visual inspection of asymmetry in funnel plots was used to estimate the potential publication bias (Bennett et al., 2004). In order to supplement the funnel plot, Begg's funnel plots (Begg and Mazumdar, 1994) and Egger's regression method (Egger et al., 1997) were performed ($P < 0.05$ was considered representative of statistically significant publication bias). Sensitivity analysis was conducted by removing each individual study in turn from the total and

re-analyzing the remainder. Sensitivity analysis was also performed excluding studies whose allele frequencies in controls exhibited a significant deviation from the Hardy–Weinberg equilibrium (HWE), given that the deviation may denote bias. HWE was estimated among the controls using the appropriate goodness-of-fit chi-square test (Rohlf and Weir, 2008). For the evaluation of the goodness-of-fit chi-square test, statistical significance was defined as $P < 0.05$ (Thakkinian et al., 2005). Statistical analysis was done using the program Review Manager 5.1.2 (2011, The Cochrane Collaboration) and the statistical software Stata10.1 (Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

The literature search identified 41 related articles through PubMed, Embase, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure. With the step of screening the title or abstract, 10 eligible studies were selected. Of the 10 articles selected, 5 studies (Bottema et al., 2010; Cheng et al., 2006; Huebner et al., 2008; Kim et al., 2007; Nieters et al., 2004) were excluded because of the incompatible study design. Finally, 5 studies (Black et al., 2009; Llanes et al., 2009; Lu et al., 2011; Miyake et al., 2011; Wang et al., 2003) including 1,411 AR cases and 3,169 controls, were included in this meta-analysis based on inclusion and exclusion criteria (Table 1). AR was defined as self-reported or a physician's diagnosis of AR based on symptoms. The distribution of genotypes in the controls was in agreement with HWE, except for one study (Llanes et al., 2009), in which the deviation from HWE in the control group was found ($P = 0.002$).

3.2. Meta-analysis

The overall analyses were performed, using allele contrast, heterozygous comparison, homozygous comparison, dominant model and recessive model (Table 2). As for allele contrast, low heterogeneity was observed in the overall analysis ($I^2 = 8\%$), in which a fixed-effect models was selected. The combined results based on all studies showed that T allele of *IL-13* SNP rs1800925 was not associated with increased AR risk (OR = 1.06, 95% CI = 0.94–1.20, Fig. 1). In heterozygous comparison,

Table 2Overall analysis of *IL-13* SNP rs1800925 and allergic rhinitis risk.

Model	OR (95% CI)	I^2 (%)	Z test P value	Begg test P value	Egger test P value
T versus C	1.06 (0.94, 1.20)	8	0.31	0.22	0.24
C/T versus C/C	1.12 (0.97, 1.29)	0	0.14	0.46	0.54
T/T versus C/C	1.00 (0.69, 1.44)	0	1.00	0.46	0.24
C/T + T/T versus C/C	1.10 (0.96, 1.27)	0	0.17	0.81	0.67
T/T versus C/C + C/T	0.91 (0.64, 1.31)	26	0.62	0.46	0.35

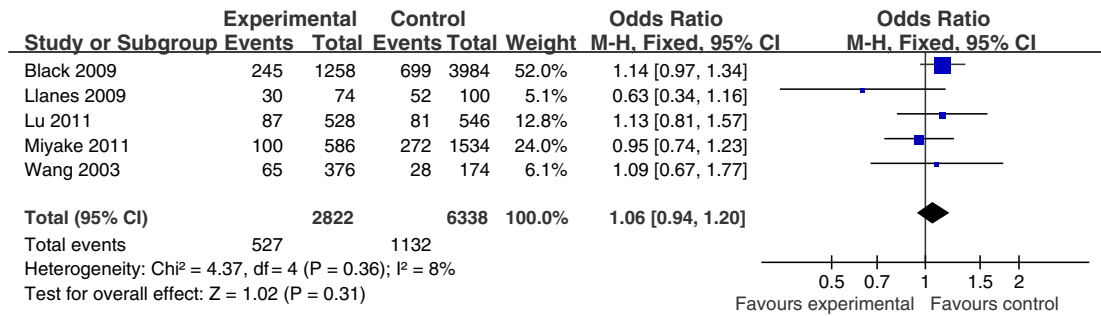


Fig. 1. Forest plot of allergic rhinitis risk associated with *IL-13* SNP rs1800925 under allele contrast (T versus C) for all subjects (fixed effects).

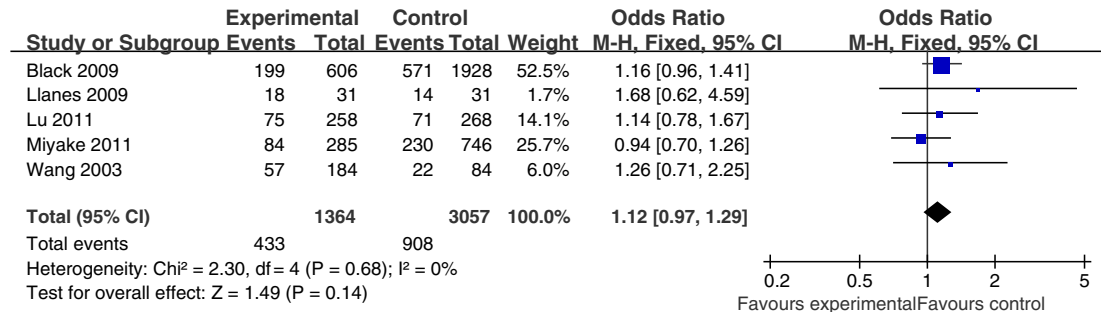


Fig. 2. Forest plot of allergic rhinitis risk associated with *IL-13* SNP rs1800925 under heterozygous comparison (C/T versus C/C) for all subjects (fixed effects).

homozygous comparison and dominant model, no heterogeneity were observed ($I^2 = 0$), and fixed-effect models were chosen. T/T genotype of *IL-13* SNP rs1800925 was not associated with increased AR risk in all subjects (heterozygous comparison: OR = 1.12, 95% CI = 0.97–1.29, Fig. 2; homozygous comparison: OR = 1.00, 95% CI = 0.69–1.44, Fig. 3; dominant mode: OR = 1.10, 95% CI = 0.96–1.27, Fig. 4). Using recessive model, moderate heterogeneity were detected in the overall analysis ($I^2 = 26\%$) and a fixed-effect model

was selected in the analysis. There was no significant associations of *IL-13* SNP rs1800925 with AR risk in all subjects (OR = 0.91, 95% CI = 0.64–1.31, Fig. 5).

3.3. Sensitivity analysis and publication bias

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled

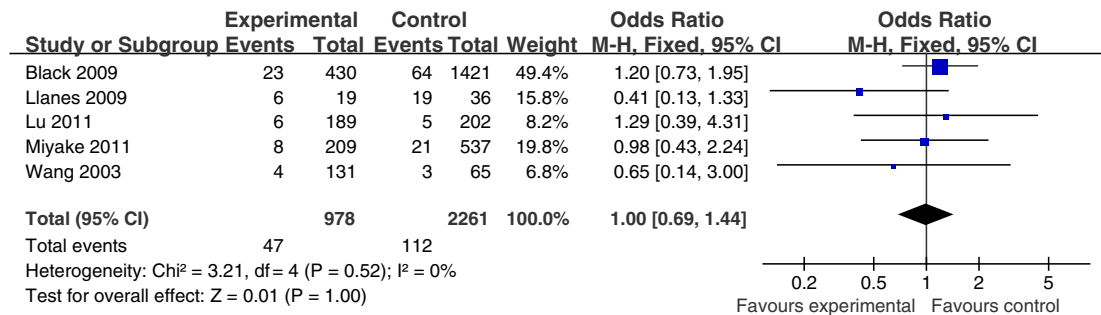


Fig. 3. Forest plot of allergic rhinitis risk associated with *IL-13* SNP rs1800925 under homozygous comparison (T/T versus C/C) for all subjects (fixed effects).

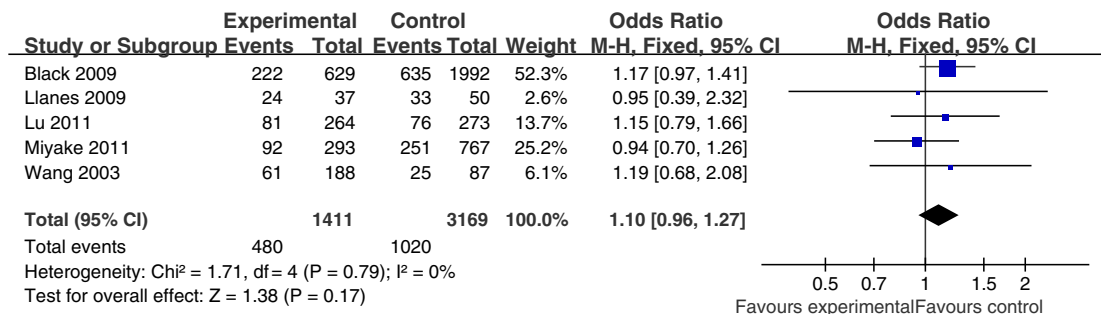


Fig. 4. Forest plot of allergic rhinitis risk associated with *IL-13* SNP rs1800925 under dominant model (C/T + T/T versus C/C) for all subjects (fixed effects).

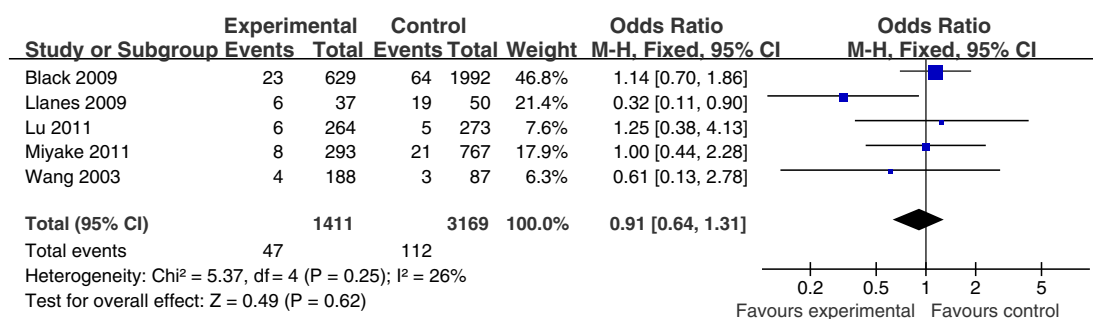


Fig. 5. Forest plot of allergic rhinitis risk associated with *IL-13* SNP rs1800925 under recessive model (T/T versus C/C + C/T) for all subjects (fixed effects).

ORs, and the corresponding pooled ORs were not materially altered (data not shown), indicating that our results were statistically robust. Exclusion of the study (Llanes et al., 2009) by Llanes et al. whose genotype distribution deviated from HWE, did not significantly change the corresponding pooled ORs (data not shown).

Funnel plots were created to assess the possible publication biases, the shape of which did not reveal any evidence of obvious asymmetry (Fig. 6). Begg's funnel plot indicated no evidence for funnel plot asymmetry in either overall analysis or subgroup analyses (Table 2; Fig. 7). Egger's test also suggested the absence of publication bias in either overall analysis or subgroup analyses (Table 2; Fig. 8).

4. Discussion

A series of studies have indicated that *IL-13* SNP rs1800925 may contribute to risk of AR. However, the results of these studies assessing the association between AR susceptibility and *IL-13* SNP rs1800925 have been contradictory. Hence, we undertook this meta-analysis, which supported that *IL-13* SNP rs1800925 was not associated with AR.

As a critical regulator of allergic response, the *IL-13* gene acted independently from other Th2 cytokines to induce a full spectrum of allergic reactions (Wills-Karp and Chiaramonte, 2003), numerous SNPs of which have been identified, and the associations between these SNPs and asthmatic and/or allergic phenotypes have been detected in several populations of distinct ethnic background (Heinzmann et al., 2003; Hoffman et al., 2004). Specially, a number of studies were conducted to investigate the associations of *IL-13* SNP rs1800925 with atopic diseases. Many studies have found the *IL-13* promoter SNP was associated with high total serum IgE levels (Graves et al., 2000; Liu et al., 2003), and asthma (Howard et al., 2001; van der Pouw Kraan et al., 1999) in different populations, whereas others

failed to confirm such findings. The present meta-analysis, which included 2,153 cases of AR and 3,931 controls, suggested that there was no association between *IL-13* SNP rs1800925 and AR susceptibility. Moreover, the results were not materially altered after the studies which did not fulfill HWE were excluded. In order to address the relationship between *IL-13* SNP rs1800925 and AR risk, we did not only performed the allele analysis but also the genotype analyses based on all studies, using different comparison models. For the allele contrast, we found no correlation of *IL-13* SNP rs1800925 T allele with AR risk ($OR = 1.52$, 95% $CI = 1.20-1.92$). We also found no association of heterozygous C/T carriers with AR risk compared to homozygous C/C carriers ($OR = 1.52$, 95% $CI = 1.20-1.92$), neither did the homozygous T/T carriers show significantly increased risk of AR ($OR = 1.52$, 95% $CI = 1.20-1.92$). Based on the dominant model, we found no significant increased risk of T allele carriers against the homozygous C/C carriers ($OR = 1.52$, 95% $CI = 1.20-1.92$). Under the recessive model, there is no increase of AR risk for homozygous T/T carriers compared with the other two genotype carriers ($OR = 1.52$, 95% $CI = 1.20-1.92$). The results seem to contradict the observations of functional studies of *IL-13*, which had suggested that *IL-13* played a pivotal role in the development of AR. In fact, it may be not uncommon that epidemiologic results do not coincide with the results of functional studies. As AR was a complicated multi-genetic disease, different genetic backgrounds and environmental exposures may contribute to this discrepancy.

Several limitations of this study should be addressed. First, the sample size was still relatively small for the analysis, and we were unable to perform subgroup analysis with respect to ethnicity, in spite of a possible role of ethnic differences in genetic backgrounds and the environment they live in. Second, only published studies were included in the meta-analysis, therefore, publication bias may have occurred, even though the use of a statistical test did not show it.

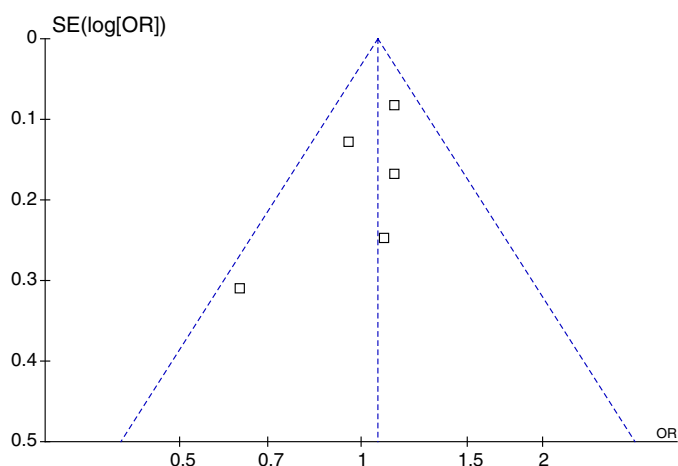


Fig. 6. Funnel plot of association between *IL-13* SNP rs1800925 and allergic rhinitis risk.

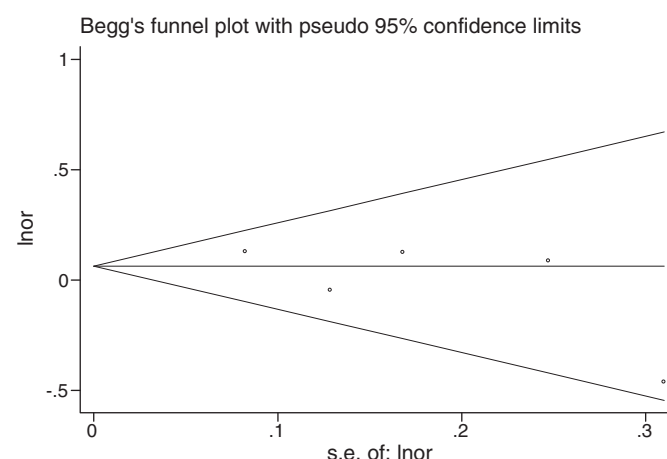


Fig. 7. Begg's funnel plot with pseudo-95% confidence limits.

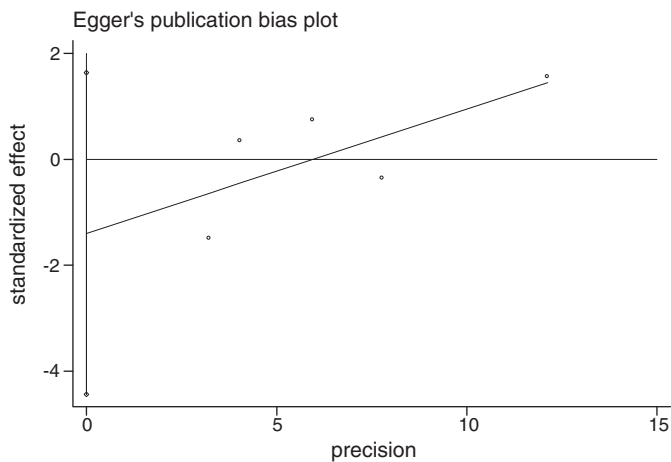


Fig. 8. Egger's publication bias plot.

Third, We applied a more liberal definition of AR, because most of the literature on AR employ less strict criteria, though Allergic Rhinitis and Its Impact on Asthma (ARIA) 2010 guidelines suggested that a diagnosis of AR should be made based on symptoms and an objective marker of allergen sensitization (positive skin prick test or allergen-specific IgE) (Brozek et al., 2010). Fourth, we were unable to obtain information from most studies on the presence or absence of a history of smoking, because of lack of the investigation of gene-environment interactions. Finally, our meta-analysis was based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available and would allow for an adjustment estimate. Despite the limitation, our meta-analysis significantly increased the statistical power of the analysis based on substantial number of cases and controls from different studies.

In conclusion, this meta-analysis supported that *IL-13* SNP rs1800925 was not associated with AR. As the included studies are currently limited, it is of great essentiality to conduct large-sample studies with wider spectrum of subjects to investigate the relationship between *IL-13* SNP rs1800925 and AR risk, which would greatly help summarize the results from published papers.

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