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Original Article

Association of *IL-13* rs20541 polymorphism and risk of allergic rhinitis: evidence from a meta-analysis

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Abstract: Background: Allergic rhinitis (AR) is an atopic disease which involves the interaction between genetic and environmental factors. Interleukin 13 (IL-13) is one of the candidate genes for AR risk, and many association studies have explored the effects of one polymorphism rs20541 in IL-13 gene on AR risk, but the conclusions are inconsistent and disputable. Therefore, we performed this meta-analysis including a total of 2313 cases and 4096 controls to more systematically clarify this issue. Methods: Studies on the correlation between IL-13 rs20541 polymorphism and AR risk were systematically searched in electronic databases including PubMed, Wangfang, Chinese National Knowledge Infrastructure (CNKI) and Embase. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to examine the strength of the correlation between the polymorphism and AR susceptibility. All statistical analyses were performed using STATA software version 12.0. Results: Overall, IL-13 rs20541 polymorphism imposed a risk-increasing effect on AR occurrence under five genetic contrasts of GlnGln vs. ArgArg, GlnGln + ArgGln vs. ArgArg, GlnGln vs. ArgGln + ArgArg, Allele Gln vs. Allele Arg, and ArgGln vs. ArgArg (OR=1.60, 95% CI=1.28-1.99; OR=1.27, 95% CI=1.07-1.50; OR=1.50, 95% CI=1.22-1.86; OR=1.21, 95% CI=1.11-1.32; OR=1.16, 95% CI=1.03-1.30). In addition, subgroup analyses by ethnicity and control source also revealed a positive correlation between the single nucleotide polymorphism and AR susceptibility in Asian, population-based, and hospital-based groups. Conclusion: IL-13 rs20541 polymorphism may be a risk factor for AR occurrence, especially in Asian people.

Keywords: *IL-13*, polymorphism, allergic rhinitis, risk

Introduction

Allergic rhinitis (AR), also known as hay fever or pollinosis, is characterized by the overproduction of T helper type 2 (Th2) cytokines, high immunoglobulin E (IgE) levels in the serum, and selective eosinophil accumulation in the nasal mucosa [1]. 9%-24% of the general population were affected by the disease, especially the people aged 20 to 40 years [2, 3]. Common symptoms of AR include itching, sneezing, excess nasal secretion, and nasal congestion and obstruction, which can disturb the work, study and sleep quality of patients [3, 4]. Other complications of the disease also include allergic conjunctivities, asthma, and atopic dermatitis [3]. Besides environmental stimuli, allergen has also been pointed to be one important factor as well [5, 6]. Furthermore, the roles of genetic polymorphisms in the incidence of AR have also been extensively explored [7], and a number of candidate genes correlated with AR have been identified utilizing position cloning and linkage analysis techniques [8, 9].

The changes in environment may cause an imbalance between Th1 and Th2 immune responses, thus causing the abnormal production of cytokines such as interleukin-4 (IL-4) and *IL-13* which are implicated in IgE-mediated inflammatory process [10, 11]. The chromosome 5q is a region frequently linked to AR, asthma, airway responsiveness, and other related phenotypes [12]. The protein encoded by *IL-13* gene located on chromosome 5q31 is an important immunoregulatory cytokine which is produced by activated Th2 cells and can cause the production of IgE by B cells [13-16]. IL-13 expression was reported to be observed in the nasal mucosa of perennial atopic rhinitis patients after allergen provocation [17, 18]. Studies also report that IL-13 may contribute to a late nasal response, so the persistent nasal blockage in AR patients may be prevented

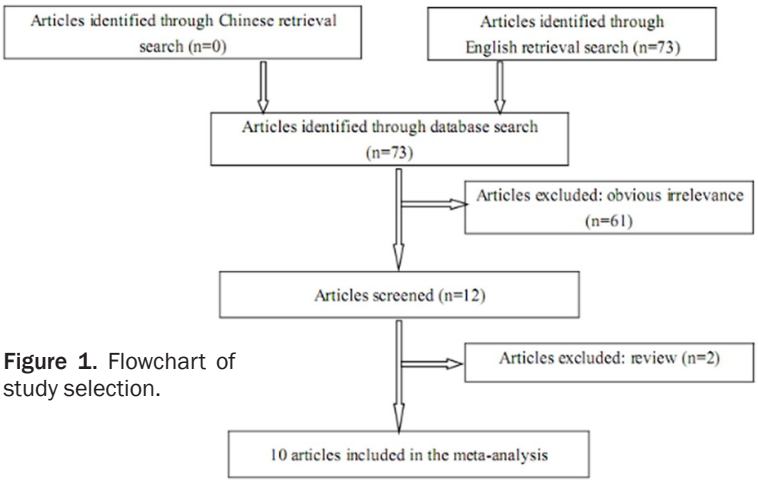

Figure 1. Flowchart of study selection.

through the inhibition of IL-13 functions [19]. *IL-13* rs20541 polymorphism located on exon 4 is a common coding single nucleotide polymorphism (SNP) which causes the replacement of arginine by glutamine at position 110/130 of the mature protein [20].

The association of *IL-13* rs20541 polymorphism with AR susceptibility has been frequently explored, but inconsistent conclusions have been drawn. To more precisely elucidate this issue, we incorporated a total of 2313 cases and 4096 controls to perform the present meta-analysis.

Materials and methods

Publication search

A systematic search of publications on the role of *IL-13* rs20541 polymorphism in the susceptibility to AR was conducted in PubMed, Medline, Embase, Cochrane Library, Wanfang, and Chinese National Knowledge Infrastructure (CNKI). Various combinations of the following keywords were used in the search strategy: "interleukin 13" or "*IL-13*", "AR" or "hay fever" or "pollinosis", and "variant" or "susceptibility" or "mutation". Potentially eligible studies were manually searched through screening the reference lists of the included studies.

Inclusion and exclusion criteria

The included studies had to meet the following criteria: (1) a case-control design; (2) evaluating the association between *IL-13* rs20541 polymorphism and AR risk; (3) offering genotype and allele frequencies in both case and control groups; and (4) full-text articles about humans. Studies were deleted from the present study if any one of the following conditions were met: (1) lack of necessary information on genotype and allele distribution; (2) letters, reviews, or editorials; (3) dealing with animals; (4) containing duplicated data; and (5) not concerning *IL-13* polymorphisms or AR susceptibility.

Data extraction

Two independent reviewers used a standardized form to extract data from the included studies. For each eligible study, the following information was collected: first author's name, publication year, country, ethnicity, method for genotyping, total numbers of cases and controls, allele and/or genotype frequency, and *P* value for Hardy-Weinberg Equilibrium (HWE) in controls. Any disagreements over data were resolved through discussion between the two reviewers.

Statistical analysis

STATA software version 12.0 was applied to perform all statistical tests. The strength of correlation between *IL-13* rs20541 polymorphism and AR risk was evaluated through calculating pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). Heterogeneity between studies was assessed by Q test, with $P<0.05$ and $P>0.05$ indicating significant and insignificant heterogeneity, respectively, which determined the use of random- and fixed-effects models, respectively, for ORs calculation. Publication bias was assessed with Begg's and Egger's tests. Whether genotype distribution in control group conformed to HWE was examined with Chi-square test. The significance of the combined ORs was determined with the Z test. *P* values of all tests were two-sided, with $P<0.05$ considered statistically significant.

Results

Study characteristics

Figure 1 shows the process of selecting eligible studies. Altogether, 73 articles were identified through the database search. Among them, 61

Table 1. Major information of the included studies on *IL-13* rs20541 polymorphism and AR risk

First author/ year	Country	Ethnicity	Control source	Sample size		Case			Control genotype and allele			Hardy-Weinberg Equilibrium	Gennotyping method
				Case	Control	ArgArg	ArgGln	GlnGln	ArgArg	ArgGln	GlnGln		
Cheng/2006	Japan	Asian	Population-based	95	94	54	33	8	45	40	9	0.980	PCR-RFLP
Lu/2011	China	Asian	Hospital-based	264	273	114	124	26	134	119	20	0.356	TaqManSNP
Nieters/2004	Germany	Caucasian	Population-based	318	321	194	104	20	207	97	17	0.212	PCR
Wang/2003	China	Asian	Population-based	188	87	85	86	17	48	35	4	0.449	PCR-RFLP
Miyake/2011	Japan	Asian	Population-based	293	766	135	126	32	379	333	54	0.095	TaqManSNP
Llanes/2008	Spain	Caucasian	Population-based	37	50	19	16	2	41	8	1	0.432	Real time-PCR
Kim/2007	Korea	Asian	Population-based	307	268	109	164	34	119	127	22	0.138	PCR-RFLP
Black/2009	UK	Caucasian	Population-based	651	2072	442	185	24	1448	570	54	0.814	PCR
Yadav/2012	Malaysia	Asian	Hospital-based	54	45	10	36	8	18	25	2	0.068	PCR-RFLP
Shazia/2013	Pakistan	Asian	Population-based	106	120	35	32	39	47	44	29	0.006	PCR-RFLP

Notes: PCR, Polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism.

Table 2. Meta-analysis results for *IL-13* rs20541 polymorphism and AR risk

	Total		Asian		Caucasian		Population-based		Hospital-based	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
GlnGln vs. ArgArg	1.60 (1.28, 1.99)	0.638	1.68 (1.29, 2.19)	0.464	1.42 (0.96, 2.11)	0.631	1.55 (1.23, 1.97)	0.779	1.89 (1.05, 3.38)	0.099
GlnGln + ArgGln vs. ArgArg	1.27 (1.07, 1.50)	0.049	1.27 (1.04, 1.55)	0.174	1.35 (0.89, 2.05)	0.025	1.23 (1.02, 1.47)	0.069	1.73 (0.78, 3.82)	0.091
GlnGln vs. ArgArg + ArgGln	1.50 (1.22, 1.86)	0.904	1.56 (1.22, 2.01)	0.767	1.37 (0.93, 2.02)	0.774	1.49 (1.19, 1.87)	0.903	1.61 (0.92, 2.82)	0.254
Gln vs. Arg	1.21 (1.11, 1.32)	0.087	1.25 (1.11, 1.40)	0.240	1.28 (0.93, 1.78)	0.040	1.20 (1.09, 1.31)	0.087	1.32 (1.04, 1.67)	0.145
ArgGln vs. ArgArg	1.16 (1.03, 1.30)	0.080	1.18 (1.01, 1.39)	0.232	1.32 (0.86, 2.03)	0.028	1.13 (1.00, 1.28)	0.093	1.35 (0.97, 1.88)	0.138

Note: P_h: *P* value of heterogeneity test.

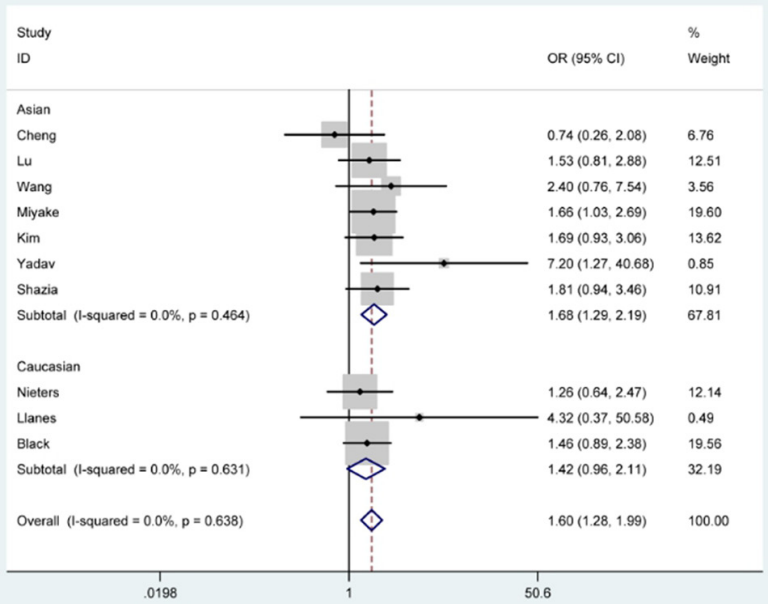

Figure 2. Forest plot for the association between *IL-13* rs20541 polymorphism and AR risk under GlnGln vs. ArgArg contrast.

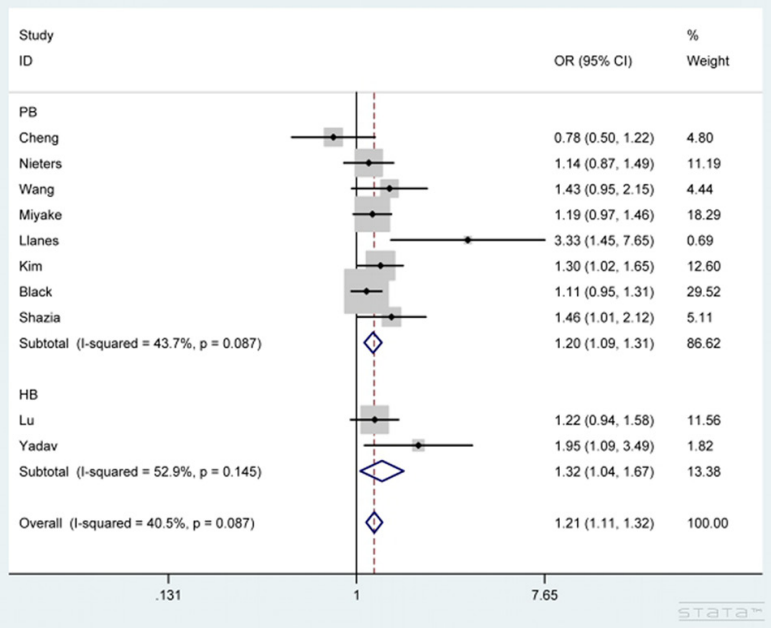

Figure 3. Forest plot for the association between *IL-13* rs20541 polymorphism and AR risk under Gln vs. Arg contrast after stratified analysis by source of control.

articles were obviously irrelevant, and 2 were reviews. As a result, a total of 10 publications were included in the present study [12, 21-29]. Principal characteristics of the eligible studies are described in **Table 1**.

Meta-analysis results

Table 2 shows the main results of the present meta-analysis. The overall ORs reflected that the single nucleotide polymorphism (SNP) increased the risk of AR under five genetic models of GlnGln vs. ArgArg (**Figure 2**), GlnGln + ArgGln vs. ArgArg, GlnGln vs. ArgGln + ArgArg, Allele Gln vs. Allele Arg (**Figure 3**), and ArgGln vs. ArgArg (OR=1.60, 95% CI=1.28-1.99; OR=1.27, 95% CI=1.07-1.50; OR=1.50, 95% CI=1.22-1.86; OR=1.21, 95% CI=1.11-1.32; OR=1.16, 95% CI=1.03-1.30). A similar trend was also shown in Asian group under the above five genetic contrasts (OR=1.68, 95% CI=1.29-2.19 (**Figure 2**); OR=1.27, 95% CI=1.04-1.55; OR=1.56, 95% CI=1.22-2.01; OR=1.25, 95% CI=1.11-1.40; OR=1.18, 95% CI=1.01-1.39), in population-based group under GlnGln vs. ArgArg, GlnGln + ArgGln vs. ArgArg, GlnGln vs. ArgGln + ArgArg, and Allele Gln vs. Allele Arg (**Figure 3**) models (OR=1.55, 95% CI=1.23-1.97; OR=1.23, 95% CI=1.02-1.47; OR=1.49, 95% CI=1.19-1.87; OR=1.20, 95% CI=1.09-1.31), and in hospital-based group under GlnGln vs. ArgArg and Allele Gln vs. Allele Arg (**Figure 3**) contrasts (OR=1.89, 95% CI=1.05-3.38; OR=1.32, 95% CI=1.04-1.67).

Under all the five comparisons, there was no significant heterogeneity except GlnGln + ArgGln vs. ArgArg model, so the fixed-effects model was employed to calculate pooled ORs, while the random-effect model was used under the exceptional contrast in which a moderately significant heterogeneity was detected.

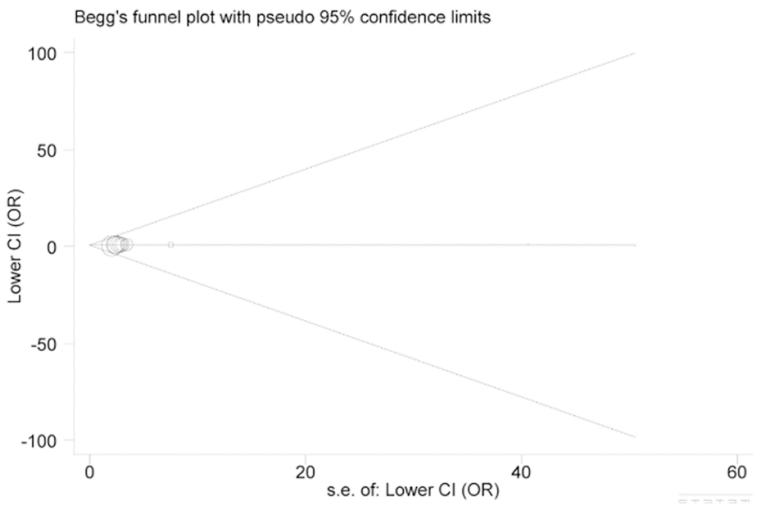

Figure 4. Begg's funnel plot of publication bias.

Sensitivity analysis

The influence of individual study on the overall results was evaluated by conducting sensitivity analysis. After sequential exclusion of each individual study, no significant difference in the overall ORs was detected, which indicated that the results of the present study were stable.

Publication bias

Begg's funnel plot and Egger's linear regression test were adopted to assess publication bias across selected studies. No evidence of significant publication bias was observed from either the symmetrical shape of funnel plots (**Figure 4**) or the results of Egger's test (P=0.548), showing publication bias was negligible.

Discussion

AR is a typical atopic disease which involves the interaction of both environmental and genetic factors. The incidence rate of the disease shows an increasing trend during the past few decades [30]. Generally speaking, atopic diseases are commonly associated with broken balance in Th1/Th2 immune responses [27]. IL-13 is selectively secreted by Th2 cells, and thus can mediate allergic inflammation and disease [31]. Additionally, it can induce a full spectrum of allergic reactions independent from other Th2 cytokines [32, 33], and many features of allergic reaction through its action on local cells [32-34]. Accelerating the secretion of IgE by activated human B cells, IL-13 can bind specifically to its receptor on mast cells, which may cause the release of mediators that can induce inflammation [24].

Since elevated levels of IgE and serum-specific IgE to common allergens can be used as a standard to diagnose AR [24], polymorphisms of genes implicated in this regulation pathway may be associated with AR risk. Among others, the SNP rs20541 in *IL-13* gene has been shown to be involved in the risk of asthma, atopic dermatitis, and AR [34-36].

Wang et al. investigated whether *IL-13* rs20541 polymorphism had an influence on AR risk in a Chinese population, and found a significantly higher serum IgE levels in patients with a Gln/Gln genotype than in those with an Arg/Arg genotype, demonstrating the involvement of the SNP in AR onset [24]. In the study by Miyake et al., the AA genotype of the SNP was observed to be positively correlated with the risk of rhinoconjunctivitis compared with the GG genotype [25]. However, another study by Llanes et al. probing into the association of the SNP with olive pollen allergy revealed an increased GA genotype frequency in patients with allergy to olive pollen [26]. The SNP was also demonstrated to confer susceptibility to AR development in Koreans in the study by Kim et al. [27]. Besides, Yadav et al. demonstrated that individuals who carried the A allele had an enhanced risk of developing AR [29]. Nevertheless, Cheng et al. found no apparent associations between *IL-13* rs20541 polymorphism and AR risk [21]. While Shazia et al. and Lu et al. failed to observe any apparent contribution of the SNP to AR onset either [12, 22].

Controversial results of the above studies may be owing to several aspects: (1) major characteristics of study subjects such as age, gender, and ethnicity significantly differed between different studies, which may affect the consistency in final results; (2) some studies only select-

ed a limited number of subjects, thus reducing the representativeness of overall results; and (3) the adjustment of data was not conducted in all studies.

Considering these discrepancies between previous findings, we carried out this meta-analysis to reduce possible bias. After statistical analysis, we found a positive correlation between the SNP and the overall AR risk under all the five genetic contrasts of GlnGln vs. ArgArg, GlnGln + ArgGln vs. ArgArg, GlnGln vs. ArgGln + ArgArg, Allele Gln vs. Allele Arg, and ArgGln vs. ArgArg. In addition, after subgroup analysis by ethnicity, a similar correlation was also showed in Asian group under the above five comparisons. In population- and hospital-based groups, this trend was also revealed under corresponding contrasts.

Compared with the previous studies, our meta-analysis had the advantages of a relatively larger sample size and a more powerful statistical tool. However, some limitations of the present study should not be omitted. First of all, the number of subjects in subgroup analyses was relatively small. Secondly, only studies published in English or Chinese language were selected, which may cause possible publication bias, even though it was not demonstrated by the statistical test. Thirdly, the majority of included studies focused on Asian populations, thus leading to possible selective bias. Last but not least, AR is a complicated disease, but the influence of possible gene-gene and gene-environment interactions on AR risk was not evaluated owing to the lack of original data.

In conclusion, the present study demonstrated that *IL-13* rs20541 polymorphism may contribute to an increased OR risk. However, more studies with larger sample sizes and more ethnicities should be performed to verify our findings in view of the above mentioned shortcomings.

Disclosure of conflict of interest

None.

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