Inflammation Research (2020) 69:911–923
https://doi.org/10.1007/s00011-020-01368-4

Inflammation Research

ORIGINAL RESEARCH ARTICLE

The association between *IL18*, *FOXP3* and *IL13* genes polymorphisms and risk of allergic rhinitis: a meta-analysis

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Received: 16 March 2020 / Revised: 12 May 2020 / Accepted: 23 May 2020 / Published online: 11 June 2020

Abstract

Objectives Allergic rhinitis (AR) is a chronic inflammatory disease of nasal mucosa. Loss of function of Th17 cells and regulatory T (Treg) cells plays a role in the pathogenesis of AR. *IL18, FOXP3,* and *IL13* are key genes in the development of AR. However, the genetic associations between *IL18, FOXP3* and *IL13* genes polymorphisms and AR risk were inconclusive yet.

Methods A meta-analysis was performed by searching through Pubmed, EMBASE, web of science and CNKI databases. The ORs and 95%CIs were used to assess the genetic association between the allelic, dominant and recessive models of *IL18*, *FOXP3* and *IL13* genes polymorphisms and AR risk.

Results A total of 15 articles (6 for *FOXP3*, 5 for *IL18*, and 5 for *IL13*) were enrolled in the present study. No association was detected between the *IL18* rs187238, rs1946518, rs360721, *FOXP3* rs2232365, rs3761548 and *IL13* rs1800925 polymorphisms and AR risk ($p > 0.05$). Significant associations were observed between the allelic ($p = 0.001$, OR 1.32, 95% CI 1.12–1.56), dominant ($p = 0.005$, OR 1.43, 95% CI 1.11–1.83) and recessive models ($p = 0.01$, OR 1.64, 95% CI 1.13, 2.40) of *IL13* rs20541 and AR risk. Subgroup analysis based on ethnicity revealed that the *IL13* rs20541 was significantly associated with AR risk in Asian population (allelic model: $p = 0.009$, OR 1.36, 95% CI 1.13–1.63, dominant model: $p = 0.005$, OR 1.43, 95% CI 1.11–1.83; recessive model: $p = 0.01$, OR 1.64, 95% CI 1.13–2.40).

Conclusions *IL13* rs20541 may contribute to the risk of AR in Asian population. To confirm these results, larger number of case–control study with more subjects is necessary in the future.

Keywords *IL18* · *FOXP3* · *IL13* · Polymorphism · Allergic rhinitis · Meta-analysis

Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease of nasal mucosa. Allergic individuals who are exposed to allergens may release IgE mediated transmitters and immunologically active cells and cytokines [1–3]. The incidence of AR worldwide is between 10 and 25% [4]. AR is influenced by both environmental factors and genetic factors [5, 6]. Previously, most studies have reported that the imbalance of Th1 and Th2 cell subsets plays a role in AR immune disorder [7, 8]. Researchers have been trying to reverse the response of naive CD^{4+} T cells to Th1 instead of Th2 [9, 10], but this does not fully elucidate the immune mechanism of AR. Recently, Th17 cells and regulatory T (Treg) cells were also shown to be involved in the pathogenesis of AR [11, 12]. And, the imbalance of CD^{4+} Th cell subsets may lead to the excessive Th2 differentiation in AR [12]. As far as current studies are concerned, polymorphic loci of relevant genes

Responsible Editor: John Di Battista.

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00011-020-01368-4) contains supplementary material, which is available to authorized users.

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in the pathogenesis of AR are one of the important ways to determine the pathogenesis and treatment of AR.

Forkhead transcription factor P3 (forkhead-box P3, FOXP3) is a characteristic transcription factor of regulatory T cells, which plays an important role in the pathogenesis of AR through the control of regulatory T cells [13]. Zhang et al. found that the *FOXP3* rs3761548 allele was associated with AR in a case–control study with 193 AR patients and 191 healthy controls in China [14]. Similar results were observed by Fodor et al. in a Hungarian population in 2011 [15]. However, negative results were also detected in other Chinese population by Zhang et al. [16].

In addition, as the main factor of Th2 cells, IL-13 could stimulate the growth and differentiation of B cells, promote the generation of IgE, and inhibit the activity of Thl cells [17]. Huebner et al. found that interleukin 13 (*IL-13*) rsl800925 was associated with rhinitis in a cohort study of 923 children in the United States [18]. Llanes et al. found that the distribution of the TT genotype of *IL-13* rsl800925 significantly decreased, which suggested that the *IL-13* rsl800925 was protective for rhinitis and asthma with olive pollen allergy in Spain [19]. However, no association was detected between the *IL13* rsl800925 and AR in Chinese Han [20] and Dutch [21] populations.

Furthermore, IL-18 is a major member of the IL-1 family. It can promote mast cells, T cells and basophils to secrete Th2 cytokines such as IL-13 and IL-4, which can enhance Th2 cell-mediated immune response as well as Th1 cell-mediated immune response [22]. Sebelova et al. have investigated three polymorphisms (− 607 C/A, − 137 G/C and − 133 C/G) of the *IL-18* gene in 539 AR patients and 312 healthy controls, and found no difference in frequencies of allele and genotype of the three polymorphisms [23]. While the results of the genetic associations between *IL-18* − 607 C/A, − 137 G/C and − 133 C/G and AR susceptibility was not inconsistent in Thai [24], Egyptian [25], and Czech [26] populations.

Considering the inconclusive results of the associations between *FOXP3*, *IL13* and *IL18* genes polymorphisms and AR risk, we aimed to investigate a precise results by using a meta-analysis.

Methods

Searching strategy

Publications were searched through Pubmed, EMBASE, web of science and China National Knowledge Infrastructure (CNKI) databases up to January, 2020. The procedure followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review. The keywords: "interleukin 18" or "*IL18*" and "interleukin 13" or "*IL13*" and "Forkhead Box Protein 3" or "*FOXP3*" and "polymorphism" or "variant" or "single nucleotide polymorphism" or "SNP" and "allergic rhinitis" or "AR" were used to retrieve the articles without language restriction. Furthermore, references of all relevant articles were retrieved to identify additional eligible studies.

Inclusion criteria and exclusion criteria

Eligible studies were included if they: (1) were case–control designed studies; (2) had available genotype frequencies in both case and control groups to estimate an odds ratios (OR) and their 95% confidence interval (CI).

Studies were excluded if they: (1) were duplicated data; (2) were case-reports, reviews or abstracts; (3) were lack of genotype frequency data.

Data extraction and quality assessment

The information from eligible studies that according to the inclusion/exclusion criteria were extracted by two independent authors (XQ and XJ). Any disagreement was resolved by discussion. The following information were extracted: Family name of the first author, year, ethnicity, mean ages, gender, genotyping-method, source of controls, number of cases and controls, number of genotypes. All included studies were evaluated using the Newcastle–Ottawa Scale (NOS) [27]. The NOS values arranged from 0 to 8. The studies were included if the NOS values ≥ 6.

Statistical analyses

Statistical analysis for the meta-analysis was conducted by Stata version 12.0 (Stata Corporation, College Station, TX, USA) and Revman 5.2 (Cochrane Collaboration). The ORs and 95% CIs were used to assess the genetic association between the allelic, dominant and recessive models of *IL18* (rs187238, rs1946518 and rs360721), *FOXP3* (rs2232365 and rs3761548) and *IL13* (rs20541 and rs1800925) genes and risk of AR. The significance of the pooled OR was assessed by the Z test, and $p_Z < 0.05$ was considered as statistically significant. The between study heterogeneity was assumed by chi-square-based Q-test and I^2-statistic [$(I^2 = 100\% \ (Q - df)/Q)$]. A p value > 0.05 or $I^2 < 50\%$ for the Q test and I^2-statistic indicated no heterogeneity among studies, and a fixed model was applied to estimate the pooled ORs. Otherwise the random model was used. Meta regression analysis was undertaken to explore potential sources of heterogeneity across studies when statistical heterogeneity was detected. The stability of the results was assessed using sensitivity analysis by excluding one study each time. Potential publication bias was undertaken by Egger's test

and Begg' s tests. p_{Egger} or $p_{Begg} < 0.05$ was considered significant.

Results

Characters of eligible publications

As shown in the Fig. 1, A total of 746 publications were originally obtained, among which 117 irrelevant papers were firstly excluded. Thus, 629 publications were eligible. Then, 122 study that was not case–control designed was eliminated. Finally, 16 publications that met the inclusion criteria were enrolled in the present study. For *FOXP3* gene, 6 articles [14–16, 28–30] encompassing 979 cases and 980 controls were included. Among them, 5 were in Asian population [14, 16, 28–30], and 1 was in Caucasian population [15]. For *IL13* gene, 5 qualified studies consisted of 879 cases and 684 controls were enrolled [20, 21, 31–33]. 4 were in Asian population [20, 31–33], and 1 was in Caucasian population [21]. For *IL18* gene, 5 publications with 1507 cases and 878 controls were included [23–26, 34]. And 3 of them were in Caucasian population [23, 25, 26], and others two were in Asian population [24, 34]. The characteristics of these included papers were summarized in Table 1. The articles were published from 2006 to 2017. The NOS scores of all included studies ranged from 7 to 8 stars, indicating that the studies were of high methodological quality (Table s1).

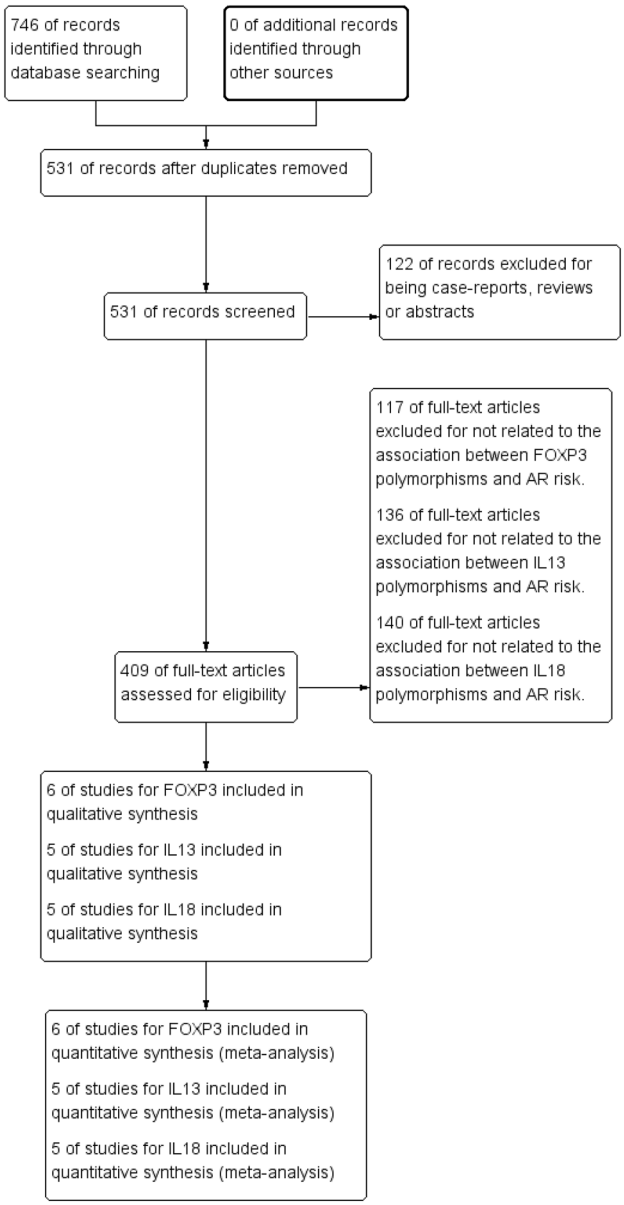


Fig. 1 PRISMA flow chart of studies inclusion and exclusion

Combined results

The results revealed the frequencies of the allelic, dominant and recessive models of *IL18* (rs187238, rs1946518 and rs360721), *FOXP3* (rs2232365 and rs3761548), and *IL13* rs1800925 were not significantly different in cases and controls ($p > 0.05$) (Tables 2, 3, 4; Fig. 2, 3, 4). In addition, statistically significant association was found between the *IL13* rs20541 and AR risk in the three genetic models (allelic model: $p = 0.001$, OR 1.32, 95% CI 1.12–1.56, dominant model: $p = 0.005$, OR 1.43, 95% CI 1.11–1.83; recessive model: $p = 0.01$, OR 1.64, 95% CI 1.13–2.40) (Table 2; Fig. 4).

Stratification analyses were conducted based on ethnicity. The results indicated that all the genetic models of *IL13* rs20541 polymorphism were significantly associated with the increased risk of AR in Asian population (allelic model: $p = 0.009$, OR 1.36, 95% CI 1.13–1.63, dominant model: $p = 0.005$, OR 1.43, 95% CI 1.11–1.83; recessive model: $p = 0.01$, OR 1.64, 95% CI 1.13–2.40). For lack of data, we failed to demonstrate the association between *IL13* rs20541 polymorphism and AR risk in Caucasian population. In addition, *IL18* rs187238, rs1946518, and rs360721 polymorphisms were not associated with AR risk neither in Asian population nor in Caucasian population ($p > 0.05$). Furthermore, the *FOXP3* rs3761548 polymorphism was found to be significantly associated with AR susceptibility in Caucasian population in three genetic models (allelic model: $p = 0.0001$, OR 0.45, 95% CI 0.30–0.68; dominant model: $p = 0.001$, OR 0.04, 95% CI 0.00–0.28; recessive model: $p = 0.009$, OR 0.44, 95% CI 0.24–0.82) (Tables 2, 3, 4).

Heterogeneity

Significant heterogeneity was found in the recessive model of *IL13* rs1800925, the allelic and dominant models of *IL18* rs1946518, and the allelic, dominant and recessive

Table 1 The characters of eligible studies

Gene	First author	Year	Ethnicity	Gender (M%)	Age	Genotyping methods	Case	Control	NOS
FOXP3	Hassannia	2014	Iran	37.4/38.1	30.2 ± 10.33/30.1 ± 10.8	PCR-SSP	102	98	8
	Fodor	2011	Hungarian	40.5/33.6	42.71 ± 12/42.45 ± 14	PCR-based Assay-on-Demand method	106	144	8
	Song	2016	Chinese	52.7/50.9	29.3 ± 10.5/29.6 ± 10.3	PCR-direct sequencing	110	110	8
	Zhang	2009	Chinese	51.8/48.7	33 ± 14/37 ± 14	PCR-direct sequencing	193	191	8
	Zhang	2012	Chinese	60.1/53.0	27.1 ± 14.8/36.2 ± 15.2	iPLEX	378	330	8
	Li	2014	Chinese	60.0/66.3	42.6 ± 11.3/NA	PCR-SSP	90	107	7
IL13	Bottema	2010	Netherland	45.2/44.1	32.8 ± 8.4/26.9 ± 5.4	MassARRAY	188	102	8
	Kim	2007	South Korea	53.4/52.2	26.1 ± 10.3/27.3 ± 11.2	PCR–RFLP	307	268	8
	Shazia	2012	Pakistani	NA	NA	PCR–RFLP	106	120	7
	Wang	2003	Chinese	NA	34.3 ± 10.2/31.3 ± 8.1	PCR–RFLP	188	87	7
	Li	2012	Chinese	60.0/66.4	42.6 ± 12.2/NA	PCR–RFLP	90	107	7
IL18	Holla	2010	Czech	49.3/51.4	32.6 ± 13.0/37.25 ± 16.0	TaqMan	633	325	7
	Ibrahim	2012	Egyptian	56/52	14.0 ± 9.9/28.5 ± 8.6	PCR–RFLP	25	25	8
	Sebelova	2007	Czech	50/NA	37 ± 14.5/38 ± 16.2	PCR–RFLP	539	312	7
	Tungtrongchitr	2017	Thailand	40.7/28	31.93 ± 12.42/26.34 ± 6.52	PCR–RFLP	150	50	8
	Lee	2006	Korean	50/51.8	NA	PCR–RFLP	160	166	7

FOXP3 forkhead-box P3, *IL* interleukin, *M* male, *NA* not available, *PCR-SSP* polymerase chain reaction method-sequence specific primers, *PCR–RFLP* Polymerase chain reaction-restricted fragment length polymorphism, *NOS* Newcastle–Ottawa Scale

Table 2 The association between the IL13 gene polymorphisms and allergic rhinitis risk

Genes	Polymorphisms	Genetic models	Subtypes	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
					Case	Control	OR [95% CI]	*p* value		*p* value	I^2 (%)
IL13	rs20541	Allelic model	Total	4	1578	1154	1.32 [1.12, 1.56]	0.001	F	0.81	0
			Asian	3	1202	950	1.36 [1.13, 1.63]	0.009	F	0.84	0
			Caucasian	1	376	204	1.12 [0.73, 1.74]	0.60	–	–	–
		Dominant model	Total	3	601	475	1.43 [1.11, 1.83]	0.005	F	0.93	0
			Asian	3	601	475	1.43 [1.11, 1.83]	0.005	F	0.93	0
			Caucasian	–	–	–	–	–	–	–	–
		Recessive model	total	3	601	475	1.64 [1.13, 2.40]	0.01	F	0.73	0
			Asian	3	601	475	1.64 [1.13, 2.40]	0.01	F	0.73	0
			Caucasian	–	–	–	–	–	–	–	–
	rs1800925	Allelic model	Total	3	932	592	1.28 [0.98, 1.66]	0.07	F	0.69	0
			Asian	2	556	388	1.18 [0.85, 1.64]	0.31	F	0.65	0
			Caucasian	1	376	204	1.45 [0.94, 2.25]	0.09	-	-	-
		Dominant model	Total	2	278	194	1.11 [0.75, 1.65]	0.61	F	0.72	0
			Asian	2	278	194	1.11 [0.75, 1.65]	0.61	F	0.72	0
			Caucasian	–	–	–	–	–	–	–	–
		Recessive model	Total	2	278	194	1.47 [0.33, 6.54]	0.62	F	0.10	64
			Asian	2	278	194	1.47 [0.33, 6.54]	0.62	F	0.10	64
			Caucasian	–	–	–	–	–	–	–	–

OR odds ratio, *CI* confidence interval, *R* random model, *F* fixed model, – not available, *IL* interleukin

models of *FOXP3* rs3761548 both in the overall group and Asian subgroup (Tables 2, 3, 4). For *IL18* rs1946518, the significant heterogeneity across studies may mainly due to the study conducted by Tungtrongchitr et al. [24]. An $I^2 = 13\%$ ($p = 0.32$) were obtained after excluded this study. For *FOXP3* rs3761548, the significant heterogeneity

Table 3 The association between the IL18 gene polymorphisms and allergic rhinitis risk

Genes	Polymorphisms	Genetic models	Subtypes	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
					Case	Control	OR [95% CI]	*p* value		*p* value	I^2 (%)
IL18	rs187238	Allelic model	Total	4	2694	1424	0.89 [0.77, 1.03]	0.12	F	0.49	0
			Asian	1	300	100	0.41 [0.15, 1.13]	0.09	–	–	–
			Caucasian	3	2394	1324	0.90 [0.78, 1.05]	0.19	F	0.94	0
		Dominant model	Total	4	1347	712	0.90 [0.75, 1.09]	0.29	F	0.57	0
			Asian	1	150	50	0.41 [0.14, 1.26]	0.12	–	–	–
			Caucasian	3	1197	662	0.92 [0.76, 1.12]	0.41	F	0.96	0
		Recessive model	total	4	1347	712	0.74 [0.53, 1.05]	0.10	F	0.92	0
			Asian	1	150	50	0.33 [0.02, 5.36]	0.43	–	–	–
			Caucasian	3	1197	662	0.75 [0.53, 1.07]	0.11	F	0.92	0
	rs1946518	Allelic model	Total	4	2964	1706	0.91 [0.69, 1.20]	0.50	R	0.008	75
			Asian	2	620	432	0.71 [0.22, 2.28]	0.57	R	0.0006	91
			Caucasian	2	2344	1274	0.96 [0.84, 1.11]	0.59	F	0.94	0
		Dominant model	Total	4	1482	853	0.92 [0.56, 1.51]	0.74	R	0.0003	84
			Asian	2	310	216	0.87 [0.14, 5.57]	0.89	R	< 0.0001	94
			Caucasian	2	1172	637	0.89 [0.73, 1.09]	0.25	F	0.92	0
		Recessive model	total	4	1482	853	0.98 [0.77, 1.25]	0.89	F	0.42	0
			Asian	2	310	216	0.77 [0.49, 1.20]	0.25	F	0.33	0
			Caucasian	2	1172	637	1.09 [0.82, 1.46]	0.55	F	0.76	0
	rs360721	Allelic model	Total	4	2694	1424	0.89 [0.77, 1.02]	0.10	F	0.79	0
			Asian	3	2394	1324	0.89 [0.77, 1.03]	0.12	F	0.77	0
			Caucasian	1	300	100	0.59 [0.19, 1.80]	0.35	–	–	–
		Dominant model	Total	4	1347	712	0.84 [0.70, 1.01]	0.07	F	0.78	0
			Asian	3	1197	662	0.85 [0.70, 1.03]	0.09	F	0.84	
			Caucasian	1	150	50	0.51 [0.16, 1.63]	0.25	–	–	–
		Recessive model	Total	4	1347	712	0.92 [0.67, 1.26]	0.60	F	0.96	0
			Asian	3	1197	662	0.92 [0.67, 1.26]	0.60	F	0.85	0
			Caucasian	1	150	50	1.01 [0.04, 25.27]	0.99	–	–	–

OR odds ratio, *CI* confidence interval, *R* random model, *F* fixed model, – not available, *IL* interleukin

across studies may mainly due to the study conducted by Hassannia et al. [29]. An $I^2 = 10\%$ ($p = 0.33$) were obtained after excluded this study.

Sensitivity analysis and publication bias

The pooled ORs were not statistically altered when the fixed model changed into random model, and a study was omitted once at a time in each genetic model, which indicated the results of the meta-analysis were stable and trustworthy (Fig. 5). Both Egger's and Begg's tests were used to evaluate the publication bias of this meta-analysis. The results revealed that there was no obvious publication bias in overall analysis for *IL18* (rs187238, rs1946518 and rs360721), *FOXP3* (rs2232365 and rs3761548), and *IL13* (rs20541 and rs1800925) polymorphisms (Fig. 6; Table s2).

Discussion

Allergic rhinitis was considered to be caused by dominant differentiation of Th2 cells and over-expression of Th2 cytokines such as IL4 and IL5, which are related to the abnormal balance between Th1 and Th2 cytokine networks [35]. The elevated level of serum total IgE is also an important factor in the pathogenesis of AR [36]. Number of studies have shown that Th2 cytokines including IL-4, IL-5, IL-9, and IL-13 were closely associated with allergic disease, of which IL-13 is currently considered to be one of the most important cytokines [38, 39]. IL-13 is a pluripotent cytokine secreted mainly by Th2 cells of $CD40^+$ [40]. It can directly promote the secretion and improve the activity of B cells, and directly induce the synthesis of excessive IgE by B cells in patients with atopic constitution, thereby increasing the risk of AR [37, 41]. In addition, IL13 can induce T cells to differentiate into Th2 cells, support the expression of Th2

cytokines (IL-4, IL-5 and IL-6), and inhibit the production of IL-12 and INF-y in Th1 cells, thus affecting the occurrence and development of AR [42].

At present, several SNPs of *IL13* gene have been found to be associated with the pathogenesis and phenotype of allergic diseases such as asthma [43], atopic dermatitis [44], and AR [31]. The human *IL-13* gene is located in region 5q31 and is a highly polymorphic gene. The relative position of 1103C/T (rs20541) within the promoter sequence to the transcription start site is − 1112, and its polymorphism may affect the binding force of nuclear protein and DNA to change the transcription level of IL-13 [45]. Huebner M et al. [18] and Lianes E et al. [19] found

Table 4 The association between the FOXP3 gene polymorphisms and allergic rhinitis risk

Genes	Polymorphisms	Genetic models	Subtypes	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
					Case	Control	OR [95% CI]	*p* value		*p* value	I^2 (%)
FOXP3	rs2232365	Allelic model	Total	4	1526	1452	1.05 [0.90, 1.23]	0.51	F	0.34	11
			Asian	4	1526	1452	1.05 [0.90, 1.23]	0.51	F	0.34	11
			Caucasian	–	–	–	–	–	–	–	–
		Dominant model	Total	4	763	726	1.08 [0.87, 1.33]	0.50	F	0.42	0
			Asian	4	763	726	1.08 [0.87, 1.33]	0.50	F	0.42	0
			Caucasian	–	–	–	–	–	–	–	–
		Recessive model	Total	4	763	726	1.03 [0.80, 1.34]	0.81	F	0.37	5
			Asian	4	763	726	1.03 [0.80, 1.34]	0.81	F	0.37	5
			Caucasian	–	–	–	–	–	–	–	–
	rs3761548	Allelic model	Total	5	1778	1746	0.90 [0.61, 1.33]	0.60	R	0.0003	81
			Asian	4	1574	1550	1.07 [0.80, 1.42]	0.67	R	0.08	56
			Caucasian	1	204	196	0.45 [0.30, 0.68]	0.0001	–	–	–
		Dominant model	Total	5	889	873	0.90 [0.57, 1.44]	0.67	R	0.01	68
			Asian	4	787	775	1.09 [0.86, 1.38]	0.46	F	0.70	0
			Caucasian	1	102	98	0.04 [0.00, 0.28]	0.001	–	–	–
		Recessive model	Total	5	889	873	0.93 [0.50, 1.72]	0.81	R	0.002	77
			Asian	4	787	775	1.13 [0.57, 2.22]	0.73	R	0.008	74
			Caucasian	1	102	98	0.44 [0.24, 0.82]	0.009	–	–	–

OR odds ratio, *CI* confidence interval, *R* random model, *F* fixed model, – not available, *FOXP3* Forkhead transcription factor P3

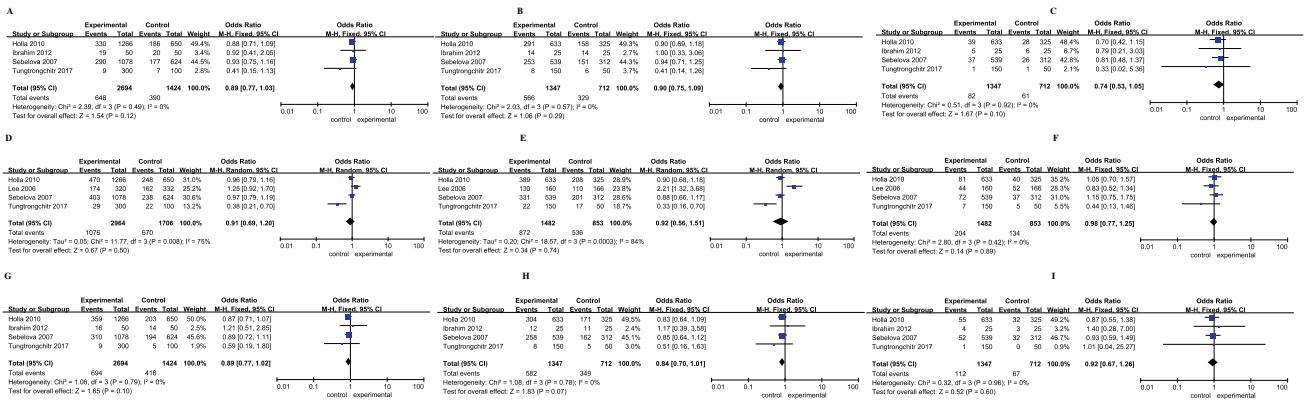


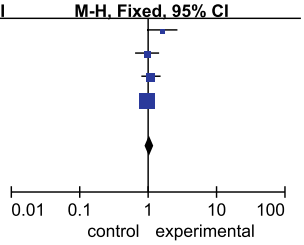
Fig. 2 Forest plots of odds ratios for the association between *IL18* gene polymorphisms and allergic rhinitis. rs187238; **a** allelic model; **b** dominant model; **c** recessive model; rs1946518; **d** allelic model; **e** dominant model; **f** recessive model; rs360721; **g** allelic model; **h** dominant model; **i** recessive model

Fig. 3 Forest plots of odds ratios for the association between *FOXP3* gene polymorphisms and allergic rhinitis. rs2232365 **a** allelic model; **b** dominant model; **c** recessive model; rs3761548 **d** allelic model; **e** dominant model; **f** recessive model

A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassannia 2014	46	204	30	196	7.9%	1.61 [0.97, 2.68]
li 2014	107	180	129	214	15.9%	0.97 [0.64, 1.45]
Zhang 2009	103	386	95	382	23.2%	1.10 [0.80, 1.52]
Zhang 2012	255	756	226	660	53.1%	0.98 [0.78, 1.22]
Total (95% CI)		**1526**		**1452**	**100.0%**	**1.05 [0.90, 1.23]**
Total events	511		480			

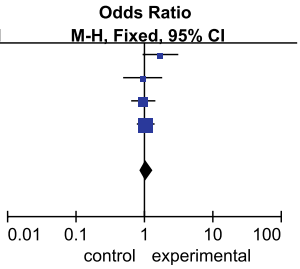
Heterogeneity: Chi² = 3.36, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.65 (P = 0.51)



B

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassannia 2014	39	102	26	98	9.9%	1.71 [0.94, 3.13]
li 2014	68	90	82	107	11.0%	0.94 [0.49, 1.82]
Zhang 2009	78	193	79	191	28.5%	0.96 [0.64, 1.44]
Zhang 2012	162	378	138	330	50.7%	1.04 [0.77, 1.41]
Total (95% CI)		**763**		**726**	**100.0%**	**1.08 [0.87, 1.33]**
Total events	347		325			

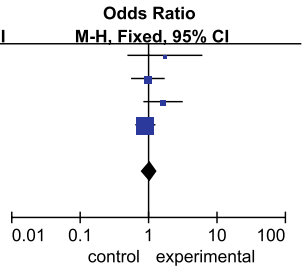
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)



C

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hassannia 2014	7	102	4	98	3.4%	1.73 [0.49, 6.11]
li 2014	39	90	47	107	21.5%	0.98 [0.55, 1.72]
Zhang 2009	25	193	16	191	12.4%	1.63 [0.84, 3.16]
Zhang 2012	93	378	88	330	62.7%	0.90 [0.64, 1.26]
Total (95% CI)		**763**		**726**	**100.0%**	**1.03 [0.80, 1.34]**
Total events	164		155			

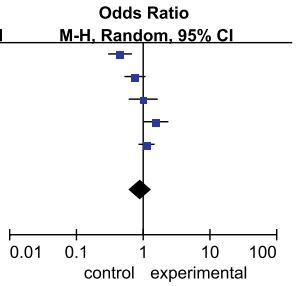
Heterogeneity: Chi² = 3.16, df = 3 (P = 0.37); I² = 5%
Test for overall effect: Z = 0.25 (P = 0.81)



D

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Fodor 2011	103	204	136	196	19.7%	0.45 [0.30, 0.68]
Hassannia 2014	79	212	127	288	20.7%	0.75 [0.52, 1.08]
Song 2016	37	220	37	220	17.9%	1.00 [0.61, 1.65]
Zhang 2009	61	386	41	382	19.4%	1.56 [1.02, 2.39]
Zhang 2012	136	756	108	660	22.3%	1.12 [0.85, 1.48]
Total (95% CI)		**1778**		**1746**	**100.0%**	**0.90 [0.61, 1.33]**
Total events	416		449			

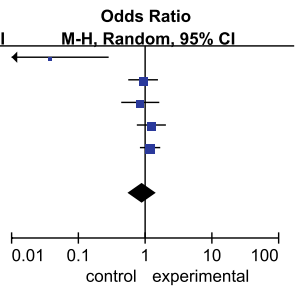
Heterogeneity: Tau² = 0.16; Chi² = 20.93, df = 4 (P = 0.0003); I² = 81%
Test for overall effect: Z = 0.52 (P = 0.60)



E

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Fodor 2011	80	102	97	98	4.6%	0.04 [0.00, 0.28]
Hassannia 2014	63	106	88	144	23.6%	0.93 [0.56, 1.56]
Song 2016	21	110	24	110	20.0%	0.85 [0.44, 1.63]
Zhang 2009	42	193	35	191	23.9%	1.24 [0.75, 2.05]
Zhang 2012	94	378	72	330	27.9%	1.19 [0.84, 1.68]
Total (95% CI)		**889**		**873**	**100.0%**	**0.90 [0.57, 1.44]**
Total events	300		316			

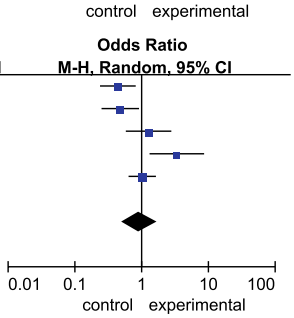
Heterogeneity: Tau² = 0.17; Chi² = 12.57, df = 4 (P = 0.01); I² = 68%
Test for overall effect: Z = 0.43 (P = 0.67)



F

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Fodor 2011	23	102	39	98	21.1%	0.44 [0.24, 0.82]
Hassannia 2014	16	106	39	144	20.7%	0.48 [0.25, 0.91]
Song 2016	16	110	13	110	18.7%	1.27 [0.58, 2.78]
Zhang 2009	19	193	6	191	16.5%	3.37 [1.31, 8.63]
Zhang 2012	42	378	36	330	23.1%	1.02 [0.64, 1.64]
Total (95% CI)		**889**		**873**	**100.0%**	**0.93 [0.50, 1.72]**
Total events	116		133			

Heterogeneity: Tau² = 0.37; Chi² = 17.23, df = 4 (P = 0.002); I² = 77%
Test for overall effect: Z = 0.24 (P = 0.81)



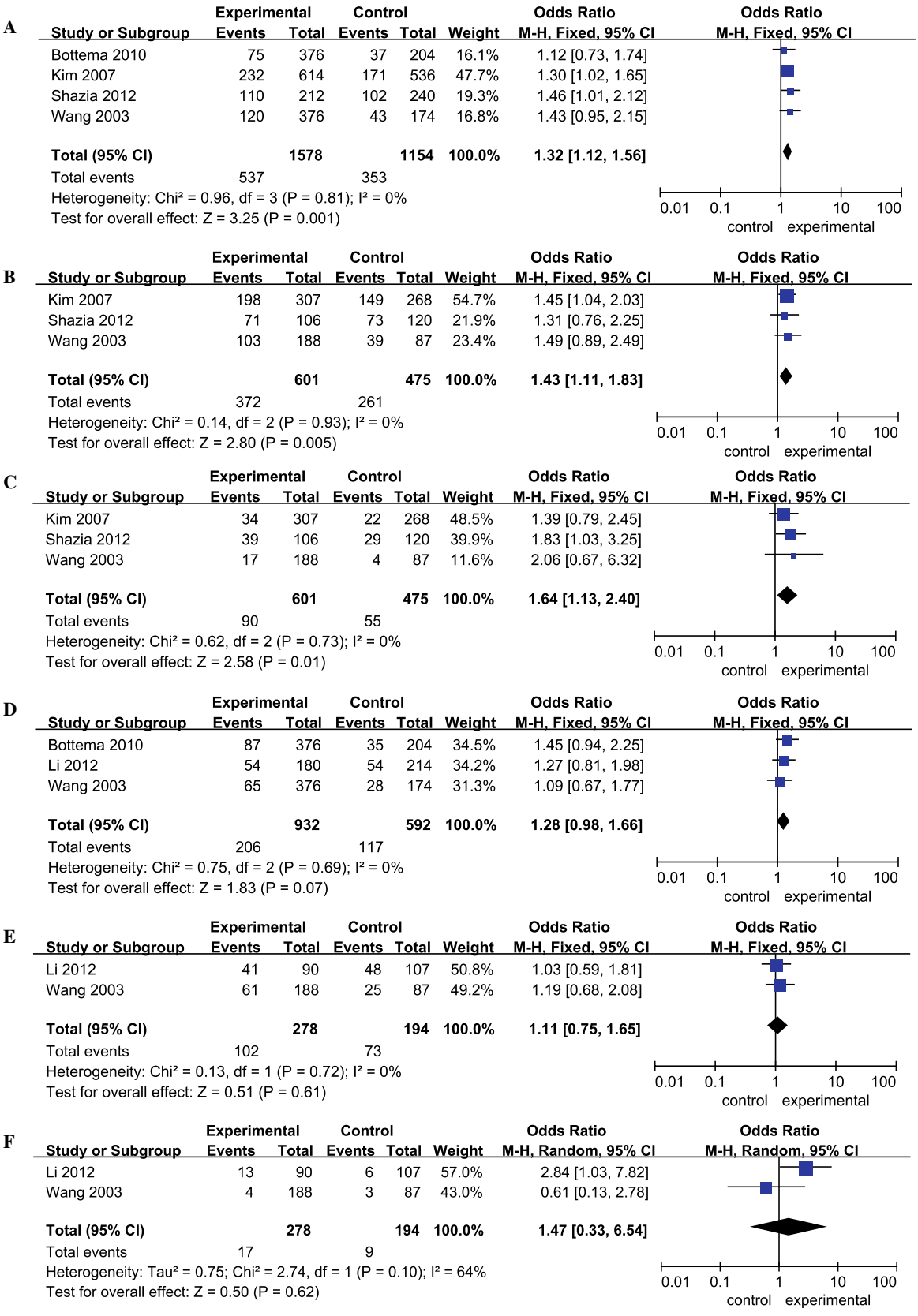


Fig. 4 Forest plots of odds ratios for the association between *IL13* gene polymorphisms and allergic rhinitis. rs20541 **a** allelic model; **b** dominant model; **c** recessive model; rs1800925 **d** allelic model; **e** dominant model; **f** recessive model

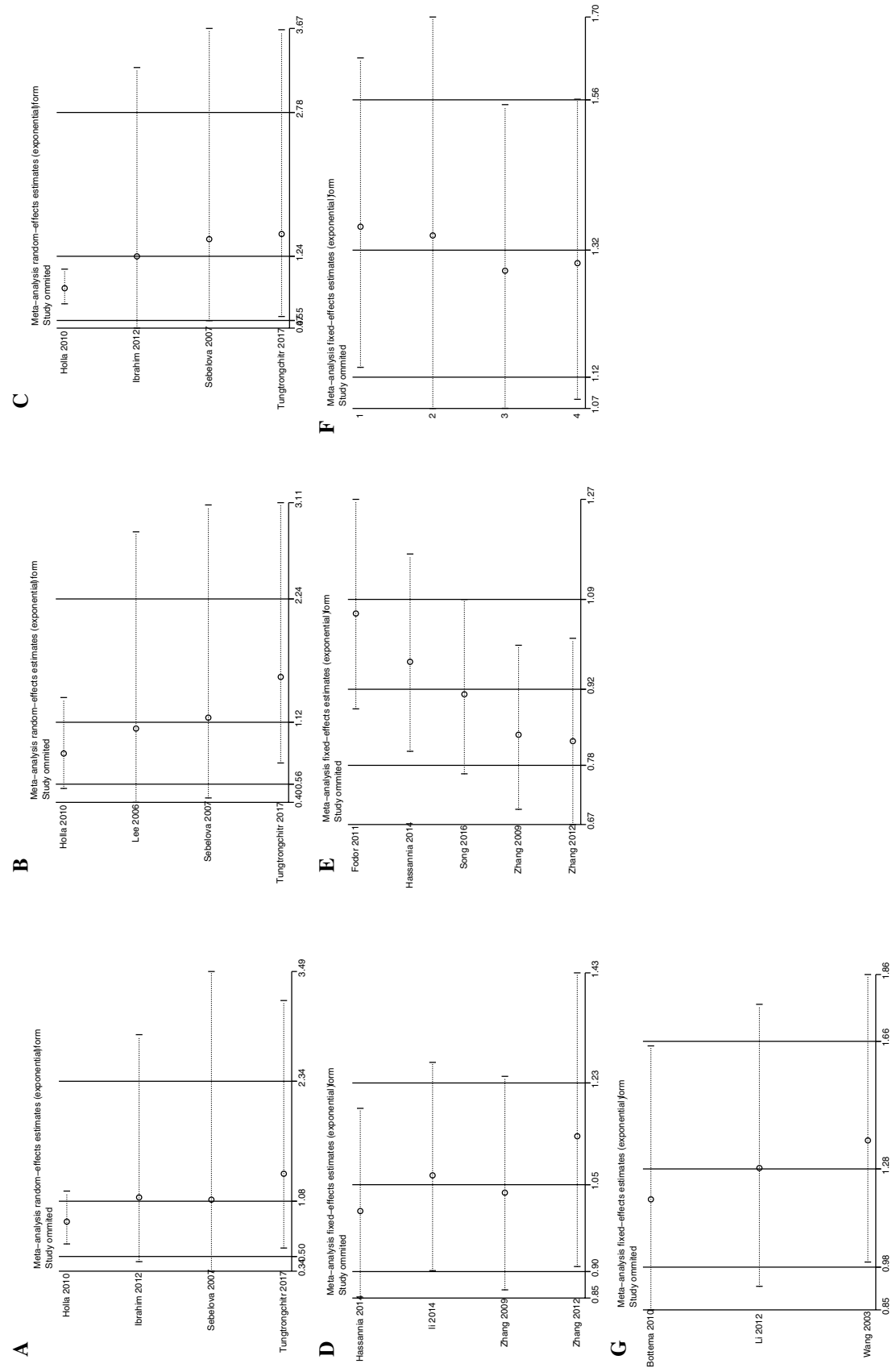


Fig. 5 Sensitivity analyses between *IL18*, *FOXP3*, *IL13* gene polymorphisms and allergic rhinitis. **a** rs187238; **b** rs1946518; **c** rs360721; **d** rs2232365; **e** rs3761548; **f** rs20541; **g** rs1800925

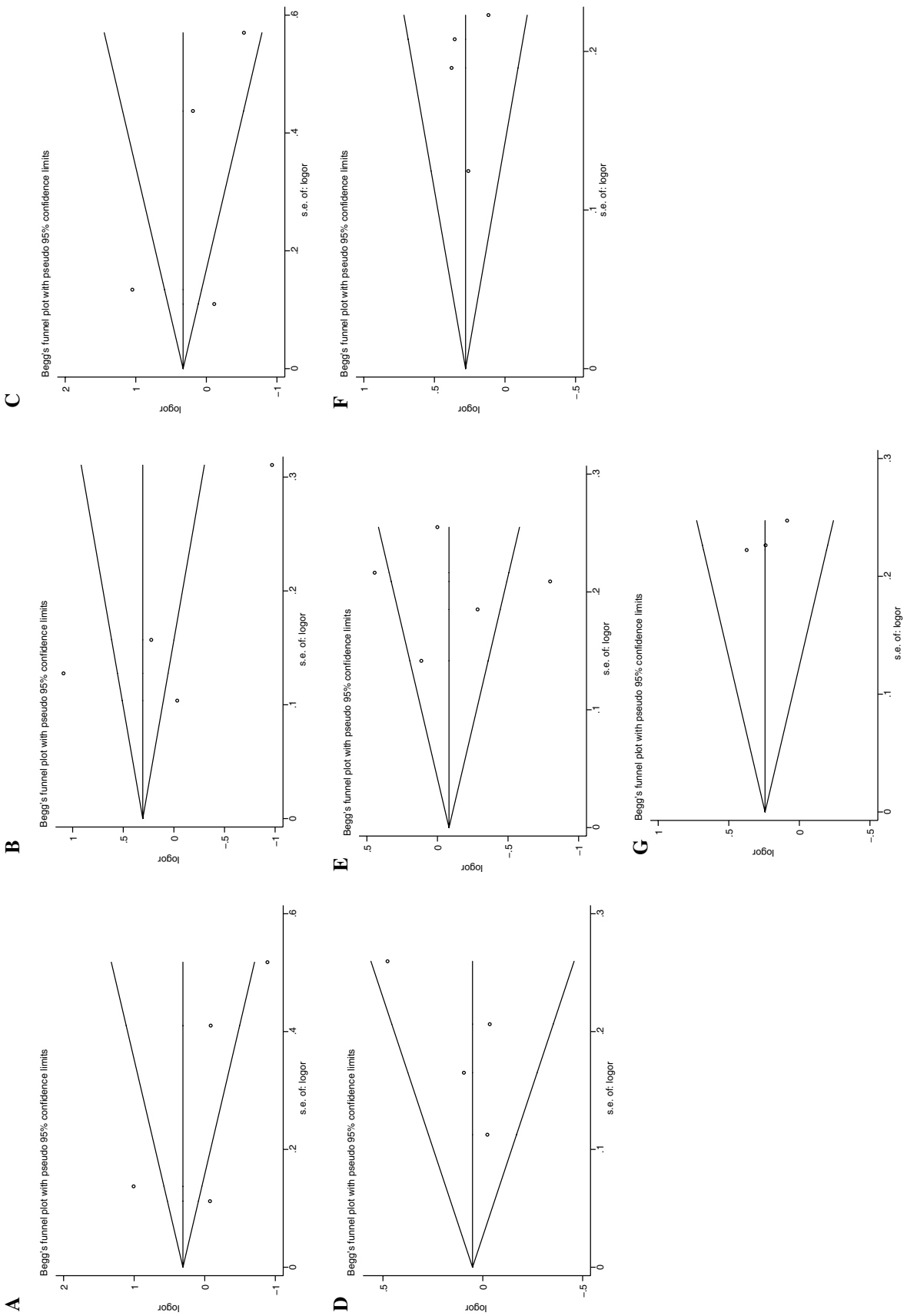


Fig. 6 Publication bias of literatures for allelic model of *IL18*, *FOXP3*, *IL13* gene polymorphisms were tested by Begg's funnel plot. **a** rs187238; **b** rs1946518; **c** rs360721; **d** rs2232365; **e** rs3761548; **f** rs20541; **g** rs1800925

that the frequency of TT genotype of the *IL13* (rs1800925) significantly reduced in AR group. Wang et al. found the *IL-13* rs20541, but not the *IL-13* rs1800925 was related to AR susceptibility [20]. There are many possible reasons for the different association between the AR group and *IL-13* in different populations. For example: (1) AR is a polygenic disease, and other genes may also be associated with susceptibility to AR; (2) differences in the selection of patients with AR; (3) the effect of IL-13 varies due to changes in dietary habits, geographical environment, human growth status and other environmental factors in different regions. In the previous studies, the results of the genetic associations between the *IL13* rs20541 and AR risk was inconsistent in different population, which may due to the limited sample size in individual study. In our meta-analysis, we demonstrated that the *IL13* rs20541 was significantly associated with the increased risk of AR in Asian population. For lack of data, we failed to came to the conclusion that *IL13* rs20541 was associated with AR in Caucasian population. Thus, large samples in multiple ethnicity and case–control designed studies may shed light on the relationship between *IL-13* rs20541 and AR risk.

FOXP3 is a member of the forkhead/winged-helix family of transcription factors [47]. FOXP3 dysfunction in humans can lead to severe systemic immune disorders, such as enteritis [48], autoimmune anemia [49], and type l diabetes [50], as well as severe allergic inflammatory disease [51]. Thus, the normal expression of *FOXP3* gene is essential to maintain the function of $CD^{4+}CD^{25+}$Treg cells and the self-stabilizing state of the whole immune system. A study found that expression of *FOXP3* protein decreased in $CD^{4+}CD^{25+}$Treg cells in asthma patients [52]. Similarly, decreased *FOXP3* expression was found in nasal secretions of AR patients [13]. Researchers speculated that SNPs in *FOXP3* may reduce the number or influence the function of $CD^{4+}CD^{25+}$ treg cells, and lead to immune tolerance disorders [53]. Zhang et al. found that the mutation of AC heterozygosity in *FOXP3* rs3761548 was correlated with the incidence of AR, while *FOXP3* rs3761547 was correlated with AR allergic to dust mites [16]. Our combined results indicated that the *FOXP3* rs3761548 was not the susceptible factor for AR. However, because the literature and sample size included in this study were relatively small, the results may be biased to some extent, which still needs to be further studied in the future.

There were limitations in our combined analysis. Firstly, the sample size and the number of included studies were relatively small, especially in Caucasian population, which may partly influence the results of the genetic association between the genes polymorphisms and the risk of AR. To further identify the findings in the present study, more articles with larger number of subjects are necessary. Secondly, both the genetic and environmental factors were determined to play a role in the development of AR. However, we failed to detected the influence of environmental factors and AR risk for lack of sufficient data. Thirdly, some genetic models displayed high heterogeneity, although subgroup analysis was performed to detect the sources of this heterogeneity.

Conclusions

Our findings suggested that the *IL13* rs20541 may contribute to the risk of AR in Asian population. To confirm this result, larger number of case–control designed studies with more subjects is necessary in the future.

Acknowledgements The present study was funded by the National Natural Science Foundation of China (Grant nos. 81873780, 61702054); Hunan Natural Science Foundation Youth Program (2019JJ50697, 2018JJ3568); The Changsha Outstanding Innovative Young People Training Scheme (kq1905047, kq1905045); The Foundation of the Education Department of Hunan Province (16A027, 19A058); The Foundation of Health and Family Planning Commission of Hunan Province (20201918); The Application Characteristic Discipline of Hunan Province; The Hunan Key Laboratory Cultivation Base of the Research and Development of Novel Pharmaceutical Preparations (No. 2016TP1029); The clinical research center of neurodegenerative diseases in Hunan province (2018SK4002); The Hunan Provincial Innovation Platform and Talents Program (No. 2018RS3105); The Hunan provincial science and technology department and Hunan provincial health and family planning commission (Grant No.[2018]85); The Natural science foundation of Hunan province (Grant No.[2017]1); The Key project of Hunan provincial commission of health and family planning (Grant No.[2017]144); The Hunan province science and technology major project (Grant No.[2016]158); Hunan Provincial Science and Technology Department Clinical Medical Technology Innovation Guide Project(2018SK51711).

Conflict of interest The authors declare that they have no competing interest.

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