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Association of IL-4 promoter polymorphisms with asthma: a meta-analysis

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ABSTRACT. This study aimed to more precisely assess the correlation between interleukin-4 (IL-4) promoter polymorphisms and the susceptibility risk of asthma. We conducted association studies on IL-4 promoter C-33T, C-589T, and G-1098T polymorphisms with asthma using data obtained from MEDLINE up to September 2011. Results showed that the polymorphisms IL-4 C-33T and C-589T were significantly associated with asthma; however, significant associations were found only in the European population. In addition, the TT+CT genotype was significantly associated with asthma in adults and no significant association was found in asthma status subgroup analyses. This meta-analysis showed that IL-4 C-589T and C-33T were associated with asthma in Europeans. To further confirm correlations between polymorphisms of the IL-4 promoter with asthma susceptibility, studies involving a larger number of patients worldwide are necessary.

Key words: IL-4; Promoter; Polymorphisms; Meta-analysis; Asthma

INTRODUCTION

Asthma is a complex inflammatory disease caused by a variety of stimuli, which is characterized by airway responsiveness, reversible airway obstruction, and inflammation. A multitude of cytokines is important in this inflammation (Zhu et al., 2000). A significant role for cytokines in the pathogenesis of asthma is evident, as they have been shown to play a critical role in immunoglobulin E (IgE) synthesis, eosinophil recruitment, and bronchial hyperresponsiveness (Renauld, 2001).

The Th2 cytokines [interleukin (IL)-4, IL-5, IL-9, IL-10, and IL-13] have a substantial effect on the pathogenesis of atopic diseases. IL-4 is produced by activated T cells, mast cells, and basophils, which participate in IgE synthesis and Th2 phenotype differentiation in T cells, and play a crucial role in the development of atopic diseases including asthma (Beghe et al., 2003).

Genome-wide association studies have suggested that an asthma susceptible locus could be mapped to chromosomes 5q31-33, covering genes encoding for human IL-4, IL-13, and IL-16. Moreover, the IL-4 gene was associated with asthma in more than three independent study populations (Liu et al., 2003; Michel et al., 2010). A polymorphism (C-589T) in the IL-4 promoter region seems to be related to elevated serum levels of IgE (Berenguer et al., 2012). Another single nucleotide polymorphism (SNP), C-33T, located in the 5'-untranslated region (UTR) of IL-4, was reported to be associated with asthma (Kim et al., 2010). Additionally, although a third polymorphism, G-1098T, has been investigated in several cohorts, its correlation with asthma varies across studies (Gervaziev et al., 2006; Amirzargar et al., 2009; Baye et al., 2011). Further investigations indicated that the polymorphisms C-589T and C-33T were associated with asthma by some authors, but by no means all (Elliott et al., 2001; Haller et al., 2009), which may be due to small sample sizes, low statistical power, and/or clinical heterogeneity.

Due to these conflicting and controversial results, combined evidence needs to be taken into account in order to assess the association between IL-4 promoter polymorphisms and asthma. In the present study, we carried out a meta-analysis to evaluate the association of IL-4 promoter polymorphisms with asthma susceptibility risk among different ethnic and asthma status groups.

MATERIAL AND METHODS

Identification and selection of relevant studies

The key words (“Interleukin-4” or “IL-4”) and (“asthma”) were used in the PUBMED database to identify relevant publications. Meanwhile, additional studies were identified by cross-referencing within original or review articles. Studies were not restricted to any particular language. Data from any fully published paper, excluding meeting or conference abstracts, were extracted. A study was included in the current meta-analysis if it conformed to the following criteria: i) an unrelated case-control design was used; ii) allele or genotype frequencies were available; and iii) frequencies of SNPs were in Hardy-Weinberg (HW) equilibrium.

Data extraction

Information of first author, year of publication, type of study design, ethnicity, age, asthma status, total sample size, number of cases and controls, genotype, haplotypes containing SNPs C-33T and C-589T, and allele frequencies were collected from each study. Two independent authors (L. Tang and H-G. Lin) extracted all data from each study and consensus was achieved for all studies.

Statistical methods

The odds ratio (OR) and the 95% confidence interval (95%CI) were calculated for each study. Variation and heterogeneity were evaluated using Cochran's Q-statistic. If significant heterogeneity was observed across studies ($P < 0.10$), the random-effect model was used for meta-analysis, otherwise, the fixed-effect model was used. The effect of heterogeneity was also measured by the I^2 value: $I^2 = 100\% \times (Q - d.f.) / Q$. Calculation of power was obtained at the 0.05 significance level, assuming an OR of 1.5 (small effect size). G*Power was used to perform the power analysis (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower).

Publication bias

Publication bias was assessed using the Egger test. A P value < 0.05 was considered to indicate statistically significant publication bias. Sensitivity analysis excluding individual studies was performed in the meta-analysis. All statistical analyses were conducted with RevMan 5 (Oxford, UK) and STATA10.0 (http://www.stata.com) programs.

RESULTS

Studies included in the meta-analysis

There were 160 papers identified through the initial search. After browsing titles and abstracts, 14 reviews were excluded, 19 articles were excluded because they were not conducted with human subjects, and 8 articles were excluded because they did not explore associations with asthma. After reading the full articles, 101 studies were excluded for not exploring IL-4 genetic polymorphisms, leaving 18 studies for full publication review (Rosenwasser et al., 1995; Laitinen et al., 1997; Sandford et al., 2000; Zhu et al., 2000; Noguchi et al., 1998, 2001; Freidin et al., 2003; Basehore et al., 2004; Park et al., 2004; Donfack et al., 2005; Gervaziev et al., 2006; Amirzargar et al., 2009; Wang et al., 2009; Beghe et al., 2003, 2010; Yang et al., 2011; Baye et al., 2011; Dmitrieva-Zdorova et al., 2012). Seven studies were excluded because they were family-based (Rosenwasser et al., 1995; Laitinen et al., 1997; Zhu et al., 2000; Noguchi et al., 1998, 2001; Beghe et al., 2003; Freidin et al., 2003). Four studies were excluded because allele frequencies were in HW disequilibrium (Gervaziev et al., 2006; Amirzargar et al., 2009; Wang et al., 2009; Dmitrieva-Zdorova et al., 2012). Meanwhile, 14 studies were added by cross-referencing (Walley and Cookson, 1996; Takabayashi et al., 2000; Suzuki et al., 2000; Hijazi and Haider, 2000; Cui et al., 2003a,b; Lee et al., 2004; Zhang et al., 2005; Isidoro-García et al., 2005; Chiang et al., 2007; Kamali-Sarvestani et al., 2007; Hosseini-Farahabadi et al., 2007; Mak et al., 2007; Rad et al., 2010). Therefore, a total of 21 studies were included in the meta-analysis (Table 1). Overall, eligible studies involved a total of 6421 asthma patients and 4755 healthy controls from 7 European, 14 Asian, and 3 African-

American sample populations. Four studies comprised two or three different subpopulations (Basehore et al., 2004; Donfack et al., 2005; Zhang et al., 2005; Baye et al., 2011). Each population was treated independently. Therefore, 30 separate comparisons were possible. The meta-analysis was performed if there were at least two comparisons; therefore, a total of 29 comparisons were performed in this meta-analysis.

Table 1. Characteristics of individual studies included in this meta-analysis.

SNP	Reference (1st author)	Country (ethnic)	Year	Subjects age	Asthma status	Number		OR, P value	Power[a] (α = 0.05, OR = 1.5)
						Case	Control		
C-589T	Basehore	USA	2004	Adult	A	233	245	1.04, 0.82	70.4
		African-American	2004	Adult	A	168	269	0.88, 0.37	67.1
		Hispanic	2004	Adult	A	116	130	1.18, 0.38	46.8
	Park	Korean	2004	Adult	A /NA	532	170	0.94, 0.76	84.2
	Beghe	UK	2009	Adult	A	299	176	1.01, 0.99	70.2
	Sandford	New Zealand	2000	Adult	A	233	143	1.39, 0.097	61.4
	Baye	Caucasian	2011	Children	A/NA	413	298	2.00, 0.00002	84.6
		African-American	2011	Children	A/NA	315	51	0.56, 0.008	60.8
	Donfack	European	2005	Adult	A/NA	126	205	0.98, 0.92	57.1
		African-American	2005	Adult	A/NA	205	183	1.17, 0.29	62.9
	Chiang	Taipei	2007	Adult	Unknown	167	112	4.06, <0.0001	51.2
	Kamali-Sarvestani	Iran	2007	Adult	A	203	112	2.05, 0.007	55.3
	Takabayashi	Japanese	2000	Children	A	100	100	4.11, <0.0001	40.9
	Lee	Korean	2004	Children	A/NA	256	100	0.88, 0.57	59.8
	Rad	Iran	2010	Adult	Unknown	64	65	0.76, 0.42	30.5
	Cui	Chinese	2003	Adult	A	98	103	0.76, 0.27	41.1
	Hijazi	Kuwaiti Arabs	2000	Adult	A/NA	84	100	1.23, 0.4	38.7
	Walley	UK	1996	Adult	A	124	59	1.34, 0.25	38.6
	Cui	Chinese	2003	Adult	A	241	175	0.84, 0.29	65.6
	Mak	Chinese	2007	Adult	A/NA	292	292	0.94, 0.67	77.9
	Hosseini	Iran	2007	Adult	A	30	50	3.14, 0.005	22.4
	Zhang	Chinese	2005	Adult	A/NA	145	156	0.83, 0.40	53.4
		Malayan	2005	Adult	A/NA	73	93	1.09, 0.72	35.9
		Hindoo	2005	Adult	A/NA	85	99	1.19, 0.49	38.5
C-33T	Yang	Chinese	2011	Adult	A/NA	202	205	0.99, 0.713	64.8
	Basehore	USA	2004	Adult	A	233	245	1.55, 0.014	70.9
		African-American	2004	Adult	A	168	269	1.04, 0.79	67.5
		Hispanic	2004	Adult	A	116	130	1.19, 0.37	47.1
	Park	Korean	2004	Adult	A/NA	532	170	0.89, 0.44	84.5
	Isidoro-García	Caucasian	2005	Adult	A/NA	133	79	1.82, 0.07	41.2
	Suzuki	Japanese	2000	Adult	A	120	120	1.02, 0.92	46.3
G-1098T	Baye	African-American	2011	Children	A/NA	315	51	0.47, 0.008	60.8

OR = odds ratio; a = power calculations assume α = 0.05 and small effect size (0.1) or OR = 1.5; SNP = single nucleotide polymorphism; A = atopic; NA = nonatopic.

Two IL-4 gene polymorphisms were investigated in the meta-analysis. The distribution of genotypes was in HW equilibrium in these studies ($P < 0.05$). Ethnicity-specific meta-analyses were conducted for European, Asian, and African-American populations. Subgroup analyses were also performed with respect to asthma status.

Main results

Results of the meta-analysis of the relationship between IL-4 promoter polymorphisms and asthma are shown in Table 2, Figures 1 and 2. Due to an insufficient number of studies, the meta-analysis of G-1098T haplotypes containing SNPs C-33T and C-589T with asthma was not conducted in this study. In this analysis, the overall ORs for IL-4 C-33T were significantly increased in asthma (OR = 1.14, 95%CI = 1.00-1.31, P = 0.04). Moreover, a significant association was revealed in Europeans (OR = 1.26, 95%CI = 1.03-1.55, P = 0.02), but not in Asians (OR = 1.03, 95%CI = 0.85-1.26, P = 0.74). Neither the TT nor the TT+CT genotype of C-33T were associated with asthma (P > 0.05). A significant association was found between C-589T and asthma (OR = 1.20, 95%CI = 1.01-1.42, P = 0.04). However, the ethnic-specific meta-analysis showed that this association only existed in Europeans (OR = 1.27, 95%CI = 1.10-1.46, P = 0.0009). The meta-analysis showed a significant association of the TT+CT genotype of C-589T with asthma (OR = 1.30, 95%CI = 1.11-1.53, P = 0.001) but not the TT genotype (OR = 1.11, 95%CI = 0.86-1.44, P = 0.43). With respect to these genotypes, results based on ethnicity showed no difference from the combined results.

Table 2. Main results of IL-4, in terms of asthma risk in this meta-analysis.

SNP	Comparison	Sample size		No. of studies	Test of association			Model	Test of heterogeneity			Publication bias
		Disease	Control		OR	95%CI	P value		Q	P value	I^2	P value (Egger's test)
C-589T	*T vs C*											
	European	3088	2502	7	1.24	1.03-1.50	0.02	F	10.3	0.11	42	0.41
	Asian	4740	3454	14	1.31	0.99-1.74	0.06	R	72	<0.00001	82	0.11
	African-American	1376	1066	3	0.85	0.58-1.25	0.42	R	8	0.02	75	0.14
	Overall	9204	6962	24	1.20	1.01-1.42	0.04	R	100	<0.00001	77	0.47
	TT vs TC+CC											
	Overall	2312	2174	15	1.11	0.86-1.44	0.43	R	24.6	0.001	60	0.10
	European	269	438	2	0.90	0.17-4.86	0.91	R	3.1	0.08	68	NA
	Asian	1838	1553	12	1.11	0.82-1.49	0.51	R	31.4	0.0009	65	0.09
	TT+TC vs CC											
	Overall	2020	1798	17	1.30	1.11-1.53	0.001	F	16.3	0.43	2	0.07
	European	602	749	3	1.29	1.03-1.62	0.03	F	2	0.89	0	0.10
	Asian	1838	1553	13	1.36	1.07-1.72	0.01	F	15.8	0.20	24	0.97
C-33T	*T vs C*											
	European	1068	1186	3	1.26	1.03-1.55	0.02	F	4.6	0.10	56	0.55
	Asian	1708	990	3	1.03	0.85-1.26	0.74	F	7.4	0.73	0	0.64
	Overall	3008	2436	7	1.14	1.00-1.31	0.04	F	8.7	0.31	15	0.08
	TT vs TC+CC											
	Overall	455	404	3	1.07	0.78-1.47	0.66	F	2	0.95	0	NA
	European	133	79	1	1.82	0.07-44.72	0.72	-		-	-	-
	Asian	322	325	2	1.07	0.78-1.47	0.69	F	1	0.99	0	NA
	TT+TC vs CC											
	Overall	455	404	3	1.08	0.69-1.69	0.75	R	5.6	0.06	64	0.08
	European	133	79	1	1.84	0.94-3.60	0.08	-		-		-
	Asian	322	325	2	0.66	0.35-1.24	0.20	F	1	0.33	0	NA

OR = odds ratio; 95%CI = 95% confidence interval; NA = not available; F = fixed-effect model; R = random-effect model.

Subgroups were also analyzed based on asthma status: unknown (atopy status nondefined); atopic asthma; and nonatopic asthma. In the atopic and nonatopic asthma subgroups, no associations between C-589T and asthma were revealed, except for TT *vs* TC+CC in the asthma group. Furthermore, no association was discovered between C-33T and asthma (Figures 3 and 4).

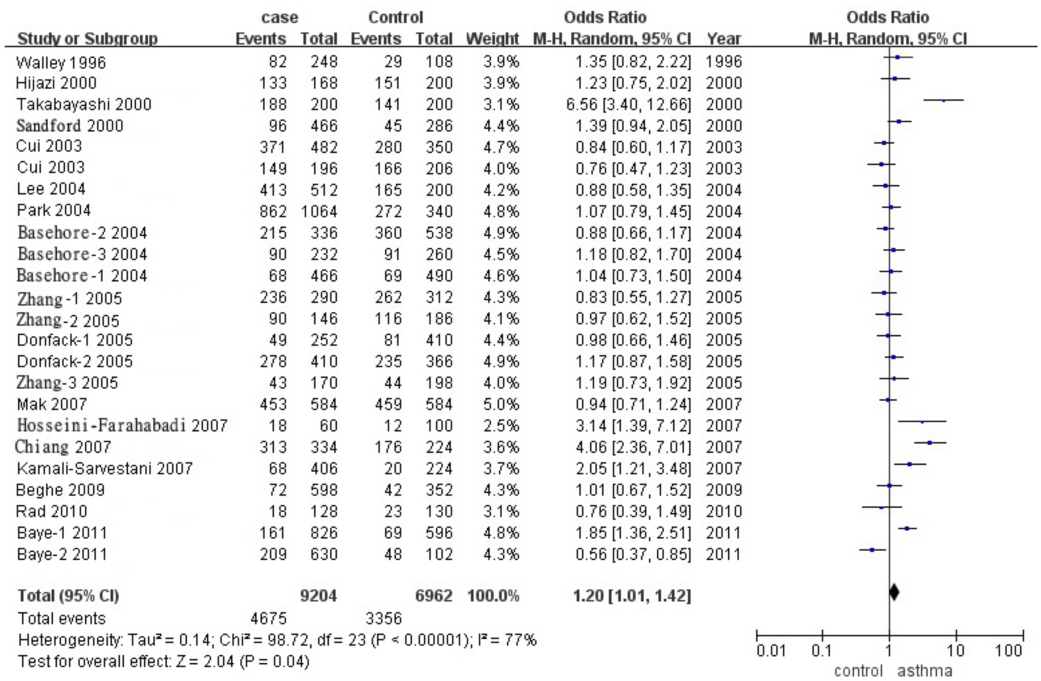

Figure 1. Odds ratio and 95% confidence interval (95%CI) from individual studies testing association of the C-589T polymorphisms and asthma.

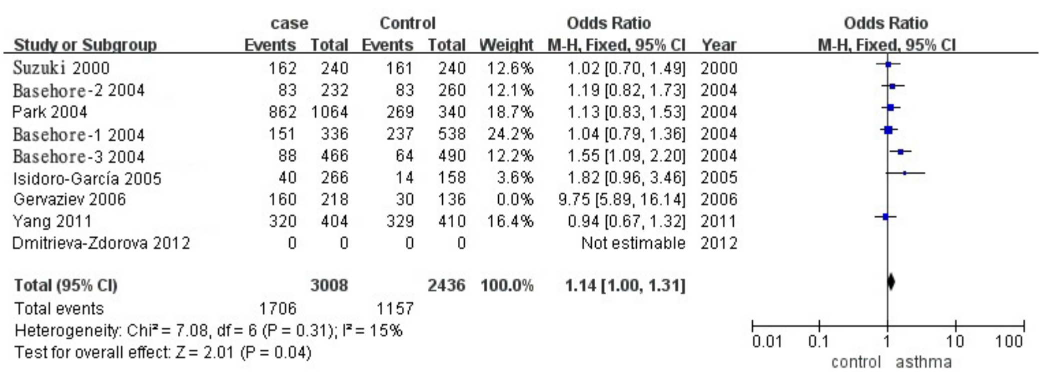

Figure 2. Odds ratio and 95% confidence interval (95%CI) from individual studies testing association of the C-33T polymorphisms and asthma.

No significant association was found between C-589T and asthma when stratified by age, except for the TT+CT (dominant) genotype in adults. This result was in agreement with the overall results of the genotype analysis (Figure 5).

Study or Subgroup	asthma Events	asthma Total	control Events	control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 by atopy asthma						
Walley	82	248	29	108	2.9%	1.35 [0.82, 2.22]
Takabayashi	188	200	141	200	2.6%	6.56 [3.40, 12.66]
Sandford	96	466	45	286	3.2%	1.39 [0.94, 2.05]
Beghe	72	598	42	352	3.1%	1.01 [0.67, 1.52]
Park	598	738	135	164	3.1%	0.92 [0.59, 1.43]
Cui	149	196	166	206	3.0%	0.76 [0.47, 1.23]
Kamali-Sarvestani	68	406	20	224	2.9%	2.05 [1.21, 3.48]
Donfack-1	32	164	67	410	3.0%	1.24 [0.78, 1.98]
Donfack-2	217	320	235	366	3.3%	1.17 [0.86, 1.61]
Mak	283	356	158	200	3.1%	1.03 [0.67, 1.58]
Basehore-1	68	466	69	490	3.2%	1.04 [0.73, 1.50]
Basehore-2	215	336	360	538	3.4%	0.88 [0.66, 1.17]
Basehore-3	90	232	91	260	3.2%	1.18 [0.82, 1.70]
Lee	321	392	164	200	3.1%	0.99 [0.64, 1.55]
Hosseini	18	60	12	100	2.3%	3.14 [1.39, 7.12]
Baye-1	105	538	35	596	3.1%	3.89 [2.60, 5.81]
Baye-2	100	300	48	102	3.0%	0.56 [0.36, 0.89]
Cui	371	482	280	350	3.3%	0.84 [0.60, 1.17]
Hijazi	96	120	25	34	2.1%	1.44 [0.60, 3.48]
Zhang-1	146	186	153	184	2.9%	0.74 [0.44, 1.25]
Zhang-2	66	114	52	104	2.9%	1.38 [0.81, 2.35]
Zhang-3	37	142	40	142	2.9%	0.90 [0.53, 1.52]
Subtotal (95% CI)		**7060**		**5616**	**65.7%**	**1.23 [1.00, 1.52]**
Total events	3418		2367			
Heterogeneity: Tau² = 0.18; Chi² = 99.90, df = 21 (P < 0.00001); I² = 79%						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.1.2 by nonatopy asthma						
Park	261	326	139	176	3.0%	1.07 [0.68, 1.68]
Donfack-1	16	88	67	410	2.7%	1.14 [0.62, 2.08]
Donfack-2	61	90	235	366	3.0%	1.17 [0.72, 1.92]
Mak	30	72	265	340	2.9%	0.20 [0.12, 0.34]
Lee	92	120	164	200	2.8%	0.72 [0.41, 1.26]
Baye-1	59	302	35	596	3.1%	3.89 [2.50, 6.07]
Baye-2	120	360	48	102	3.1%	0.56 [0.36, 0.88]
Hijazi	37	48	126	166	2.4%	1.07 [0.50, 2.29]
Zhang-1	90	104	109	136	2.5%	1.59 [0.79, 3.22]
Zhang-2	24	32	54	82	2.1%	1.56 [0.62, 3.91]
Zhang-3	6	28	4	56	1.4%	3.55 [0.91, 13.81]
Subtotal (95% CI)		**1570**		**2630**	**28.9%**	**1.09 [0.65, 1.83]**
Total events	796		1246			
Heterogeneity: Tau² = 0.64; Chi² = 84.54, df = 10 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.1.3 unknown						
Chiang 2007	313	334	176	224	2.9%	4.06 [2.36, 7.01]
Rad 2010	18	128	23	130	2.6%	0.76 [0.39, 1.49]
Subtotal (95% CI)		**462**		**354**	**5.4%**	**1.78 [0.34, 9.19]**
Total events	331		199			
Heterogeneity: Tau² = 1.31; Chi² = 14.41, df = 1 (P = 0.0001); I² = 93%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**9092**		**8600**	**100.0%**	**1.22 [0.99, 1.49]**
Total events	4545		3812			
Heterogeneity: Tau² = 0.30; Chi² = 208.18, df = 34 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%						

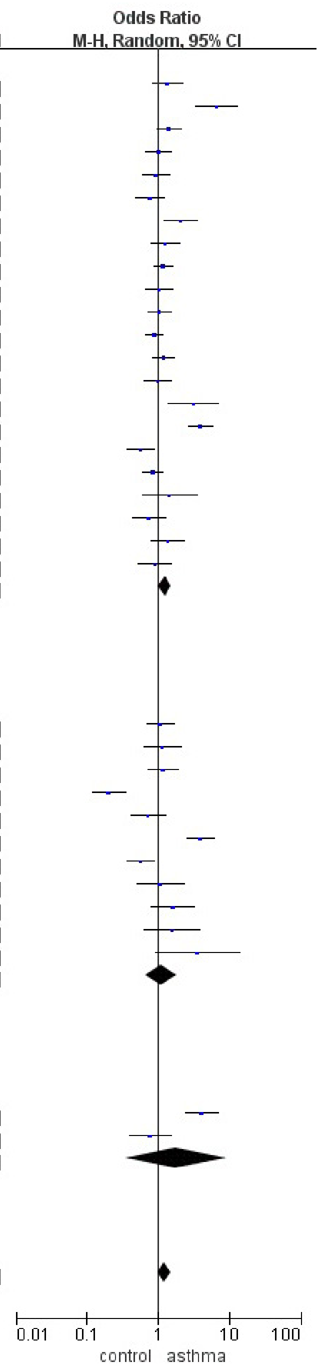

Figure 3. Forest plot of asthma risk associated with the C-589T polymorphism in the stratified analyses by asthma status.

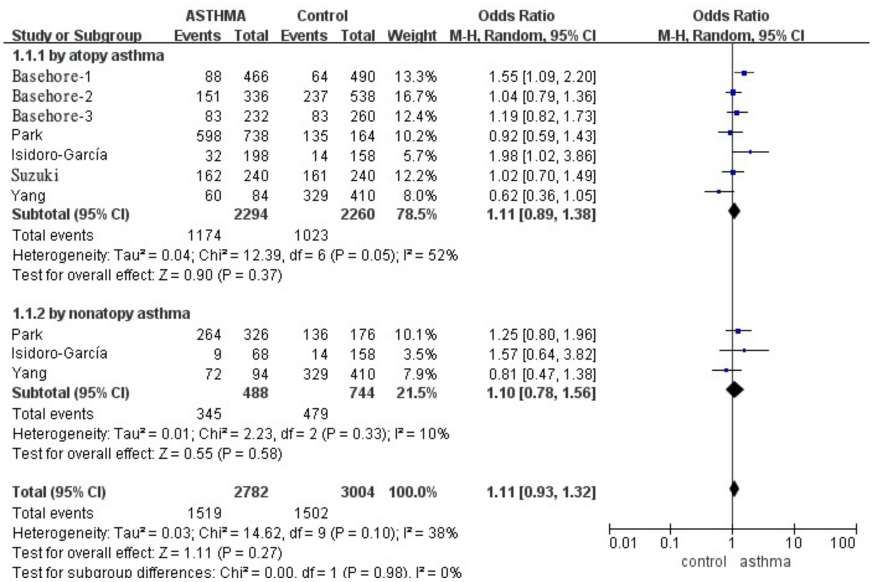

Figure 4. Forest plot of asthma risk associated with the C-33T polymorphism in the stratified analyses by asthma status.

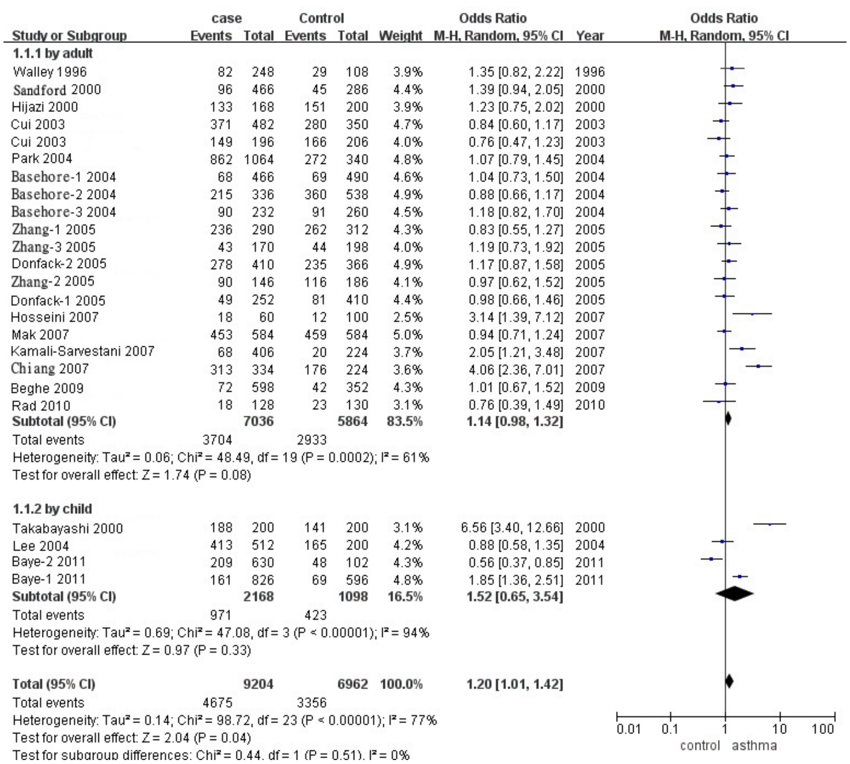

Figure 5. Forest plot of asthma risk associated with the C-589T polymorphism in the stratified analyses by age.

Heterogeneity and publication bias

There was heterogeneity for C-589T, the T allele, and genotype in the meta-analysis. Significant heterogeneity was found with respect to Asian origin, asthma status, and age. Sensitivity analysis excluding individual studies was performed if the meta-analysis achieved similar results, which indicated the robustness of the meta-analysis. Furthermore, the Egger test revealed no evidence of publication bias (Table 2).

DISCUSSION

In the present study, we conducted a meta-analysis to assess the genetic association between the IL-4 promoters C-589T, C-33T, and G-1098T polymorphisms and asthma. The results of this meta-analysis provide strong evidence of association between C-589T and C-33T with asthma in certain populations.

IL-4 is an important factor in the pathogenesis of allergies, which has been verified using animal models (Pessi et al., 2005). IL-4 has clearly been shown to play a crucial role in the pathogenesis of allergic diseases including asthma, and IL-4 increases airway responsiveness by recruiting eosinophils into the airway in patients with allergic asthma (Dizier et al., 1999).

It is reasonable to infer that scaling expression of IL-4 might lead to atopic diseases. Therefore, it is highly possible that polymorphisms of the IL-4 promoter region would most likely contribute to its increasing expression. A large number of SNPs of IL-4 have been identified, which have shown to be significantly correlated with disease risks. For example, two general SNPs have been implicated in allergic diseases (including asthma) in many studies. rs2243250 (-589C/T) was reported to be associated with increased binding of a nuclear transcription factor. The other SNP (-33C/T; rs2070874) was located in the 5'-UTR. Both SNPs were found to be in linkage disequilibrium in European and Asian populations (Donfack et al., 2005; Yang et al., 2011).

In the present meta-analysis, we investigated 21 studies (6421 cases and 4755 controls) to assess the association of IL-4 gene promoter polymorphisms with asthma. Compared with a previous meta-analysis by Li et al. (2008), we found a significant association of IL-4 promoter polymorphisms (C-589T and C-33T) with asthma. The IL-4-589T allele has been shown to be associated with pathogenesis of asthma in populations and family-based cohorts (Noguchi et al., 1998; Beghe et al., 2003). Genetic heterogeneity or statistical power may contribute to the different results of case-control and family-based studies. For C-589T, the TT+CT genotype, and not the TT genotype, was significantly associated with asthma. Although the dominant model (CC+CT/TT) was not associated with asthma (OR = 0.90, 95%CI = 0.69-1.184, P = 0.44), the recessive model (CC/CT+TT) was significantly associated with asthma (OR = 1.30, 95%CI = 1.11-1.53, P = 0.001). This result may suggest a recessive effect of the C allele. However, for C-33T, no significant association was found between genotypes and asthma, which may be due to the limitation of the available studies.

The association between IL-4 C-589T and asthma was only found among individuals of European origin, and not in individuals of Asian or African-American origin (OR = 1.31, 95%CI = 0.99-1.74, P = 0.06 and OR = 0.85, 95%CI = 0.58-1.25, P = 0.42, respectively). Ethnic differences may not affect the pathogenesis of asthma in different populations. Furthermore, the discrepancy of individual studies may be due to small sample sizes, poor statistical power (power <80), or clinical heterogeneity.

Results of the association between C-33T and asthma were slightly different. The association between IL-4 C-33T and asthma was identified in the European origin group but not in the Asian origin group. Genotype analysis revealed no significant association between C-33T and asthma, although we could not elucidate the genetic effect on the pathogenesis of asthma due to insufficiency of studies. The contradictory results among the European origin, Asian origin, and African-American origin groups might indicate genetic heterogeneity of asthma among these three populations.

Results based on asthma status and age differed from the combined results, which might imply that asthma status and age may not be contributing factors on the pathogenesis of asthma. To clarify the association between IL-4 promoter SNPs and asthma, more research with more SNPs needs to be considered.

Heterogeneity was detected both in the allele and genotype analyses, while the sensitivity analysis and publication bias analysis demonstrated the authenticity of this study. Since no significant associations were detected between the C-589T and C-33T polymorphisms and asthma in most published studies reported, publication bias is likely not a major problem for this meta-analysis.

Nevertheless, several limitations of this meta-analysis should be considered. First, considering the association between C-589T and asthma, heterogeneity was discovered in the Asian origin group. However, based on the sensitivity analysis, the overall effect was not influenced by heterogeneity. Second, the number of studies and subjects included in this meta-analysis were relatively small. There were less than three studies included for the polymorphism meta-analysis in subgroups. Therefore, more studies are needed for further analysis. Third, due to lack of sufficient studies, we eliminated the meta-analysis of G-1098T, and it is possible that several other variants in the IL-4 promoter may be associated with asthma susceptibility. Therefore, further research is required.

In conclusion, this meta-analysis, which included 13,536 subjects, demonstrated that IL-4 promoter polymorphisms were associated with asthma susceptibility only in European groups. To identify associations between polymorphisms in IL-4 promoter SNPs and asthma susceptibility, more studies with a larger number of patients are needed.

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