

Interleukin-4 -589C/T Polymorphism is Associated with Increased Pediatric Asthma Risk: A Meta-Analysis

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Abstract—*IL4* -589C/T polymorphism has been implicated in susceptibility to pediatric asthma risk. Several studies investigated the association of this polymorphism with pediatric asthma in different populations. However, the results were contradictory. A meta-analysis was conducted to assess the association between *IL4* -589C/T polymorphism and pediatric asthma risk. Databases including Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wangfang were searched to find relevant studies. Odds ratios (ORs) with 95 % confidence intervals (CIs) were used to assess the strength of associations. A significant association was found between *IL4* -589C/T polymorphism and pediatric asthma risk (OR=1.53, 95% CI 1.27–1.85). In the subgroup analyses by ethnicity, the significant association was found among Caucasians (OR=1.70, 95 % CI 1.38–2.09) and Asians (OR=1.58, 95 % CI 1.23–2.04). Our results suggested that *IL4* -589C/T polymorphism conferred a risk factor of pediatric asthma.

KEY WORDS: asthma; IL-4; meta-analysis; genetic.

INTRODUCTION

Asthma is a common respiratory disease characterized by intermittent airway obstruction and respiratory symptoms that are caused by acute and chronic bronchial inflammation. The development of asthma appears to be determined by genetic and environmental factors. Many genes have been shown to be involved in its pathogenesis [1].

Asthmatics have elevated interleukin-4 (IL-4) protein levels in serum and bronchoalveolar lavage fluid (BAL), increased IL-4 mRNA and protein in bronchial biopsies, and increased numbers of (T)-cells expressing IL-4 mRNA in BAL and bronchial biopsies [2–4]. In a murine asthma model, sIL-4R significantly inhibited AHR and IgE production when administered at the time of sensitization [5]. In addition, anti-IL-4 monoclonal antibody reduced IgE production and AHR in murine asthma models [6].

The region of chromosome 5q31 that contains the *IL4* gene has been linked to total serum IgE levels [7]. A

nucleotide substitution (C/T) at position –589 of the *IL4* gene promoter is present in approximately 27 % of white subjects [8]. The *IL4* -589 T allele was associated with increased *IL4* gene expression *in vitro* and increased total serum IgE levels *in vivo*. To identify whether the *IL4* -589C/T polymorphism is involved in the pathogenesis of pediatric asthma *in vivo*, many studies concerning this allelic variation and pediatric asthma risk have been broadly performed [9–23]. However, there is still uncertainty about the risk for pediatric asthma and *IL4* -589C/T polymorphism. Therefore, we performed a meta-analysis to identify statistical evidence for an association between the *IL4* -589C/T polymorphism and pediatric asthma risk.

MATERIALS AND METHODS

Publication Search

Published studies were identified through a computerized search of Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wangfang databases (last search was updated on August, 2014). The search terms were used as follows: asthma and (interleukin-4 or interleukin 4 or IL-4). We also perused the

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reference lists of all retrieved articles and relevant reviews. There was no language restriction.

Inclusion and Exclusion Criteria

Eligible studies had to meet the following criteria: (a) case-control and cohort studies were considered, (b) the study explored the correlation between *IL4* -589C/T polymorphism and pediatric asthma risk. Major exclusion criteria were: (a) no control population, (b) no available genotype frequency, (c) duplication of the previous publications, the largest or most recent publication was selected.

Qualitative Assessment

Two authors completed the quality assessment independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. We considered a study awarded 0–3, 4–6, or 7–9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Data Extraction

Information was extracted from all eligible publications independently by two authors according to the

inclusion criteria listed above. The following information was extracted from each study: first author, publication year, racial background, atopic status, sample size, genotype numbers of cases and controls, and odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs).

Statistical Analysis

The association between *IL4* -589C/T polymorphism and pediatric asthma risk was assessed using OR with 95 % CI. Dominant model was used in this meta-analysis, because most of the studies reported the results in this model. Heterogeneity among studies was calculated using the χ^2 -based Cochran's Q-statistic test ($P < 0.10$ was considered statistically significant heterogeneity), the inconsistency index I^2 statistic was also calculated to observe between-study variability that was due to heterogeneity rather than chance. This statistic, which was documented by percentage, yields result ranging from 0 to 100 % ($I^2 = 0$ –25 %, no heterogeneity; $I^2 = 25$ –50 %, moderate heterogeneity; $I^2 = 50$ –75 %, large heterogeneity; $I^2 = 75$ –100 %, extreme heterogeneity). A random effects model using the method of DerSimonian and Laird was used in this meta-analysis. Sensitivity analyses were conducted by deleting a single study each time involved in the meta-analysis to identify the potential influence of the

Table 1. Characteristics of the Studies

First author	Year	Ethnicity	Atopic	No. of case	No. of control	Quality score	Case			Control		
							TT	CT	CC	TT	CT	CC
Walley	1996	Caucasian	NA	124	59	7	13	55	56	5	23	31
Takabayashi	2000	Asian	Atopic	100	100	7	51	43	6	51	39	10
Lee	2004	Asian	NA	256	100	6	168	77	9	68	29	3
Liu	2005	Asian	NA	76	60	8	45	29	2	34	23	3
Schubert	2006	Caucasian	NA	231	270	9	10	78	143	7	74	189
Kabesch	2006	Caucasian	NA	73	773	9	2	29	42	21	188	564
Attab	2008	Caucasian	NA	40	40	8	0	9	31	0	7	33
de Faria	2008	Mixed	Atopic	88	202	7	9	41	38	27	108	67
Wu	2010	Asian	NA	252	227	7	163	83	6	132	84	11
Zhang	2010	Asian	NA	291	665	6	169	112	10	401	233	31
Huang	2011	Asian	NA	100	122	6	80	19	1	75	43	4
Baye 1	2011	Caucasian	NA	413	298	7	16	130	267	4	61	233
Baye 2	2011	African American	NA	315	51	9	140	140	35	14	25	12
Hwang	2012	Asian	NA	188	376	9	136	51	1	275	89	12
Ramphul 1	2014	Asian	NA	190	189	8	20	67	103	14	49	126
Ramphul 2	2014	Asian	NA	192	192	8	130	55	7	127	60	5
Li	2014	Asian	NA	500	523	6	324	150	17	338	144	21

NA not available

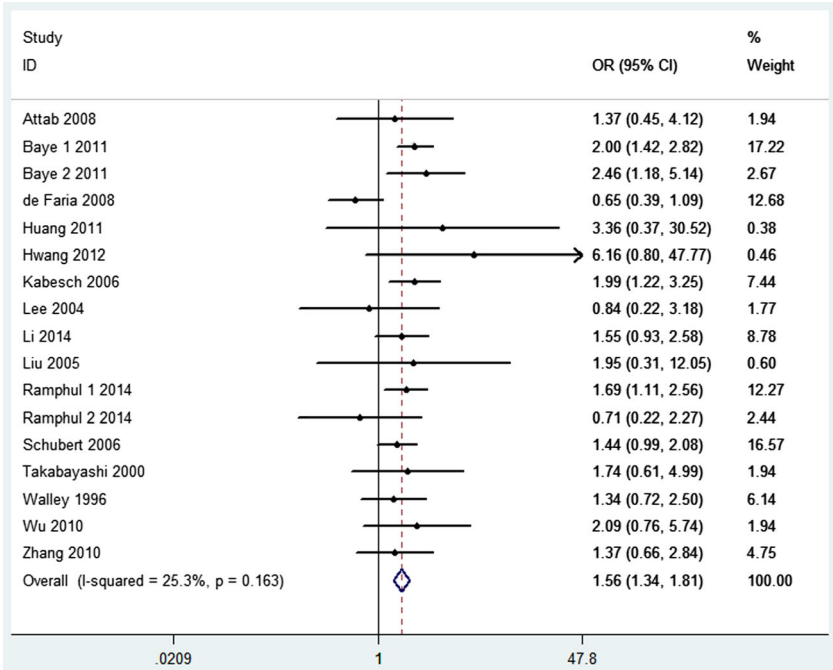


Fig. 1. Meta-analysis of the association between *IL4* -589C/T polymorphism and pediatric asthma risk.

individual data set on the pooled ORs. To explore the source of the heterogeneity, Galbraith plots were used. Potential publication bias was assessed by Egger's weighted regression method. All statistical analyses were conducted using the RevMan software and STATA 11.0 software (Stata Corporation, College Station, TX). All *P* values were two-sided.

RESULTS

Study Characteristics

After a comprehensive literature search applying our inclusion criteria, 15 relevant studies which comprised 3427 cases and 4247 controls were identified in the final analysis.

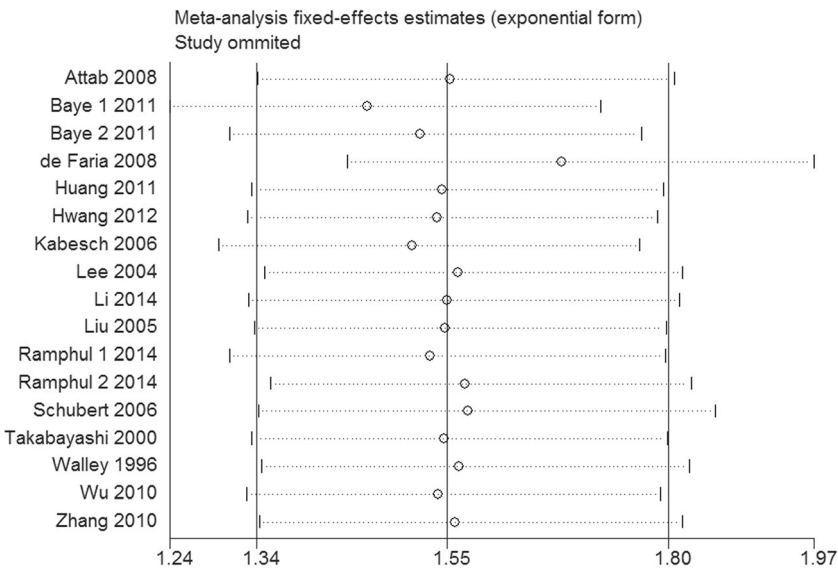


Fig. 2. Sensitivity analysis for *IL4* -589C/T polymorphism and pediatric asthma risk.

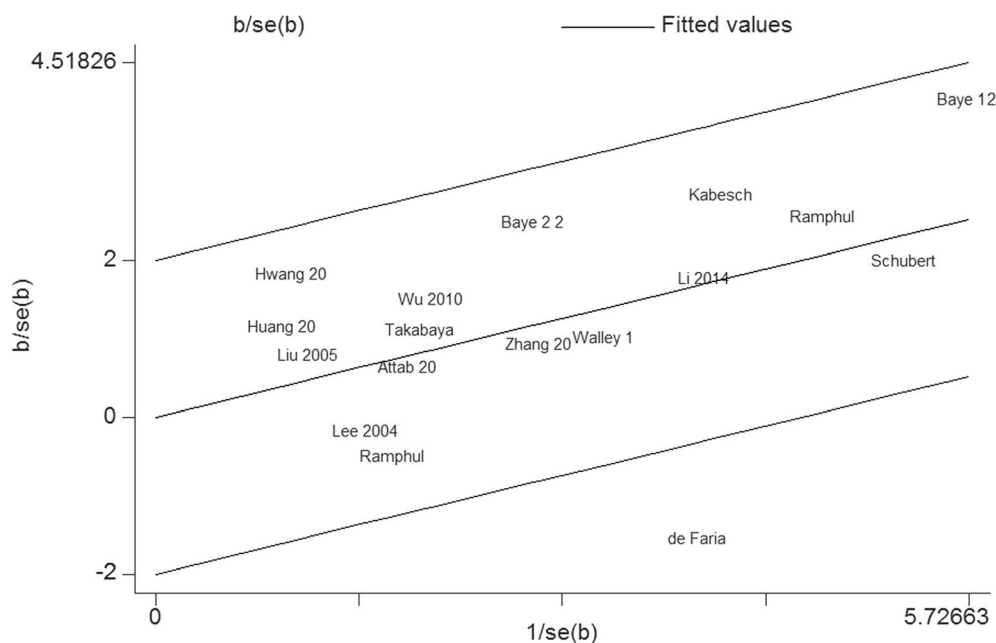


Fig. 3. Galbraith plot of *IL4* -589C/T polymorphism and pediatric asthma risk.

Two studies reported two case-control studies. Therefore, a total of 17 studies were included in this meta-analysis. There was only one study with African Americans, while the rest of the studies used Caucasians or Asians. All studies were assessed by NOS. The quality scores ranged from 6 to 9, suggesting that the methodological quality was acceptable. The main study characteristics are summarized in Table 1.

QUANTITATIVE DATA SYNTHESIS

A significant association was found between *IL4* -589C/T polymorphism and pediatric asthma risk

(OR=1.53, 95% CI, 1.27–1.85, Fig. 1). In the subgroup analyses by ethnicity, the significant association was found among Caucasians (OR=1.70, 95 % CI 1.38–2.09) and Asians (OR=1.58, 95 % CI 1.23–2.04).

We conducted the one-way sensitivity analysis to evaluate the stability of the meta-analysis. The statistical significance of the results was not altered when any single study was omitted (Fig. 2). The Galbraith plot was used to find the source of the heterogeneity. As shown in Fig. 3, one study was the outliers. After excluding these studies, the between-study heterogeneity effectively decreased and there was no obvious heterogeneity among the 24 remaining studies ($I^2=0\%$, $P=0.85$). Besides, the result was still

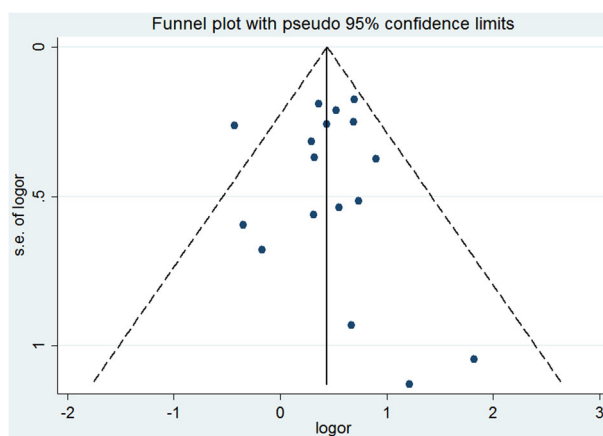


Fig. 4. Funnel plot for *IL4* -589C/T polymorphism and pediatric asthma risk.

statistically significant (OR=1.68, 95% CI, 1.44–1.97). Egger's test did not indicate significant publication bias ($P=0.472$, Fig. 4).

DISCUSSION

This current meta-analysis of 17 studies including 3427 cases and 4247 controls systematically evaluated the association between *IL4* -589C/T polymorphism and pediatric asthma risk. The results indicated that *IL4* -589C/T polymorphism was a conspicuous high risk factor for developing childhood asthma. In the subgroup analysis by ethnicity, asthma risk was increased in Caucasians and Asians who carried *IL4* -589C/T polymorphism, suggesting a possible influence among environmental exposures and different genetic backgrounds. There was only one study with African Americans. Thus, more studies are needed to confirm if *IL4* -589C/T polymorphism could influence the pediatric asthma risk in African Americans.

Lama *et al.* suggested that serum level of IL-4 was significantly higher in steroid-naïve group of asthmatic children compared to the healthy control subjects [24]. Shahid *et al.* [25] have shown an increased concentration of exhaled IL-4 in steroid-naïve group of asthmatic children. In addition to the primary role of IL-4 in allergic sensitization, it also affects further development of allergic airway disease. The role of IL-4 in the initiation and development of allergic asthma generated the hope that blocking IL-4 signaling would result in clinical benefit, and several approaches to block either IL-4 or IL-4R α have been used [26]. Rosenwasser and coworkers indicated that the *IL4* -589 T allele was associated with higher binding of transcription factors and increased transcription compared with the -589C allele [8]. It was possible that *IL4* -589C/T polymorphism may confer the pediatric asthma risk.

The present meta-analysis should be interpreted with caution, several limitations merit consideration. First, due to lacking of the original data of the eligible studies, we could not perform other subgroup analyses based on gender, life style, and so on. Second, the numbers of published studies were not sufficient for a comprehensive analysis, particularly for Africans. However, our meta-analysis also had some merits. First, we investigated the association between *IL4* -589C/T polymorphism and pediatric asthma risk for the first time. Second, there was low heterogeneity in this meta-analysis.

This meta-analysis suggested that the *IL4* -589C/T polymorphism may be associated with pediatric asthma

development. Further studies with a larger sample size are needed to further assess the presence of an association.

Conflicts of Interest. The authors declare no conflicts of interest.

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