ORIGINAL ARTICLE

Association Between *CC Motif Chemokine Ligand 5 (CCL5)* Polymorphisms and Asthma Risk: An Updated Meta-analysis

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Abstract

Background: Findings regarding the associations between the *CC motif chemokine ligand 5* (CCL5) -403G/A and -28C/G polymorphisms and asthma risk are controversial. We performed a meta-analysis to determine whether *CCL5* polymorphisms are associated with asthma risk.
Methods: We searched the Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases for studies published before June 2013. The strength of associations was calculated using ORs with 95% CIs.
Results: Twenty case-control studies were included in this meta-analysis. We did not observe a significant association between the *CCL5* -403G/A polymorphism and asthma risk (OR, 1.10; 95% CI, 0.93-1.30; *P*=.25). The *CCL5* -28C/G polymorphism, however, was associated with a significantly elevated asthma risk (OR, 1.17; 95% CI, 1.02-1.33; *P*=.02). Subgroup analyses found that the *CCL5* -28C/G polymorphism was significantly associated with asthma risk in Asians (OR, 1.16; 95% CI, 1.01-1.33; *P*=.04) and children (OR, 1.29; 95% CI, 1.03-1.63; *P*=.03).
Conclusions: This meta-analysis suggests that the *CCL5* -28C/G polymorphism is a risk factor for asthma.

Key words: Asthma. CCL5. Meta-analysis. Polymorphism.

Resumen

Introducción: Existen discrepancias entre la asociación del riesgo de padecer asma y diferentes polimorfismos del ligando de la quimiocina CC5 (CCL5). En este trabajo se ha realizado un meta-análisis para determinar si los polimorfismos CCL5-403G / A y CCL5-28C / G se asocian con el riesgo de asma bronquial.
Métodos: Se utilizaron diversas bases de datos para realizar las búsquedas de estudios publicados antes de junio de 2013, incluyendo: PubMed, EMBASE, CNKI (Infraestructura del Conocimiento Nacional Chino) y Wanfang Se calcularon los odd ratios combinados (OR) con intervalos de confianza del 95% (IC).
Resultados: Se incluyeron un total de 20 estudios de casos y controles. No se encontró una asociación significativa entre el polimorfismo CCL5-403G / A y el riesgo de asma (OR = 1,10, IC del 95%: 0,93 a 1,30, p = 0,25). Por el contrario, el polimorfismo CCL5-28C / G, se asoció con un riesgo significativamente elevado de asma (OR = 1,17, IC del 95%: 1,02 a 1,33, p = 0,02). En los análisis de subgrupos, el riesgo de asma fue significativamente mayor en los asiáticos con el polimorfismo CCL5-28C / G (OR = 1.16, 95% IC 1,01-1,33, P = 0,04) y los niños (OR = 1.29, 95% IC 1,03-1,63, P = 0,03).
Conclusiones: Este meta-análisis sugiere que el polimorfismo CCL5-28C / G es un factor de riesgo significativo para padecer asma bronquial.

Palabras clave: Asma. CCL5. Meta-análisis. Polimorfismo.

Introduction

Asthma is a chronic inflammatory condition of the airways characterized by recurrent episodes of reversible airway obstruction and increased bronchial hyperresponsiveness. CC motif chemokine ligand 5 (CCL5, also called RANTES) is secreted by many cell types, including endothelial cells, smooth muscle cells, macrophages, platelets, and activated T cells. It is involved in chronic airway inflammation through the recruitment of inflammatory cells, such as chemotactic eosinophils, lymphocytes, neutrophils, and monocytes [1-3]. Berkman et al [4] found that CCL5 mRNA was elevated in airways of patients with mild asthma. In addition, increased CCL5 levels have been detected in the bronchoalveolar lavage fluid of patients with asthma [5]. The above findings suggest that CCL5 may play an important role in the pathogenesis of asthma and that *CCL5* may be a candidate gene for asthma.

CCL5 is located on chromosome 7q11.2–q12. Several studies have assessed the associations between *CCL5* polymorphisms and asthma risk [6-25]. Most of the studies have focused on 2 polymorphisms, -403G/A (rs2107538) and -28C/G (rs2280788), but the results have been inconsistent. Meta-analysis is a good method to provide more credible evidence by systematically summarizing the existing data. Until now, 3 meta-analyses have been reported [26-29]. Zhang and coworkers [26] suggested that *CCL5* 403G/A and -28C/G were not significantly associated with asthma risk, but Fang and colleagues [27] indicated that the -28C/G polymorphism may contribute to asthma development, especially in children and Asians [27]. Lu et al [28], in turn, found no associations between the 403G/A polymorphism and risk of pediatric asthma. While they did find an association with the -28C/G polymorphism in the overall group, the ethnicity-stratified analysis suggested that the risk was not significant. Therefore, the exact role of *CCL5* in asthma development is still somewhat controversial. Because several new studies with more data have been published since these 3 meta-analyses, we performed an updated meta-analysis to determine with greater precision the relationship between *CCL5* -403G/A and -28C/G polymorphisms and asthma risk.

Methods

Publication Search

We searched the electronic databases Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang for all relevant articles using the search terms: (*asthma or asthmatic*) and (*CC motif chemokine ligand 5 or CCL5 or RANTES*) and (*polymorphism or mutation or variant*). All eligible articles were retrieved, and their references were checked for other relevant studies.

Study Selection

Studies included in this meta-analysis had to meet the following criteria: *1*) evaluation of the *CCL5* -403G/A and/or -28C/G polymorphisms and asthma risk; *2*) case-control design; and *3*) availability of genotype distributions in both cases and controls for estimating an OR with a 95% CI. When serial studies of the same population from the same group were reported, the largest study was included.

Data Extraction

Two investigators (HH and WN) independently extracted data from the studies included. The following information was collected from each study: first author, year of publication, original country, ethnicity, age group, atopic status, sample size, and genotype number in cases and controls. We verified the accuracy of the data by comparing collection forms between investigators. In the event of discrepancies, the full text of the article was checked.

Statistical Analysis

A meta-analysis was performed when data from at least 3 similar studies were available. The strength of the associations between the *CCL5* polymorphisms and asthma risk was measured by ORs and 95% CIs. The statistical significance of the summary OR was determined using the Z test. OR1, OR2, and OR3 were calculated for the genotypes as follows: *1*) AA vs GG (OR1), GA vs GG (OR2), and AA vs GA (OR3) for the -403G/A polymorphism and *2*) GG vs CC (OR1), GC vs CC (OR2), and GG vs GC (OR3) for the -28C/G polymorphism. These pairwise differences were used to identify the most appropriate genetic model [29], which was then used to collapse the 3 genotypes into 2 groups (except in the case of a codominant model) and to pool the results. Considering the heterogeneity among results from different studies, a random effects model was used.

Hardy-Weinberg equilibrium (HWE) was evaluated using the χ^2 test. $P<.05$ was considered representative of departure from HWE. Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics. For the I^2 metric, we considered low, moderate, and high I^2 values to be 25%, 50%, and 75%, respectively. Subgroup analyses were performed by stratifying according to ethnicity, age group, and atopic status. Studies with evidence of significant departure from HWE were not included in the meta-analysis, but they were pooled in the sensitivity analysis. We also performed an additional sensitivity analysis by excluding studies from Chinese journals. To check potential publication bias, a standard error of log (OR) for each study was plotted against its log (OR). Funnel plot asymmetry was assessed by Egger's linear regression test and $P<.05$ was considered to represent statistically significant publication bias [30]. All statistical tests were performed using STATA 11.0 software.

Results

Study Characteristics

As shown in Figure 1, 20 case-control studies met the inclusion criteria [6-25]. Because the studies by Al-Abdulhadi et al [11] and Undarmaa et al [23] presented 2 independent case-control studies, 22 studies were finally included in our meta-analysis. There were 20 studies of the -403G/A polymorphism and 15 studies of the -28C/G polymorphism. Eleven studies were performed in Asians, 10 in whites, and

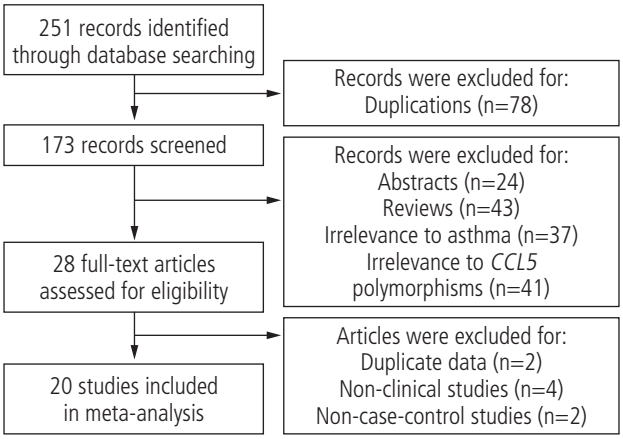

Figure 1. Flow diagram showing study identification, inclusion, and exclusion.

1 in African Americans. Seven studies were performed in adults and 13 in children. Two studies included atopic asthma patients and 8 included both atopic and nonatopic asthma patients, but it was possible to extract separate data for these patients. The characteristics of each study are presented in Table 1. Genotype frequencies and HWE examination results are listed in Table 2.

Quantitative Data Synthesis

CCL5 -403G/A Polymorphism

Twenty studies investigated the association between the -403G/A polymorphism and asthma risk. Four studies [11,17,25] were not in HWE and were therefore excluded from the meta-analysis. The total sample sizes for case and control groups were 3905 and 4055, respectively. The estimated OR1, OR2, and OR3 values were 1.08, 0.97, and 1.11, respectively (Table 3). These estimates suggested a recessive genetic model and therefore GG and GA were combined and compared with AA. The pooled OR was 1.10 (95% CI, 0.93-1.30; P=.25) (Figure 2). There was no significant heterogeneity (I^2=0%, P=.95). In the analysis stratified by ethnicity, no significant associations were found for the studies in Asians (OR, 1.13; 95% CI, 0.93-1.36; P=.21) or whites (OR, 1.02; 95% CI, 0.71-1.48; P=.90). In the subgroup analysis by age, the *CCL5* -403G/A polymorphism was not associated with pediatric asthma risk (OR, 1.13; 95% CI, 0.90-1.43; P=.29) or adult asthma risk (OR, 1.17; 95% CI, 0.89-1.56; P=.26). Finally,

Table 1. Characteristics of the Case-Control Studies Included in Meta-Analysis

First Author	Year	Country	Ethnicity	Age Group	Atopic Status	Cases (No.)	Controls (No.)	Genotyping Method
Fryer [6]	2000	UK	White	Adult	Mixed[a]	120	74	PCR-RFLP
Szalai [7]	2001	Hungary	White	Child	Mixed	160	303	PCR-RFLP
Hizawa [8]	2002	Japan	Asian	Adult	Mixed	298	311	PCR-RFLP
Yao [9]	2003	China	Asian	Child	NA	182	107	PCR-RFLP
Wang [10]	2004	China	Asian	Child	Atopic	100	90	PCR-RFCP
Al-Abdulhadi 1 [11]	2005	UK	White	Adult	Mixed[a]	79	96	PCR-RFLP
Al-Abdulhadi 2 [11]	2005	UK	White	Child	Mixed[a]	83	38	PCR-RFLP
Leung [12]	2005	China	Asian	Child	Mixed[a]	129	64	PCR-RFLP
Moissidis [13]	2005	USA	African American	Mixed	Mixed	61	131	PCR-RFLP
Liu CH [14]	2005	China	Asian	Child	NA	287	53	PCR-RFLP
Liu M [15]	2005	China	Asian	Child	NA	32	32	PCR-RFLP
Schubert [16]	2006	Germany	White	Child	NA	231	270	PCR-RFLP
Lachheb [17]	2007	Tunisia	White	Child	Mixed[a]	210	224	PCR-RFLP
Muro [18]	2007	Spain	White	Adult	Mixed[a]	306	242	PCR-RFLP
Ungvari [19]	2007	Hungary	White	Child	Mixed	254	260	PCR-RFLP
Sohn [20]	2008	Korea	Asian	Child	Mixed[a]	326	253	PCR-RFLP
Daley [21]	2009	Australia	White	Mixed	NA	642	749	Illumina
Hua [22]	2009	China	Asian	Child	NA	192	192	PCR-RFLP
Undarmaa 1 [23]	2010	Japan	Asian	Child	Atopic	325	336	TaqMan
Undarmaa 2 [23]	2010	Japan	Asian	Adult	Atopic	367	676	TaqMan
Kaneko [24]	2013	Japan	Asian	Adult	Mixed[a]	880	1329	TaqMan
Nahas [25]	2013	Lebanon	White	Adult	Mixed	40	38	PCR-RFLP

Abbreviations: NA, not available; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism.
[a]Separate data were available.

Table 2. Distribution of *CCL5* Genotypes Among Asthma Patients and Controls

Study	Asthma Patients 11[a]	12[b]	22[c]	Controls 11[a]	12[b]	22[c]	Hardy-Weinberg Equilibrium
-403G/A							
Szalai [7]	75	39	6	51	21	2	Yes
Hizawa [8]	122	32	6	211	84	8	Yes
Yao [9]	146	108	44	140	137	34	Yes
Wang [10]	98	65	19	60	41	6	Yes
Al-Abdulhadi 1 [11]	17	51	11	86	6	4	No
Al-Abdulhadi 2 [11]	30	47	6	35	2	1	No
Leung [12]	60	53	16	37	21	8	Yes
Moissidis [13]	16	34	11	35	72	24	Yes
Liu CH [14]	102	141	44	15	32	6	Yes
Liu M [15]	17	13	2	16	14	2	Yes
Schubert [16]	142	78	11	175	85	10	Yes
Lachheb [17]	140	50	20	174	40	10	No
Muro [18]	202	93	11	165	69	8	Yes
Ungvari [19]	188	59	7	199	56	5	Yes
Sohn [20]	109	146	71	97	107	49	Yes
Daley [21]	435	181	19	467	245	32	Yes
Hua [22]	74	93	25	68	98	26	Yes
Undarmaa 1 [23]	144	145	36	145	152	39	Yes
Undarmaa 2 [23]	155	167	45	289	306	81	Yes
Kaneko [24]	30	10	0	30	8	0	No
-28C/G							
Szalai [7]	144	16	0	284	19	0	Yes
Hizawa [8]	216	70	12	243	62	6	Yes
Yao [9]	134	39	9	83	23	1	Yes
Wang [10]	65	31	4	72	17	1	Yes
Moissidis [13]	59	2	0	129	0	0	Yes
Liu CH [14]	44	14	0	40	13	0	Yes
Liu M [15]	25	6	1	29	3	0	Yes
Schubert [16]	163	35	12	190	29	5	No
Lachheb [17]	289	17	0	228	14	0	Yes
Sohn [20]	218	93	15	174	66	13	Yes
Hua [22]	154	36	2	163	27	2	Yes
Undarmaa 1 [23]	250	67	8	243	86	7	Yes
Undarmaa 2 [23]	261	98	8	490	171	15	Yes
Kaneko [24]	625	210	22	984	310	35	Yes
Nahas [25]	40	0	0	37	1	0	Yes

[a]GG or CC.
[b]GA or CG.
[c]AA or GG.

in the subgroup analysis according to atopic status, the *CCL5* -403G/A polymorphism was not significantly associated with the risk of either atopic asthma (OR, 1.02; 95% CI, 0.77-1.34; *P*=.90) or nonatopic asthma (OR, 1.01; 95% CI, 0.42-2.44; *P*=.99).

We performed a sensitivity analysis to evaluate the stability of the meta-analysis. The result did not change on including the studies with evidence of departure from HWE [11,17,25] (OR, 1.16; 95% CI, 0.99-1.37; *P*=.06). or on excluding the studies published in Chinese journals (OR, 1.10; 95% CI, 0.92-1.30; *P*=.29).

The funnel plot did not reveal evidence of obvious asymmetry (Figure 3), and this result was further supported by Egger's test (*P*= .207).

Table 3. Determination of the Genetic Effects of *CCL5* Polymorphisms on Asthma and Subgroup Analyses

Polymorphisms	Study	Sample Size Cases	Controls	No. of Studies	Test of Association OR (95% CI)	Z	*P* Value	Model	Heterogeneity χ^2	*P* Value	I^2 (%)
-403G/A											
AA vs. GG	Overall	2458	2493	16	1.08 (0.91-1.29)	0.90	.37	R	7.69	.94	0.0
GA vs. GG	Overall	3532	3679	16	0.97 (0.86-1.09)	0.56	.58	R	19.81	.18	24.0
AA vs. GA	Overall	1820	1864	16	1.11 (0.94-1.33)	1.21	.23	R	7.67	.94	0.0
AA vs. GA+GG	Overall	3905	4055	16	1.10 (0.93-1.30)	1.14	.25	R	7.26	.95	0.0
AA vs. GA+GG	Asian	2138	2026	9	1.13 (0.93-1.36)	1.26	.21	R	3.49	.90	0.0
AA vs. GA+GG	White	1706	1898	6	1.02 (0.71-1.48)	0.12	.90	R	3.46	.63	0.0
AA vs. GA+GG	Children	1887	1602	9	1.13 (0.90-1.43)	1.05	.29	R	2.79	.95	0.0
AA vs. GA+GG	Adult	1091	1303	4	1.17 (0.89-1.56)	1.12	.26	R	1.38	.71	0.0
AA vs. GA+GG	Atopic	1071	1362	5	1.02 (0.77-1.34)	0.13	.90	R	0.52	.97	0.0
AA vs. GA+GG	Nonatopic	184	350	3	1.01 (0.42-2.44)	0.02	.99	R	0.81	.67	0.0
-28C/G											
GG vs. CC	Overall	2605	3279	14	1.19 (0.85-1.65)	1.02	.31	R	0.56	.58	0.0
GC vs. CC	Overall	3223	4011	14	1.11 (0.98-1.26)	1.60	.11	R	13.86	.38	6.0
GG vs. GC	Overall	780	892	14	1.09 (0.77-1.53)	0.49	.63	R	4.76	.78	0.0
GG+GC vs. CC	Overall	3304	4091	14	1.17 (1.02-1.33)	2.25	.02	R	10.70	.64	0.0
GG+GC vs. CC	Asian	2737	3379	10	1.16 (1.01-1.33)	2.04	.04	R	6.70	.67	0.0
GG+GC vs. CC	White	506	583	3	1.24 (0.75-2.03)	0.84	.40	R	1.88	.39	0.0
GG+GC vs. CC	Children	1375	1366	8	1.29 (1.03-1.63)	2.18	.03	R	5.19	.64	0.0
GG+GC vs. CC	Adult	1868	2596	5	1.10 (0.93-1.30)	1.13	.26	R	2.18	.70	0.0
GG+GC vs. CC	Atopic	1505	2926	6	1.07 (0.87-1.32)	0.67	.51	R	5.11	.40	2.0
GG+GC vs. CC	Nonatopic	776	1824	3	0.87 (0.52-1.45)	0.54	.59	R	4.49	.11	55.0

Abbreviation: R, random-effects model.

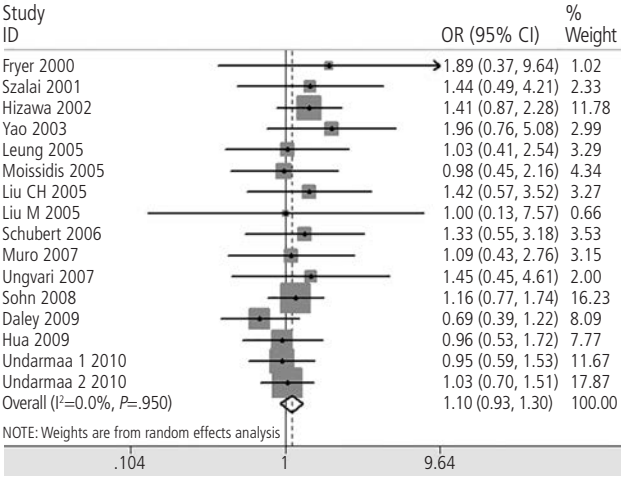

Figure 2. Meta-analysis for the association between asthma risk and the *CCL5* -403G/A polymorphism.

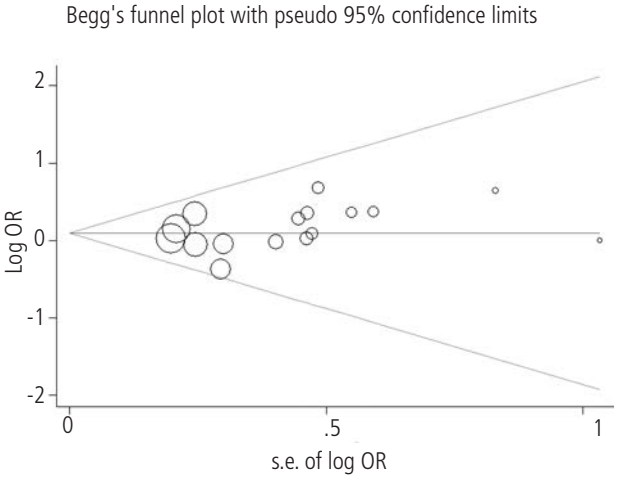

Figure 3. Funnel plot for asthma risk and the *CCL5* -403G/A polymorphism.

CCL5 -28C/G Polymorphism

Fifteen studies identified an association between the *CCL5* -28C/G polymorphism and asthma risk. One study with departure from HWE was not included [17]. Thus, a total of 3304 cases and 4091 controls were included in this meta-analysis. The estimated OR1, OR2, and OR3 values were 1.19, 1.11, and 1.09, respectively (Table 3). These estimates suggested a dominant genetic model and therefore GG and GC were combined and compared with CC. The pooled OR was 1.17 (95% CI, 1.02-1.33; *P*=.02) (Figure 4). No significant heterogeneity was observed (I^2=0%, *P*=.64). Subgroup analysis was performed by ethnicity. A statistically significant finding was found in Asians (OR, 1.16; 95% CI, 1.01-1.33; *P*=.04) but not in whites (OR, 1.24; 95% CI, 0.75-2.03; *P*=.39). In the age-stratified analysis, a statistically significantly increased asthma risk was found in children (OR, 1.29; 95% CI, 1.03-1.63; *P*=.03), but not in adults (OR,1.10; 95% CI, 0.93-1.30; *P*=.26). In terms of atopic status, we did not observe a significant association between the -28C/G polymorphism and risk of either atopic asthma (OR, 1.07; 95% CI, 0.87-1.32; *P*=.51) or nonatopic asthma (OR, 0.87; 95% CI, 0.52-1.45; *P*=.59).

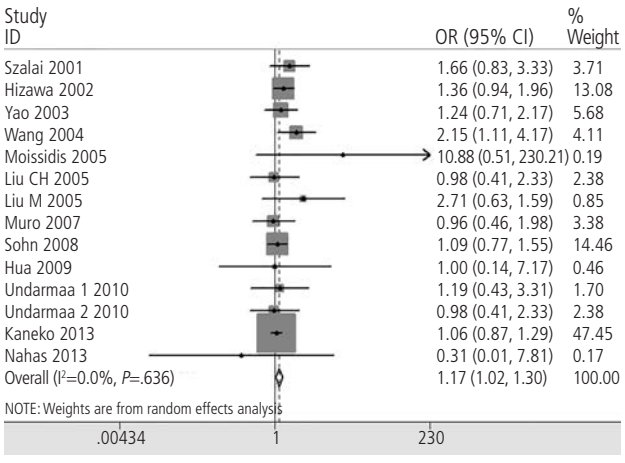

Figure 4. Meta-analysis for the association between asthma risk and the *CCL5* -28C/G polymorphism.

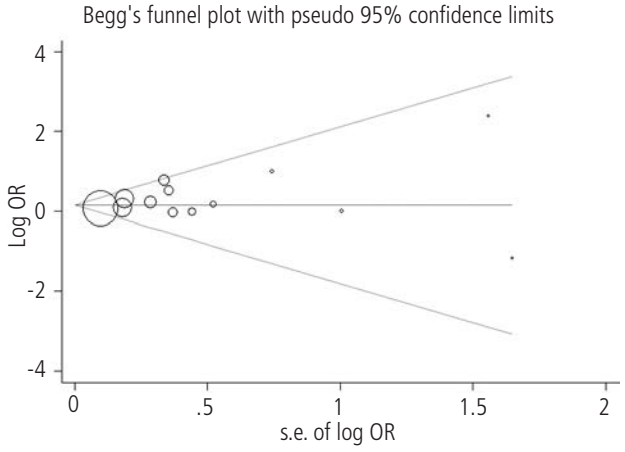

Figure 5. Funnel plot for asthma risk and the *CCL5* -28C/G polymorphism.

The sensitivity analysis showed no substantial modification of estimates after inclusion of the study not in HWE (OR, 1.19; 95% CI, 1.05-1.36; *P*=.007). However, when the studies from Chinese journals were excluded, the result was altered (OR, 1.13; 95% CI, 0.98-1.30; *P*=.08). The shape of the funnel plot was symmetrical (Figure 5), and Egger's test indicated the absence of publication bias (*P*=.192).

Discussion

The main finding of this meta-analysis is that genotypes GG and GC of the *CCL5* -28C/G polymorphism are potential risk factors for developing asthma. Our results suggest that individuals carrying either of these genotypes might have an increased asthma risk. In the subgroup analysis by ethnicity, no significant associations were observed in whites, but asthma risk was increased in Asians. It is possible that different lifestyles, diets, and environments may account for this apparent discrepancy. These issues should be investigated in future studies. In the subgroup analysis stratified by age, the *CCL5* -28C/G polymorphism was associated only with increased pediatric asthma risk, demonstrating that even the same variant in the same gene may have a different effect on the pathogenesis and occurrence of asthma in different individuals. We also carried out a subgroup analysis according to atopic status. There was no significant association between the *CCL5* -28C/G polymorphism and atopic asthma risk, suggesting that this polymorphism does not influence the etiology of atopic asthma. We found that the *CCL5* -403G/A polymorphism may play no role in the development of asthma. Moreover, in the subgroup analyses based on ethnicity, age group, and atopic status, no significant associations were observed.

CCL5 polymorphisms have been widely investigated in relation to the risk of asthma. However, results from previous studies are ambiguous due to their small sample size. Although 3 meta-analyses have been published, their results are also conflicting. Zhang et al [26] suggested that the *CCL5* -403G/A polymorphism was significantly associated with atopic asthma. Our meta-analysis showed no such association. We checked the studies included in the meta-analysis by Zhang et al. One of the studies investigating the association between the -28C/G polymorphism and atopic asthma [10] was pooled with the studies focusing on the -403G/A polymorphism. When this study was omitted, the result was no longer statistically significant. In addition, Zhang et al and Fang et al [27] reported different results on the association between the -28C/G polymorphism and asthma. The reason for the discrepancy stemmed from the fact that they included different studies. The study performed by Wang et al [10] was not included in Zhang's meta-analysis [26]. However, the study with departure from HWE [17], which might have biased results, was included in Fang's meta-analysis, which additionally included a reduplicate study [31]. Thus, results from the meta-analyses by Zhang et al and Fang et al are not reliable. Our meta-analysis included some large-scale studies and is thus more conclusive and more powerful. Another meta-analysis by Lu et al [28] focused on the relationship between *CCL5* polymorphisms and pediatric asthma risk, and concluded that there were no significant associations. However, only 7 studies were analyzed. A positive association between these polymorphisms and pediatric asthma could not be ruled out because studies with small sample sizes may have had insufficient statistical power to detect even the slightest effect. Our meta-analysis included 20 studies, and found a moderate but significant association between the -28C/G polymorphism and pediatric asthma.

There is evidence for an in vivo role of CCL5 as a chemoattractant in allergic inflammation derived from a study showing that neutralization of CCL5 with a receptor antagonist significantly inhibited both lymphocyte and eosinophil recruitment [32]. Eosinophils could cause tissue damage and promote allergic disease in the lung through the release of toxic proteases, lipid mediators, cytokines, and oxygen free radicals [33]. T cells, in turn, have been reported as a source of proallergic cytokines including IL-4 and IL-13 [34]. Taken together, these results indicate that *CCL5* may play a critical role in the pathogenesis of asthma. *CCL5* is one of the most studied candidate genes for asthma. A previous study showed that the luciferase reporter plasmid containing -403A expressed significantly higher transcriptional activity than -403G in

Hela cells [35], indicating that *CCL5* -403A is responsible for elevated transcriptional activity. The *CCL5* polymorphism -28G has also been associated with increased transcription of the *CCL5* gene [35]. Thus, it is biologically plausible that these 2 polymorphisms might influence asthma risk. However, only the -28C/G polymorphism was significantly associated with asthma risk. The reason why no influence was detected for the -403G/A polymorphism is unclear. More studies are needed to address this issue.

The results of our meta-analysis are reliable. First, there was no significant heterogeneity in most of the comparisons. Second, funnel plots and Egger's tests found no significant publication bias. However, some limitations should be pointed out. First, asthma is a complex disease that results from combined effects of multiple factors, including inherited and environmental factors. Some environmental factors may strongly influence the development of asthma. A lack of consideration of these factors may affect results regarding the significance of an independent role of *CCL5* polymorphisms in asthma development. Second, even though no significant publication bias was found by funnel plot analysis or formal statistical tests, it was impossible to exclude potential publication bias completely, because small studies with null results tend not to be published. Third, the overall results were based on unadjusted data, whereas a baseline risk-adjusted analysis could be performed if individual data were available to allow adjustment. Fourth, the sensitivity analysis revealed that the results were robust. More studies are still needed to confirm our findings. Finally, all the studies included in this meta-analysis used a case-control design, which is susceptible to recall and selection biases.

In conclusion, this meta-analysis found a significant association between the *CCL5* -28C/G polymorphism and asthma risk. Further studies in more ethnic groups are warranted to validate these results.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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