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Review Article

Negative association between chitinase 3-Like-1 C-131G polymorphism and asthma-from a meta-analysis

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Abstract: The *CHI3L1* gene has been widely regarded as a genetic candidate for asthma. Since the identification of functional polymorphism, *CHI3L1* gene -131C/G (rs4950928), numbers of studies have been performed to estimate the relationship between it and asthma, but the results remain inconclusive. The present meta-analysis was conducted to evaluate the real association of *CHI3L1* C-131G polymorphism on risk of asthma on 3,777 asthma cases and 7,844 controls from 10 published studies by searching PubMed, EMBASE and CNKI databases and reference lists of relevant articles. A random-effects or fixed-effects model was used to estimate the overall and stratification effect sizes on *CHI3L1* C-131G polymorphism on the risk of asthma as appropriate. However, we failed to find any significant association between the *CHI3L1* C-131G polymorphism and the risk of asthma for different genetic models (recessive model: OR=1.18, 95% CI: 0.91-1.53 and dominant model: OR=0.94, 95% CI: 0.72-1.21, respectively). In stratified analysis by ethnicity and age, we still did not detect any significant associations in different subgroup for all genetic models. Our study suggested that the *CHI3L1* C-131G polymorphism alone may not contribute to asthma development of asthma risk.

Keywords: *CHI3L1* C-131G, polymorphism, association, susceptibility, asthma

Introduction

Asthma is one of the most common chronic lung diseases all over the world and affects people with all genders, races and ages [1]. It was estimated that approximately 300 million people currently have asthma worldwide, and the prevalence globally increases by 50% every decade [2, 3]. The pathogenesis and etiology of asthma is very complex and not fully understood [4]. Although environmental factors can account for some of the increase in incidence [5], different genetic background individuals in the same environmental exposures showed different susceptibility to asthma, which indicated that genetic factors may play a substantial role in the pathogenesis of asthma [6, 7].

The *CHI3L1* gene is located on chromosome 1q32.1 with 10 exons long and codes for the protein chitinase 3-like-1 (CHI3L1), which is a 40-kDa protein (YKL-40) expressed in the human bronchial smooth muscle cells and other epithelial cells [8]. Thus, the *CHI3L1* gene has been widely regarded as a genetic candidate for asthma. In 2008, Ober et al [9] first carried out a genome wide association study (GWAS) in population of European descent by reviewing numerous genes associated with atopic asthma and found that the single nucleotide polymorphism (SNP) in *CHI3L1* gene -131C/G (rs4950928) in the promoter region was associated with increase CHI3L1 levels, increased secretion of YKL-40 and the severity of asthma, bronchial hyper-responsiveness, and reduced pulmonary function. Due to such critical functional influence, it is feasible to postulate that polymorphism of *CHI3L1* -131C/G contributes to the development of asthma.

A number of molecular epidemiological studies have been performed to estimate the relationship between *CHI3L1* -131C/G polymorphism and asthma [9-18], but the results remain inconclusive. To better shed light on these conflicting findings and to quantify the potential between-study heterogeneity, provide better statistical power to detect smaller effect sizes,

Table 1. Baseline characteristics of qualified studies included in the meta-analysis

Author (ref*)	Year	Country/ Ethnicity	Design	Case					Control					Genotype method	HWE#	MAF	NOS (stars*)
				Sample size	Age (yr)	Genotype			Sample size	Age (yr)	Genotype			Source of control				
						CC	CG	GG			CC	CG	GG					
Ober, C et al [9]	2009	Germany/ Caucasian	CC	344	10.1 (6-16)	227	100	17	294	7.9 (4-16)	150	120	24	HCC	TaqMan	0.37	0.27	6
		USA/Caucasian	CC	99	24.4 (7-74)	69	25	5	198	31.6 (18-69)	111	80	7					
Rathcke, C. N et al [10]	2009	Denmark/ Caucasian	CS	517	46.20 (30.63-61.72)	343	144	30	5526	46.20 (30.63-61.72)	3495	1803	228	PCS	TaqMan	0.81	0.20	5
Cunningham, J et al [11]	2011	Scotland/ Caucasian	CS	400	10.4±4.0	256	144$		671	10.4±4.0	389	282$		HCS	TaqMan	>0.05	NA	5
Shao, J. L et al [12]	2011	China/Asian	CC	255	39.5±14.9	169	80	6	263	38.9±10.0	197	61	5	HCC	PCR-RFLP	0.91	0.13	7
Ortega, H et al [13]	2013	USA/African-American	CS	285	NA	148	137$		37	36.0 (24.0-48.0)	18	19$		HCS	KASPar assays	NA	NA	5
James, A. J et al [14]	2014	Denmark/ Caucasian	CC	151	Mild to moderate asthma: 43.4±1.6 Severe asthma: 50.2±1.4 COPD: 64.3±1.1	96	45	10	57	40 (21-77)	40	14	3	HCC	Centaurus Nanogen	0.25	0.18	7
Hansen, J. W et al [15]	2015	Denmark/ Caucasian	CC	1118	Asthma: 30 (29-30) Asthma with rhinitis: 30 (30-31)	680	394	44	262	33 (32-34)	167	87	8	HCC	Centaurus Nanogen	0.41	0.20	6
Li, J. M et al [16]	2015	China/Asian	CC	316	2.2±1.4	192	111	13	297	2.3±1.5	217	71	9	HCC	ARRAY-IPLEX	0.29	0.15	7
Naglot, S et al [17]	2015	Indian/ Asian	CC	100	37.5 (18-78)	68	32	0	50	27 (21-52)	19	31	0	PCC	PCR-RFLP	0.00	0.31	7
Ramphul, K et al [18]	2015	Mauritius/ Asian	CC	192	3-12	122	64	6	189	18-22	121	63	5	HCC	TaqMan	0.34	0.19	6

*The ref was referred to the reference numbers in this study. #Hardy-Weinberg equilibrium (HWE) test and $the minor allele frequency (MAF) were calculated in control group for each study. NA, data not available. CC, case-control; CS, cross-sectional; PCC, population-based case-control study; PCS, population-based cross-section study; HCC, hospital-based case-control study; HCS, hospital-based cross-section study.

we conducted a comprehensive meta-analysis on 10 published studies from 2008 to 2016 with 3,777 asthma cases and 7,844 controls relating variant of the *CHI3L1* -131C/G to the risk of developing asthma.

Material and methods

This study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting systematic reviews and meta-analyses. Study selection, data extraction, and quality assessment were completed independently by two investigators. Disagreement was resolved through discussion. If the discussion did not lead to a consensus, Professor Tang made the final decision.

Identification and eligibility of relevant studies

We attempted to include all the studies that determined the genotype distribution of *CHI3L1* -131C/G polymorphism in cases with asthma, and (i) in healthy controls or (ii) in diseased controls (free of asthma) in the meta-analysis.

We first identified studies by searching the electronic literature PubMed and Embase for relevant reports in English and CNKI for papers in Chinese (from January 1996 to December 2016), using the search terms "(chitinase 3-like-1 or CHI3L1) and (asthma) and (gene or polymorphism or allele or genotype or variant or variation or mutation)". We chose articles which conducted among human subjects. Eligible studies were then identified by further searching the studies on the association between *CHI3L1* -131C/G polymorphism and asthma risk and restricted attention to the studies that satisfied all of the following criteria: Studies related to the *CHI3L1* polymorphism was determined regardless of sample size and study design; each genotype frequency was reported, and there was sufficient information for extraction of data; If studies had partly overlapped subjects, only the one with a larger and/or latest sample size was selected for the analysis. Additional studies were identified by hands-on searches from references of original studies or review articles on this topic. According to these criteria, we finally included 10 papers in our meta-analysis.

Data extraction and conversion

The data was independently extracted by two investigators until they reached a consensus on all of the items. Data extracted included the first author's name, publication year, study design, ethnicity of population, genotype method, source of control and the number of cases and controls for *CHI3L1* -131C/G genotypes from these articles. The frequencies of the alleles and the genotypic distributions were extracted or calculated for both cases and controls. We merged the original data into the control group or case group if the study did not provide corresponding data. For some studies without sufficient information for extraction of data, we tried to contact with the studies' authors by sending emails from their articles to request missing data. In addition, it was tested whether the distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium (HWE) for each study and calculated the frequency of the minor allele for *CHI3L1* -131C/G polymorphism.

Quality assessment and study stratification

We used the Newcastle-Ottawa scale (NOS) method to assess the observational included studies. The NOS is composed of three parts (8 entries): selection, comparability and exposure. A quality item is given only one star for the study in selection and exposure, and a quality item is given at most two stars for the study in comparability. It is a semi-quantitative scale, and a score of 0-9 stars is assigned to each study. Studies whose scores were more than 6 stars were considered to be of relatively high quality [19]. The scores of included studies were shown in **Table 1**.

Meta-analysis

Our meta-analysis evaluated the relationship between the *CHI3L1* -131C/G polymorphism and the risk of asthma for each study by odds ratio (OR) with 95% confidence intervals (95% CI). For all studies, we calculated the ORs for the: (i) Separate pairwise comparisons, (ii) allele contrast, (iii) recessive model and (iv) dominant model. In addition, we conducted stratification analysis by ethnicity and age. A sensitivity analysis, which examines the effect of excluding specific studies, was also performed [20]. Our meta-analysis was subjected

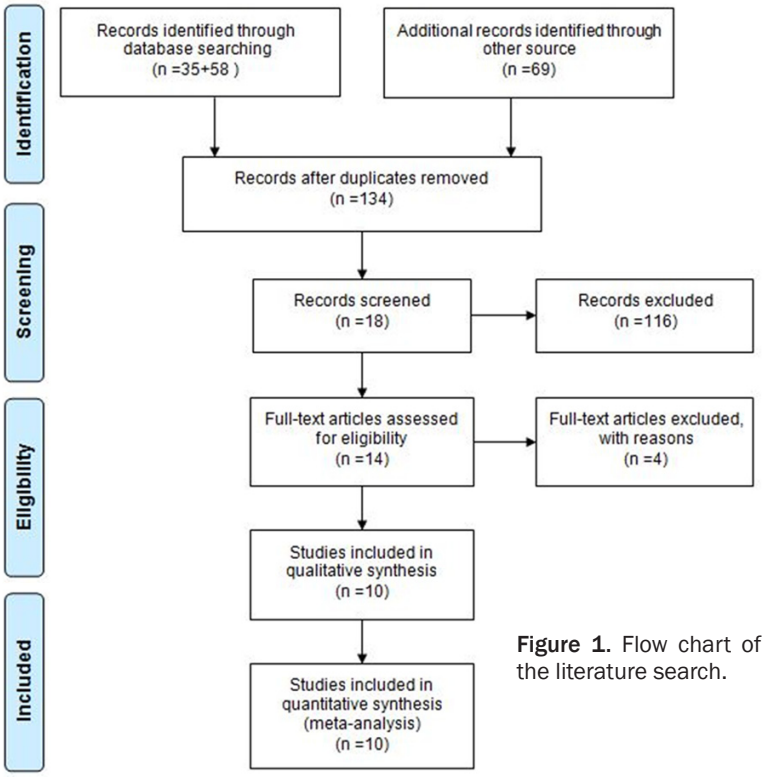

Figure 1. Flow chart of the literature search.

to sensitivity analysis for studies with the controls not in HWE (P<0.05) and studies which were out of the funnel plot's borderline.

We used the χ^2-based Q statistic test to assess the heterogeneity, and it was considered significant for P<0.05. Heterogeneity was quantified with the I^2 metric, which was independent of the number of studies in the meta-analysis. I^2 takes values between 0 and 100%, with higher values denoting greater degree of heterogeneity (I^2>50% was considered significant) [21]. We used the fixed-effects model and the random-effects model based on the Mantel-Haenszel method and the DerSimonian and Laird method, respectively, to combine values from each of the studies. When the effects were assumed to be heterogeneous, the random-effects model was then used; otherwise, the fix-effects model was more appropriate [22]. In addition, we further conducted meta-regression analyses to estimate the source of heterogeneity. Publication bias was assessed according to the Begg adjusted rank correlation test and the Egger regression asymmetry test [23, 24]. All analysis was done by using the Stata soft (v.12.0). All the P values were two-sided.

Results

Literature search

The study selection process is shown in **Figure 1**. A total of 160 articles (PubMed 35, Embase 58 and CNKI 69) were identified from the databases, and 26 duplicates were excluded using EndNote (X7). In addition, 52 articles were excluded based on a review of the titles and abstracts, and 14 full-text articles were assessed for eligibility; 4 articles were excluded due to did not study on -131C/G polymorphism. Finally, a total of 10 articles were included in this meta-analysis.

Eligible studies and study characteristics

The selected study baseline characteristics from the qualified studies included in the meta-analysis are provided in **Table 1**. For 10 studies, 5 studies were based on Caucasian population, 4 studies on Asian population and 1 study on African-American population. 7 studies were based on adult asthma participants and 4 on children asthma participants (one study [9] was based on both adult and children asthma participants). 8 studies were case-control study design and 2 studies were cross-sectional study design.

Summary statistics

Data from 10 articles that detected the association between the *CHI3L1* -131C/G polymorphism and asthma risk were included in the meta-analysis. The overall frequency (%) of minor G allele frequency (MAF) was 0.18/0.19 for cases and controls. The frequency of the MAF for each study polymorphism for controls is shown in **Table 1**. All studies indicated that the distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium except for one studies ([16]), indicating genotyping errors and/or population stratification [20]; In addition, one study [13] did not provide sufficient information to test the Hardy-

Table 2. Summary ORs and heterogeneity results for relationship between the *CHI3L1* C-131G polymorphism and Asthma

Genetic model	Population	Studies	OR	95% CI	P*	I^2 (%)
CG vs CC	All studies	10	0.89	0.65-1.22	0.00	83.3
	Asian	4&	1.01	0.55-1.84	0.00	86.4
	Caucasian	5&	0.79	0.58-1.07	0.01	72.8
	Children	4#	0.99	0.49-2.02	0.00	90.9
	Adult	7#	0.84	0.58-1.22	0.00	80.5
GG vs CC	All studies	10	1.13	0.87-1.47	0.27	20.3
	Asian	4&	1.45	0.79-2.67	0.92	0.0
	Caucasian	5&	1.07	0.79-1.43	0.10	49.3
	Children	4#	0.80	0.50-1.28	0.06	64.0
	Adult	7#	1.33	0.97-1.83	0.99	0.0
Allele contrast	All studies	10	0.96	0.76-1.21	0.00	80.4
	Asian	4&	1.05	0.67-1.64	0.00	83.0
	Caucasian	5&	0.88	0.68-1.14	0.00	74.9
	Children	4#	0.99	0.55-1.79	0.00	91.3
	Adult	7#	0.96	0.74-1.23	0.00	71.6
Recessive model	All studies	10	1.18	0.91-1.53	0.56	0.0
	Asian	4&	1.29	0.70-2.37	0.98	0.0
	Caucasian	5&	1.15	0.86-1.54	0.22	30.2
	Children	4#	0.84	0.53-1.35	0.25	28.0
	Adult	7#	1.38	0.99-1.90	0.99	0.0
Dominant model	All studies	10	0.94	0.72-1.21	0.00	81.9
	Asian	4&	1.01	0.56-1.82	0.00	86.4
	Caucasian	5&	0.81	0.64-1.03	0.01	70.40
	Children	4#	0.92	0.57-1.50	0.00	88.6
	Adult	7#	0.88	0.65-1.21	0.00	75.3

*Test for heterogeneity: Random-effects model was used when *P* value for heterogeneity test <0.05 and I^2>50%; otherwise, fixed-effects model was used. #One study [9] on both adult and Children. &Excluded one study on African-American population.

Weinberg equilibrium. Therefore, a sensitivity analysis was performed by excluding these two studies.

Main results, stratification, and sensitivity analyses

The evaluation results of the relationship of *CHI3L1* -131C/G polymorphism with asthma are presented in **Table 2**. **Figure 2** shows the overall results for the association between the polymorphism and the risk of asthma (in dominant model).

As it shown in **Table 2**, we failed to find any significant association between the *CHI3L1* -131C/G polymorphism and the risk of asthma for all genetic models (CG vs GG: OR=0.89, 95% CI: 0.65-1.22; GG vs CC: OR=1.13, 95% CI: 0.87-1.47; Allele contrast: OR=0.96, 95% CI: 0.76-1.21; recessive model: OR=1.18, 95% CI: 0.91-1.53 and dominant model: OR=0.94, 95% CI: 0.72-1.21, respectively). In stratified analysis by ethnicity and age, we still did not find any significant associations in different subgroup for all genetic models.

Further sensitivity analysis for HWE almost did not alter the pattern of result in dominant model (OR=0.83, 95% CI: 0.65-1.07). In addition, since there were four studies out of the funnel plot's borderline, we also conducted sensitivity analysis by excluding these studies, but the result was still consistent with the overall effect in dominant model (OR=0.92, 95% CI: 0.81-1.04).

Source of heterogeneity and publication bias

From **Table 2**, we found that the heterogeneity between studies was observed in overall comparisons as well as subgroup analyses. We estimated the possible source of heterogeneity in both dominant and recessive genetic models by ethnicity (Asian or Caucasian), age (children or adult), HWE (in HWE or not), source of control (from hospital based or population based) and study design (case-control or cross-sectional study design) by meta-regression analyses. It revealed that none of these five factors could influent significant between-study heterogeneity in genetic models for the polymorphism: ethnicity (*P*=0.77 in dominant model and *P*=0.75 in recessive model), age (*P*=0.21 in dominant model and *P*=0.14 in recessive model), HWE (*P*=0.31 in dominant model and *P*=0.50 in recessive model), source of control (*P*=0.87 in dominant model and *P*=0.39 in recessive model) and study design (*P*=0.44 in dominant model and *P*=0.39 in recessive model).

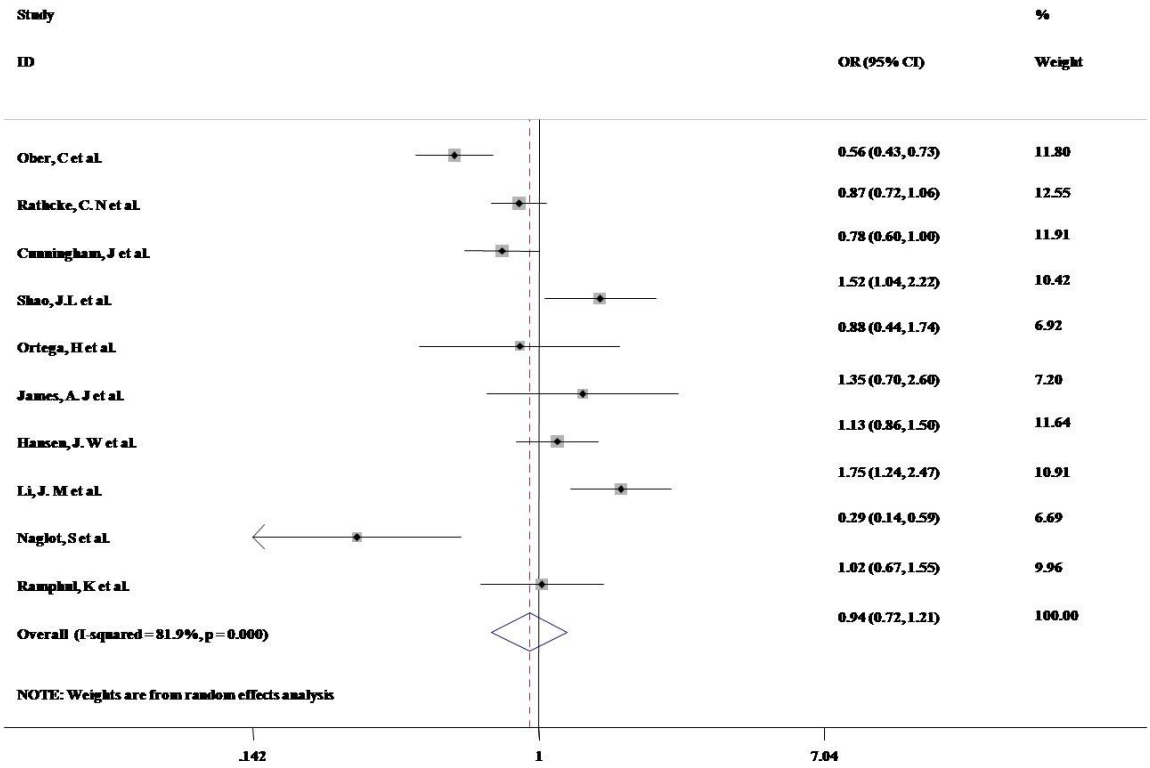

Figure 2. ORs (log scale) of Asthma associated with *CHI3L1* C-131G polymorphism for dominant genetic model. The graph shows individual and pooled estimates for all studies.

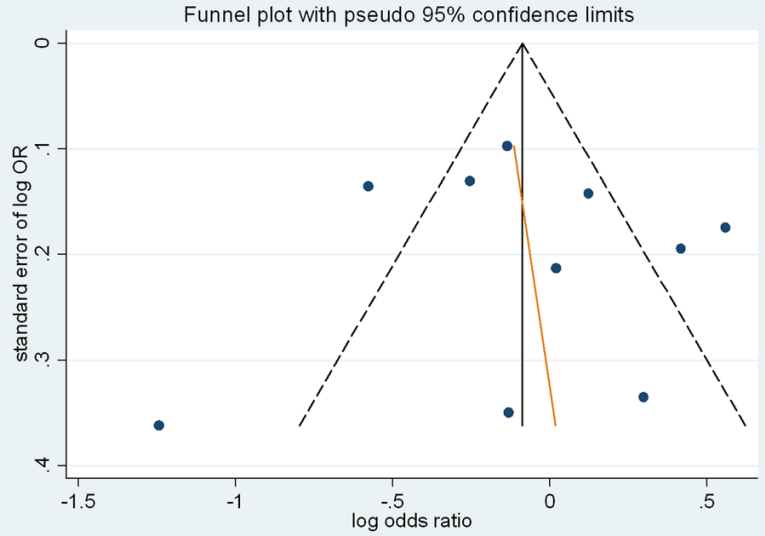

Figure 3. Evaluation of publication bias for all studies using funnel plots.

The potential presence of publication bias was estimated by using a funnel plot of evaluation of log-odds ratio for the genotype GG+ CG versus CC against the reciprocal of its standard error (**Figure 3**). As it shown, we failed to observe any significant funnel asymmetry which could indicate publication bias, although four studies were out of the funnel plot's borderline. We further conducted the Egger regression asymmetry test and the Begg adjusted rank correlation tests to estimate the publication bias of included literatures in the meta-analysis. As the results, no publication bias was found for the polymorphism and risk of Asthma in both dominant and recessive genetic models (Egger test: P=0.81 in dominant model and P=0.85 in recessive model; Begg: P=0.93 in dominant model and P=0.54 in recessive model).

Discussion

Out meta-analysis results showed that there was no significant relationship between *CHI3L1* -131C/G polymorphism and asthma. This finding manifested that the *CHI3L1* -131C/G geno-

type did not show any association with the susceptibility to asthma alone, even when stratified by subgroup.

To our knowledge, this was the first comprehensive meta-analysis to estimate the association of *CHI3L1* -131C/G polymorphism risk of asthma on 10 published studies with 3,777 asthma cases and 7,844 controls, which could provide better power to detect smaller effect sizes. Its strength was based on the accumulation of published data giving greater information to detect real differences. In order to estimate the power of the study, we used the Power and Precision 4 software to conduct the power calculation by respectively accumulating the frequency of *CHI3L1* G allele in case (0.18) and control (0.19) group from all studies and the result shown the power of our study is over 80%.

In the current meta-analysis, the effects of separate pairwise comparisons, allele contrast, dominant and recessive genetic models were estimated. Subgroup analysis by ethnicity and age, and sensitivity analysis for studies not in HWE and studies which were out of the funnel plot's borderline, were performed. In addition, we further evaluated the source of heterogeneity by meta-regression and the publication bias of included literatures by Egger regression asymmetry test and the Begg adjusted rank correlation tests.

Our finding that *CHI3L1* -131C/G polymorphism was not associated with asthma is consistent with the findings of other studies [15, 17, 25]. Although one previous genome-wide association studies [9] concluded that *CHI3L1* -131C/G polymorphism is associated with asthma, and several studies were consistent with it, our finding is in contrast to them. Several potential reasons may explain it: (1) the pathogenesis of asthma is very complex, and maybe more than one regulatory gene play functional role in pathogenesis of asthma; (2) the sample sizes were modest by GWAS standards; (3) the studies that found positive associations used case-control or cross-sectional design, lacking of cohort study to generate more powerful conclusion; (4) studies did not evaluate possible gene-environment interactions that influence the estimate of associations (e.g. ethnicity, environmental pollution, climate, lifestyle). Therefore, it is very important to conduct the meta-analysis to estimate the variant of the *CHI3L1* -131C/G to the risk of asthma by collecting each molecular epidemiological study on examining the association between *CHI3L1* -131C/G polymorphism and asthma.

Despite the clear strengths of our study, some limitations merit serious consideration. First, non-English/Chinese, non-indexed, and non-published studies literature were not reviewed in our meta-analysis, thus might introduce some bias [26]; Second, only the unadjusted pooled ORs were calculated, since data for possible confounding factors which can influence the estimates of associations (e.g. age, sex, family history) were not provided.

In summary, our present meta-analysis did not find a relationship between asthma and *CHI3L1* -131C/G polymorphism, suggesting that the *CHI3L1* -131C/G polymorphism may not be a significant susceptibility factor for asthma independently. Prospective and more gene-environment interactions studies are needed to clarify the real role of *CHI3L1* gene to the development of asthma.

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Disclosure of conflict of interest

None.

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