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Correlation between the genetic polymorphism of *ORMDL3* gene and asthma risk: a meta-analysis

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ABSTRACT. While increasing scientific evidence suggests that the *ORMDL3* rs7216389 polymorphism may contribute to a higher susceptibility to asthma, many of the current studies have yielded inconclusive results. This meta-analysis aimed to assess the association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma. An extensive literature search for relevant studies was conducted in PubMed, Embase, the Web of Science, the Cochrane Library, Chinese National Knowledge Infrastructure, and Google Scholar. This meta-analysis was performed using the STATA 12.0 software. Crude odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Thirteen studies were included with a total of 14,851 subjects, comprised of 6739 patients with asthma and 8112 healthy controls. Our meta-analysis results revealed that the *ORMDL3* rs7216389 polymorphism may be associated with an increased risk of asthma (allele model: OR = 1.39, 95%CI = 1.27-1.52, P < 0.001; dominant model: OR = 1.46, 95%CI = 1.31-1.62, P < 0.001; recessive model: OR = 1.57, 95%CI = 1.37-1.81, P < 0.001; homozygous model: OR = 1.58, 95%CI = 1.32-1.90, P < 0.001; heterozygous model: OR = 1.54, 95%CI = 1.30-1.82, P < 0.001). We also found significant associations in our subgroup analyses based on ethnicity and type of asthma. However, in our subgroup analysis based

on sources of controls, an association was found in the population-based case-control subgroup but not in the hospital-based case-control subgroup. This meta-analysis indicates that *ORMDL3* rs7216389 may contribute to increasing susceptibility to asthma.

Key words: *ORMDL3*; rs7216389; Polymorphism; Asthma; Meta-analysis

INTRODUCTION

Asthma is a common chronic and complex inflammatory respiratory disease characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing (Wang et al., 2013). As the incidence and mortality of asthma are increasing, so is its negative impact on modern society (Busse et al., 1995). While the exact mechanisms underlying the development and progression of asthma have not yet been fully uncovered, both genetic and environmental factors are known to be involved (Akhabir and Sandford, 2011). Environmental factors, including allergens, poor air quality, and frequent smoking, obviously increase the risk of asthma; however, they are much more clearly related to the provocation of asthma attacks and to asthma severity than they are to asthma susceptibility (Huncharek and Kupelnick, 2000). Likewise, dozens of studies have investigated the genetic associations of asthma, but few of them have been successfully replicated across multiple populations. Among these studies, many have identified *ORMDL3* as a potential asthma candidate gene and the single-nucleotide polymorphism (SNP) rs7216389 as a major susceptibility locus (Moffatt et al., 2007; Flory et al., 2009; Verlaan et al., 2009; Blekic et al., 2013).

The *ORMDL3* gene is located on chromosome 17q21. It belongs to a family of genes, with three members in humans (*ORMDL1*, *ORMDL2*, and *ORMDL3*), that is responsible for encoding transmembrane proteins of the endoplasmic reticulum (Wu et al., 2009). Though our current understanding of the role of *ORMDL3* is limited, it is known to be involved in sphingolipid metabolism, as well as in the regulation of Ca^{2+} uptake from the cytosol to the endoplasmic reticulum (Verlaan et al., 2009). The SNP rs7216389, which controls the expression of the *ORMDL3* gene, has been one of the most extensively polymorphisms studied. In a study by Galanter et al. (2008), the association between SNPs in the *ORMDL3* gene and childhood asthma was found to be significant in multiple ethnic groups, including Puerto Ricans and Mexicans, but not in African-Americans. Likewise, Hirota et al. (2008) found that the SNP rs7216389 was correlated with an increased risk of asthma in a Japanese population. Moreover, Leung et al. (2009) found that asthma diagnosis was related to rs11650680 and five other SNPs, including rs7216389, in a Hong Kong population. Kang et al. (2012) also found the *ORMDL3* block of SNPs, including rs7216389, might be associated with asthma susceptibility in Korean children. However, Jin et al. (2010) found no association between SNPs within *ORMDL3* and childhood asthma in Beijing, China, but did find genetic association with atopy. A study by Sun et al. (2010) separated the experimental group into patients with mild or severe asthma and found that there was no significant difference in the rs7216389 TT genotype between the mild group and controls, while the rate of the T-allele in the severe group was higher than in the other two.

Several factors may account for these conflicting findings. First, they might result from the insufficient power of individual studies, indicating that a large number of subjects may be needed to detect a small relative risk. Second, there may be remarkable differences in the type and severity of asthma represented in each study. Another reason may be ethnic dif-

ferences in allele frequencies and genotypes. We have therefore constructed a meta-analysis to derive a more comprehensive assessment of the association between the *ORMDL3* rs7216289 polymorphism and the risk of asthma.

MATERIAL AND METHODS

Literature search

In order to identify relevant studies, we conducted a literature search in the following electronic databases: PubMed, Embase, the Web of Science, the Cochrane Library, Chinese National Knowledge Infrastructure, and Google Scholar. The last retrieval was conducted on February 11, 2014. A comprehensive and exhaustive search strategy was formulated in an attempt to identify all of the relevant studies, regardless of language or publication status, using the following medical subject headings and their entry terms: ("*ORMDL3*" or "rs7216289") and ("single nucleotide polymorphism" or "SNP") and ("asthma" or "children asthma" or "adult asthma"). Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies.

Selection criteria

This meta-analysis included case-control studies investigating the association between *ORMDL3* rs7216389 and the risk of asthma. Included candidate studies had to be original and had to report the genotype frequencies in patients and controls, or their estimated odds ratios (ORs). Moreover, all patients had to meet the diagnostic criteria for asthma. When duplicate publications of the same study were found, the report with the most complete data was included in this meta-analysis.

Data extraction

Two investigators independently extracted the following data using a standard table: surname of first author, year of publication, country of origin, ethnicity, source of controls, number of patients and controls, age, genotyping method, type of asthma, P value of Hardy-Weinberg equilibrium (HWE), minor allele frequency in patients and controls, allele and genotype frequency, etc. Ethnicities were categorized as Caucasian, Asian, or African. We also classified patients with asthma into adult and childhood groups. In addition, when studies included patients of more than one ethnicity, we extracted the relevant genotype data separately according to ethnicity for the subgroup analysis. Any disagreements were resolved by discussion between the two investigators. Data not presented in table form or in the main text are available upon request.

Quality assessment

The strengthening the reporting of genetic association studies (STREGA) quality score system was used to assess the qualities of all studies included (Ohtani et al., 2013). The STREGA system includes 22 assessment items related to quality appraisal, with STREGA scores higher than 14 indicating a moderate to high quality. Two authors independently assessed the quality of studies included. Discrepancies over quality scores were resolved by discussion between all the authors.

Statistical analysis

Statistical analyses were performed using the Stata software version 12.0 (Stata Corp., College Station, TX, USA). As the first step in this meta-analysis, we tested the significance of the deviation of genotype distributions at the polymorphic site from that expected from HWE in the control sample for each of the case-control data sets selected (Leonard and Wolff, 2013). Association between *ORMDL3* and risk of asthma was assessed using the pooled ORs with their corresponding 95%CIs. The significance of the pooled ORs was determined by the Z-test, with $P < 0.05$ considered to be statistically significant (Kinugasa et al., 2013). Between-study heterogeneity was tested using Cochran's Q statistic and the I^2 metric (Toulis et al., 2012). When no heterogeneity was found with $P > 0.05$ or $I^2 < 50\%$, a fixed effect model was applied to estimate the pooled ORs and 95%CIs. Otherwise, a random effect model was used. In addition to an overall analysis, stratified analyses were performed based on ethnic group, type of asthma, and source of controls, where applicable. One-way sensitivity analysis was conducted by omitting individual studies in turn to reflect the influence of individual datasets on the pooled results (Syrjanen, 2012). Potential publication bias was examined visually by Begg's funnel plot of the OR estimates in a logarithmic scale against its standard error. The degree of asymmetry was tested using the Egger test (Syrjanen, 2012).

RESULTS

Baseline characteristics of studies included

The flow chart of retrieved and excluded studies with their reasons for exclusion is shown in Figure 1. Based on our search strategy, the primary screening identified 141 potentially relevant articles. In accordance with the inclusion criteria, thirteen case-control studies were selected for this meta-analysis, including a total of 6739 asthma patients and 8112 controls (Galanter et al., 2008; Hirota et al., 2008; Tavendale et al., 2008; Leung et al., 2009; Jin et al., 2010; Sun et al., 2010; Binia et al., 2011; Fang et al., 2011; Yu et al., 2011; Chi et al., 2012; Kang et al., 2012; Sy et al., 2012; Yang et al., 2012). The publication years of the studies included ranged from 2008 to 2012. All selected studies concentrated on the association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma. Of the thirteen studies, eleven were population-based case-control studies (Galanter et al., 2008; Hirota et al., 2008; Tavendale et al., 2008; Leung et al., 2009; Binia et al., 2011; Fang et al., 2011; Yu et al., 2011; Chi et al., 2012; Kang et al., 2012; Sy et al., 2012; Yang et al., 2012) and two were hospital-based (Jin et al., 2010; Sun et al., 2010). The polymerase chain reaction (PCR)-restriction fragment length polymorphism and TaqMan genotyping methods were used in most studies (Hirota et al., 2008; Tavendale et al., 2008; Leung et al., 2009; Jin et al., 2010; Sun et al., 2010; Binia et al., 2011; Fang et al., 2011; Yu et al., 2011; Chi et al., 2012; Kang et al., 2012; Sy et al., 2012), while the allele-specific PCR and MassARRAY were applied in the other two studies (Galanter et al., 2008; Yang et al., 2012). The genotype frequencies of controls in three studies significantly deviated from HWE ($P < 0.05$) (Leung et al., 2009; Sun et al., 2010; Chi et al., 2012). The qualities of all studies included were moderately high, with STREGA scores higher than 14. Further details on the main characteristics of each study can be found in Table 1.

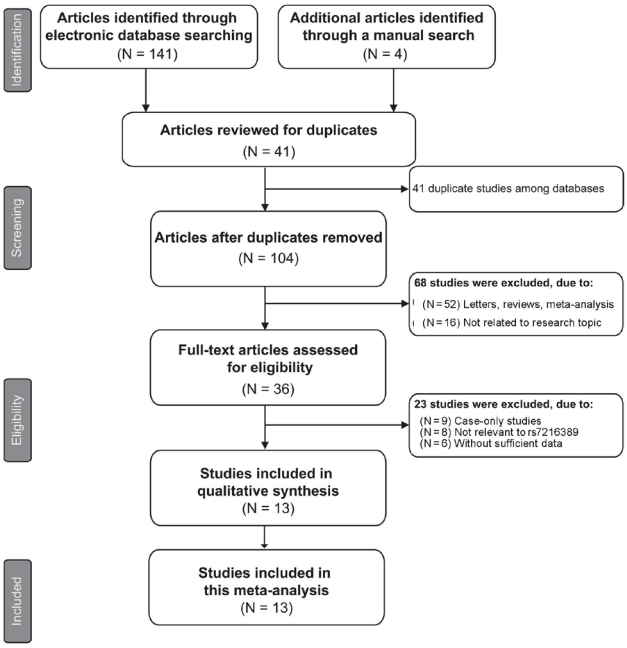

Figure 1. Flow chart of the study selection procedure. Thirteen case-control studies were included.

Table 1. Characteristics and quality assessment of the studies included.

First author, year	Country	Ethnicity	Source of control	Cases (N, age)	Controls (N, age)	Genotype method	Subjects' ages at diagnosis	HWE P value	MAF (case/control)	Quality scores
Galanter et al., 2008	USA	African	PCC	259, range 12-24	169, range 12-24	AS-PCR	Childhood asthma	0.392	0.838, 0.784	14
		Caucasian		652, range 10-19	1033, NA	AS-PCR	Childhood asthma	0.188	0.696, 0.661	15
Hirota et al., 2008	Japan	Asian	PCC	545, mean 9.5	738, mean 49	TaqMan	Childhood asthma	0.378	0.782, 0.713	18
Tavendale et al., 2008	UK	Caucasian	PCC	1279, mean 10.4	1541, mean 7.5	TaqMan	Childhood asthma	0.425	0.559, 0.464	17
Leung et al., 2009	China	Asian	PCC	315, mean 11.1	192, mean 11.8	PCR-RFLP	Childhood asthma	0.010	0.803, 0.768	16
Jin et al., 2010	China	Asian	HCC	220, mean 5.8	208, mean 7.15	TaqMan	Childhood asthma	0.529	0.741, 0.697	16
Sun et al., 2010	China	Asian	HCC	178, mean 12.5	100, mean 13.4	PCR-RFLP	Childhood asthma	<0.001	0.713, 0.520	15
Binia et al., 2011	UK	Caucasian	PCC	385, NA	1429, NA	TaqMan	Severe asthma	0.383	0.561, 0.473	14
							Childhood asthma	0.174	0.645, 0.473	
							Adult asthma	0.259	0.491, 0.473	
Fang et al., 2011	China	Asian	PCC	696, mean 28.7	637, mean 29.1	PCR-RFLP	Adult asthma	0.628	0.737, 0.692	18
Yu et al., 2011	Korea	Asian	PCC	786, mean 8.98	522, mean 9.69	PCR-RFLP	Childhood asthma	0.123	0.774, 0.730	19
Kang et al., 2012	Korea	Asian	PCC	775, mean 8.98	451, mean 9.63	TaqMan	Childhood asthma	0.562	0.763, 0.714	17
Sy et al., 2012	China	Asian	PCC	345, mean 44.2	464, mean 42,5	TaqMan	Adult asthma	0.008	0.778, 0.749	16
Yang et al., 2012	China	Asian	PCC	152, mean 5.9	190, mean 6	MassARRAY	Childhood asthma	0.392	0.780, 0.682	15
Chi et al., 2012	China	Asian	PCC	152, mean 39.8	140, mean 41.9	PCR-RFLP	Adult asthma	0.188	0.816, 0.629	19

HWE = Hardy-Weinberg equilibrium; MAF = minor allele frequencies; PCC = population-based case-control study; HCC = hospital-based case-control study; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; NA = data not available.

Association between *ORMDL3* and risk of asthma

As illustrated in Table 2, the overall analysis suggested that the T-allele of the *ORMDL3* rs7216389 polymorphism was associated with a 1.39-fold (95%CI = 1.27-1.52) increased risk of asthma (Figure 2A). Specifically, the homozygote genotype (TT) risk was

Table 2. Meta-analysis of the association between the *ORMDL3* rs7216389 polymorphism and asthma risk.

Subgroups	No. of study	T allele *vs* C allele			TT + TC *vs* CC			TT *vs* TC + CC			TT *vs* CC			TT *vs* TC		
		OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Ethnicity																
Asian	10	1.42	1.25-1.62	<0.001	1.19	1.00-1.41	0.045	1.67	1.37-2.05	<0.001	1.45	1.14-1.83	0.002	1.70	1.34-2.17	<0.001
Caucasian	3	1.35	1.18-1.55	<0.001	1.65	1.44-1.89	<0.001	1.40	1.15-1.71	0.001	1.88	1.48-2.38	<0.001	1.26	1.09-1.46	0.002
African	1	1.42	1.00-2.02	0.047	1.15	0.39-3.39	0.793	1.58	1.05-2.38	0.028	1.35	0.45-3.99	0.592	1.61	1.06-2.45	0.027
Subjects' ages																
Childhood asthma	10	1.42	1.28-1.57	<0.001	1.55	1.25-1.92	<0.001	1.48	1.37-1.60	<0.001	1.80	1.41-2.30	<0.001	1.39	1.29-1.52	<0.001
Adult asthma	4	1.38	1.03-1.84	0.029	0.91	0.67-1.25	0.570	1.57	1.35-1.82	<0.001	1.15	0.88-1.51	0.310	2.42	1.13-5.20	0.023
Source of control																
PCC	11	1.33	1.25-1.48	<0.001	1.25	1.02-1.53	0.028	1.57	1.35-1.82	<0.001	1.53	1.26-1.84	<0.001	1.57	1.31-1.88	<0.001
HCC	2	1.68	0.92-3.06	0.093	1.94	0.99-3.83	0.054	1.65	0.97-2.80	0.062	2.17	1.00-4.40	0.053	1.33	0.94-1.86	0.104
Overall	14	1.39	1.27-1.52	<0.001	1.46	1.31-1.62	<0.001	1.57	1.37-1.81	<0.001	1.58	1.32-1.90	<0.001	1.54	1.30-1.82	<0.001

PCC = population-based case-control study; HCC = hospital-based case-control study; OR = odd ratios; CI = confidence interval.

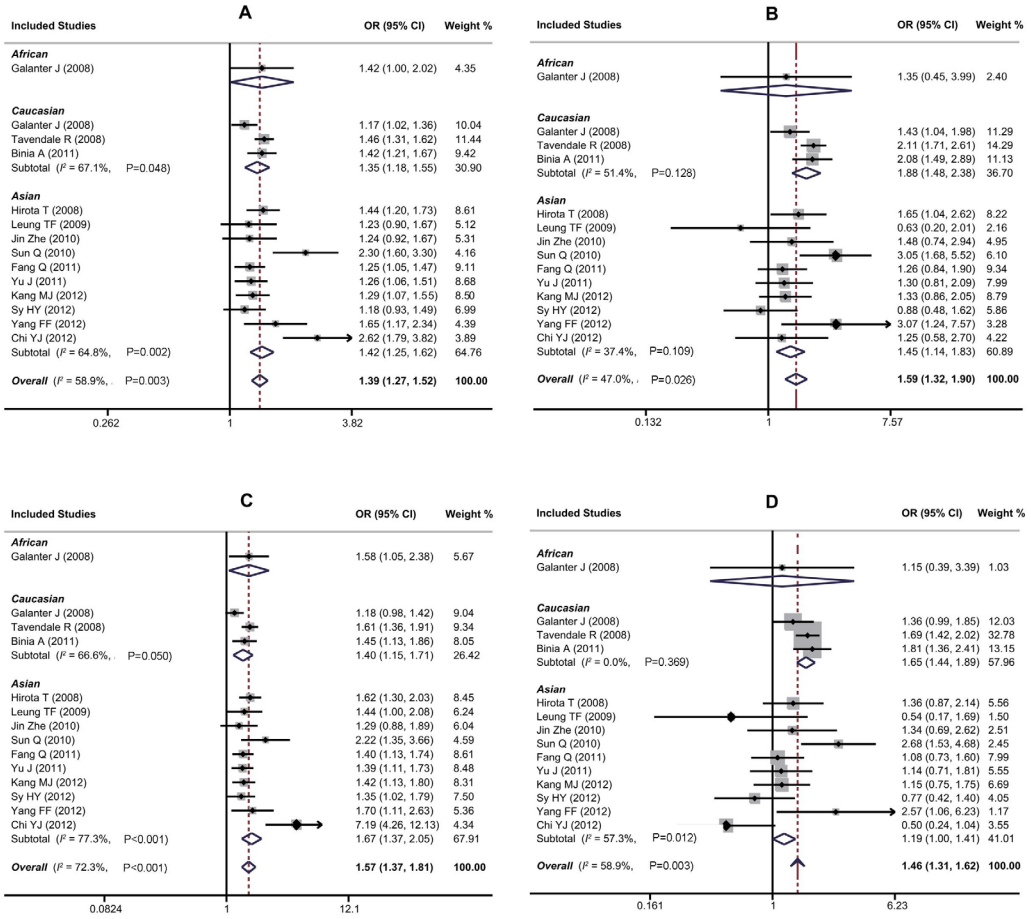

Figure 2. Forest plot of ORs for the association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma in subgroup analysis based on ethnicity. **A.** T allele *vs* C allele; **B.** TT *vs* CC; **C.** TT *vs* TC + CC; **D.** TT + TC *vs* CC. OR = odds ratios.

1.58-fold (95%CI = 1.32-1.90) compared with CC genotype (Figure 2B); and 1.54-fold (95%CI = 1.30-1.82) compared with the heterozygote genotype (TC). When considering the sum of two genotypes, the homozygote genotype (TT) risk was 1.57-fold (95%CI = 1.37-1.81) compared to the other two genotypes (Figure 2C), while the risk considering TT and TC together were 1.46-fold (95%CI = 1.27-1.52) (Figure 2D). Between-study heterogeneity was obvious in the overall analysis, indicating the necessity of subgroup analyses to explore possible sources of heterogeneity. Interestingly, in the analysis stratified by ethnicity, we found that the associations between the *ORMDL3* rs7216389 polymorphism and the risk of asthma were significant among all ethnicities, including Asian, Caucasian, as well as African (Figure 2). From a subgroup analysis based on patients' ages, we found that the associations in the childhood and adult asthma subgroups were both significant (Figure 3). Considering

the sources of controls, a subgroup analysis showed that the association was only found in population-based case-control studies ($P < 0.05$ under all genetic models), but not in hospital-based case-control studies ($P > 0.05$ under all genetic models).

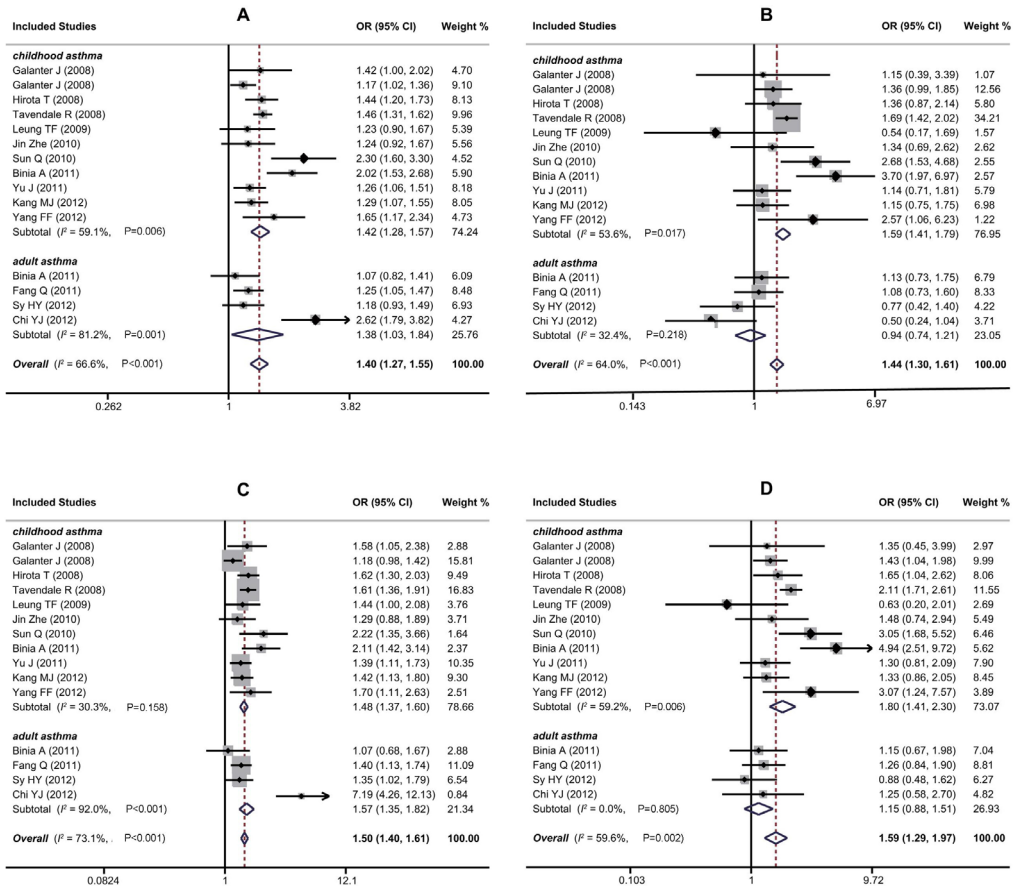

Figure 3. Forest plot of ORs for the association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma in subgroup analysis based on subjects' ages. **A.** T allele *vs* C allele; **B.** TT + TC *vs* CC; **C.** TT *vs* TC + CC; **D.** TT *vs* CC. OR = odds ratios.

Sensitivity analysis and publication bias

In order to detect the stability of the results, we conducted one-way sensitivity analyses by sequentially excluding individual studies. We found that no one individual study influenced the pooled ORs for either the rs7216389 polymorphism or asthma, proving the stability of the results. In addition, the potential publication bias of the included studies was assessed by Begg's funnel plot and the Egger linear regression test. The Begg's funnel plot did not show any substantial asymmetry (Figure 4). The Egger test also did not show any statistical evidence of publication bias ($t = 2.45$; $P = 0.071$).

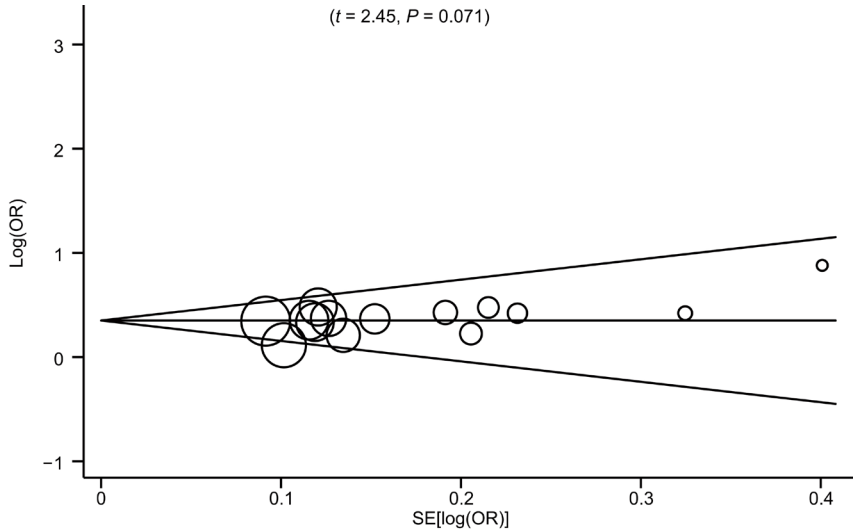

Figure 4. Begg's funnel plots of publication bias for the overall association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma.

DISCUSSION

Asthma remains one of the most common chronic respiratory disorders worldwide and its incidence and mortality are increasing (Busse et al., 1995). Asthma is thought to be a polygenic disease caused by complex interactions between genetic and environmental factors (Faussner and Dempke, 2012). Numerous studies have reported on the association between the *ORMDL3* rs7216389 polymorphism and asthma risk but with inconclusive results, perhaps partially due to the small effect of the polymorphism on asthma risk and the relatively small sample sizes used. To the best of our knowledge, the present study may be the most comprehensive overview of the association between the *ORMDL3* rs7216389 polymorphism and susceptibility to asthma.

According to the overall findings of our meta-analysis, the T-allele of the *ORMDL3* rs7216389 polymorphism was associated with an increased risk of asthma and thus can be considered a marker of genetic susceptibility to asthma. It is also worth noting that the risk conferred by the homozygous genotype (TT) was obviously higher than that of the heterozygous TC genotype, which conformed to our expectations. Furthermore, on the basis of the other models tested herein, the function of the T-allele in increasing the incidence of asthma was proved significant. Although there are no confirmed explanations of the underlying mechanism associating the rs7216389 SNP and asthma, several potential mechanisms have been considered. One such explanation points to the association between the rs7216389 SNP and the increased IgE levels and severity of bronchial hyper-responsiveness, which are the most important intermediate phenotypes of asthma (Yu et al., 2011). Another possibility is that the rs7216389 SNP regulates the expression of *ORMDL3*, whose function is to facilitate endoplasmic reticulum mediating inflammatory responses, which influence the regulation of allergen sensitization (Madore et al., 2008).

Since individuals with different ethnic backgrounds may be affected by diverse genetic and environmental factors, the same polymorphism may play different roles in different populations (Zhang et al., 2011). In order to explore whether the same polymorphism possesses different functions in asthma susceptibility among different ethnic populations, we conducted a subgroup analysis based on ethnicity. Our results indicated that in all three subgroups: Asians, Caucasians, and Africans, the association was evident, indicating that the mutation might play identical roles across different ethnicities. However, we should keep in mind that only one study with a small sample size has been conducted in African populations and thus our analysis of this subgroup may have had insufficient statistical power to detect a slight effect, or may have generated a fluctuated risk estimate (Galanter et al., 2008). Considering these limitations, our results on the African subgroup should be interpreted with caution.

According to a study by Moffat et al. (2010), the genetic inducements and symptoms of childhood and adult asthma are probably different. However, according to the results of our subgroup analysis based on subjects' ages, the *ORMDL3* rs7216389 polymorphism was significantly associated with both childhood and adult asthma. These results illustrated that the disease mechanism of childhood asthma possibly overlaps that of adult asthma. However, the limited sample size of adult asthma patients may have limited the statistical power of our analysis since only four studies distinguished enrolled subjects' ages (Binia et al., 2011; Fang et al., 2011; Chi et al., 2012; Sy et al., 2012). As for our subgroup analysis based on the source of controls, we can conclude that the source of controls was possibly a factor contributing to heterogeneity. As was shown in our results, all P values for the population-based case-control subgroup were <0.05, indicating statistical confidence that the association exists. However, the association was insignificant for the hospital-based case-control subgroup under all genetic models. Since genotype distributions in population-based controls may be more similar to normal, population-based controls may be more reliable than hospital-based controls. We should also note that limited sample sizes might have led to the different results because only two of the studies included used hospital-based case-controls (Jin et al., 2010; Sun et al., 2010).

Compared with previous similar studies, our study had several methodological strengths. Firstly, previous systematic reviews did not investigate the association between the *ORMDL3* rs7216389 polymorphism and the risk of asthma in detail. To the best of our knowledge, our study was the first attempt to explore the effect of the *ORMDL3* rs7216389 polymorphism on asthma risk. Our study was also the first to investigate variances in subjects' ages and sources of controls for this association; and our results revealed that sources of controls might have impacted findings regarding this association to a certain extent. However, several potential limitations of our study also warrant mention. First, in the subgroup analysis by ethnicity, there was only one study, with a small sample size, focused on Africans (Galanter et al., 2008). Likewise, the number of studies using hospital-based case-control design was relatively small, indicating limited statistical power to explore the real association. Second, care must be taken when interpreting these data because the development of asthma, like other complex diseases, is a multistep process involving the interplay of multiple factors. As a result, the effects of individual polymorphisms are unlikely to be substantial and may be of limited value in predicting risk. Third, our results were based on unadjusted estimates. If individual data points were available, we would have been able to conduct a more precise analysis by adjusting other covariates including age, gender, and environmental factors as well as lifestyle. Therefore, given these limitations, our conclusions should be interpreted cautiously.

In conclusion, despite these limitations, the present meta-analysis supports the growing evidence that the *ORMDL3* rs7216389 polymorphism is a risk factor for susceptibility to asthma. We believe that the identification of this genetic risk factor could be helpful in the early detection and selective chemoprevention of asthma. Due to the limitations mentioned above, out meta-analysis might have had insufficient power to detect gene-environment interactions and thus additional research is needed to determine the exact mechanisms of asthma and the influence of gene polymorphisms in different ethnic groups.

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