

GENETIC DETERMINANTS

Association between Angiotensin-Converting Enzyme I/D Polymorphism and Asthma Risk: A Meta-Analysis Involving 11,897 Subjects

QUN-LI DING, M.S., SHI-FANG SUN, B.S., CHAO CAO, M.S., AND ZAI-CHUN DENG, M.S.*

Department of Respiratory Medicine, Affiliated Hospital, Medicine College, Ningbo University, Ningbo, China.

Background. Genetic susceptibility to asthma has been a research focus in the scientific community. Several studies have been conducted in recent years to evaluate the risk of asthma and insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme (ACE). However, the results remain conflicting rather than conclusive. **Methods.** We carried out a search in Medline, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) database for relevant studies. Data were extracted using a standardized form and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association. **Results.** Our meta-analysis on 11,897 subjects from all available studies showed that the DD genotype was associated with increased asthma risk than those with the II (OR = 1.59, 95% CI = 1.20–2.12) or ID/II (OR = 1.62, 95% CI = 1.24–2.10) genotype. Stratified analyses by ethnicity (Europeans and Asians) and age (adults and children) obtained statistically similar results in the two genetic models. In the subgroup analysis by source of controls, the DD genotype was associated with a significantly elevated risk of asthma among population-based controls (DD vs. II: OR = 2.27, 95% CI = 1.45–3.56) but not hospital-based controls (DD vs. II: OR = 1.18, 95% CI = 0.93–1.49). **Conclusions.** This meta-analysis provides strong evidence that the I/D polymorphism of ACE is associated with asthma risk. Additional well-designed large studies were required for the validation of our results, especially in African populations.

Keywords angiotensin-converting enzyme, asthma, meta-analysis, polymorphism

INTRODUCTION

Asthma is a human pulmonary disease characterized by chronic inflammation of the airways and bronchial hyper-responsiveness (1). It is a common multifactorial disease of varying severity, and the etiology is attributable to both environmental and genetic factors. Examination of genetic polymorphisms may explain individual differences in asthma risk. Several candidate genes are implicated in the pathogenesis of asthma, one of which is the angiotensin-converting enzyme (ACE) gene.

ACE is a zinc metallopeptidase whose main function is to catabolize the proinflammatory mediator bradykinin and to thus exert an anti-inflammatory effect (2). The ACE gene spans 21 kb, is located on the 17th chromosome q23, and consists of 26 exons and 25 introns. ACE polymorphism was caused by a 287-bp insertion or deletion (ID) in intron 16 (3). The I/D polymorphism of ACE has been shown to be associated with differences in plasma ACE level and with the expression level of membrane-bound ACE in human peripheral mononuclear cells (4, 5).

Previous studies revealed that polymorphism of ACE was implicated in susceptibility to asthma, but some studies reported apparent conflicting results (6–21). Considering the relatively small sample size in each study, it is possible to perform a quantitative synthesis of the evidence with rigorous methods. To investigate a

possible association between ACE polymorphism and asthma, we performed a meta-analysis from all the available relevant studies, including 2465 asthmatics and 9432 controls.

MATERIALS AND METHODS

Identification and Eligibility of Relevant Studies

We carried out a search in Medline, EMBASE, and Chinese National Knowledge Infrastructure (CNKI), covering all papers published up to August 2011, using the search terms: (ACE OR angiotensin-converting enzyme) AND (gene OR polymorphism OR genetic variant) AND (asthma). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Only published studies with full-text articles were included. If studies had partly overlapped subjects, only the most recent or complete study was selected.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) published in English or in Chinese; (b) use a case-control design; (c) validated genotyping methods should have been used, (d) supplied the available genotype frequencies in cases and controls; and (e) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were (a) no control group; (b) duplicate of previous publication; and (c) enrolled patients were using ACE inhibitors, or angiotensin II receptor antagonists.

*Corresponding author: Zai-Chun Deng, Department of Respiratory Medicine, Affiliated Hospital, Medicine College, Ningbo University, Ningbo 315020, China; Tel: +8675487035778; Fax: +8675487380487; E-mail: dengzaichun982136@hotmail.com

Data Extraction

Information was carefully extracted from all the eligible studies independently by two authors according to the inclusion criteria listed above. The results were compared, and disagreements were resolved by discussion and consensus. From each study, the following information was extracted: first author's surname, year of publication, ethnic descent of the study population (European, Asian, or both), definition of case, age, characteristics of controls, numbers of eligible cases and controls, and genotype distributions in cases and controls and available subgroups.

Statistical Analysis

The Hardy–Weinberg equilibrium (HWE) was used to compare the observed genotype frequencies with expected genotype frequencies in controls for all studies. OR and 95% CI were used to assess the strength of association between ACE polymorphism and asthma risk. The significance of the combined OR was determined by the Z-test, in which $p < .05$ was considered significant. Stratified analyses were performed by ethnicity, age, and sources of control. The χ^2 -based Q statistical test was used for the assessment of the between-study heterogeneity, which was considered significant for $p < .1$. When the effects were assessed to be homogenous, the fixed-effect model was used; otherwise, the random-effect model was applied. We also used the statistics of I^2 to efficiently test the heterogeneity, with $I^2 < 25\%$, $I^2 = 25\text{--}75\%$, and $I^2 > 75\%$ to represent low, moderate, and high degrees of inconsistency, respectively (22). Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias (23). All analyses were performed with Stata (Version 10.0,

Stata Corporation, College Station, TX, USA) and Review Manager (Version 5.0.0, The Cochrane Collaboration, Oxford, UK) using two-sided p -values.

RESULTS

Characteristics of Studies

Studies relevant to the searching words were originally retrieved. The electronic database searches identified 116 studies. Eighty-nine studies that were deemed irrelevant to ACE gene polymorphism or asthma were subsequently excluded. Twenty-seven publications that specifically addressed the association between ACE polymorphism and asthma risk were found to be eligible at this preliminary stage. Of these studies, two studies were subsequently excluded due to insufficient genotyping information (24, 25), four studies were excluded because the genetic distributions of the control group were not in agreement with HWE (26–29), four studies were excluded because the same authors published several reports on the same patients (30–33), and one was excluded because it did not contain a control group (34). Thus, a total of 16 case–control studies were ultimately analyzed, including six studies of European descent (6, 9, 11, 16, 20, 21), eight studies of Asian descent (8, 10, 12, 14, 15, 17–19), and two studies of both European and Asian descent (7, 13). Of these studies, four studies were conducted with children (13, 14, 18, 19), ten with adults (6, 8–10, 12, 15–17, 20, 21), and one study was conducted with children and adults (7). However, one study did not present the ages of patients (11). The study characteristics were summarized in Table 1. Cases in half of the studies were diagnosed according to American Thoracic Society criteria, and most of the controls were selected from population-based

TABLE 1.—Study characteristics from published studies included in meta-analysis of ACE polymorphism and asthma susceptibility.

Author	Year	Ethnicity	Age	Asthma definition	Source of controls	Sample size	HWE
Benessiano (6)	1997	European	Adults	Symptom, ATS criteria	Hospital based	79/87	0.07
Gao (7)	1998	European	Not described	Not described	Normal controls	150/150	0.62
		Asian	Children (100), Adults (200)	Not described	Normal controls	300/100	0.69
Tomita (8)	1998	Asian	Adults	Spirometry, ATS criteria	Healthy controls	71/142	0.47
Hollá (9)	1999	European	Adults	Questionnaire, ATS criteria	Healthy controls	161/141	0.42
Nakahama (10)	1999	Asian	Adults	ATS criteria	Normal controls	119/208	0.94
Chagani (11)	1999	European	Not described	Asthma severity	Normal controls	231/292	0.26
Lee (12)	2000	Asian	Adults	Clinical history, Symptom, Spirometry, ATS criteria	Healthy controls	310/121	0.13
Winchester (13)	2000	European	Adults(childhood asthma)	Questionnaire (with history of childhood asthma)	Healthy controls	20/416	0.21
		Asian	Adults(childhood asthma)	Questionnaire (with history of childhood asthma)	Healthy controls	6/275	0.77
Qin (14)	2000	Asian	Children	Chinese asthma diagnosis criteria	Healthy controls	52/40	0.29
Gao (15)	2000	Asian	Adults	Symptom, bronchial hyper-responsiveness	Healthy controls	50/50	0.63
Yildiz (16)	2004	European	Adults	Clinical history, symptom, spirometry, ATS criteria	Healthy controls	42/46	0.38
Lu (17)	2004	Asian	Adults	Chinese asthma diagnosis criteria	Healthy controls	18/15	0.27
Guo (18)	2006	Asian	Children	Not described	Healthy controls	52/72	0.36
Lue (19)	2006	Asian	Children	Clinical history, symptom, spirometry, ATS criteria	Healthy controls	105/102	0.25
Eryüksel (20)	2009	European	Adults	Questionnaire, ATS criteria	Healthy controls	97/96	0.88
Lee (21)	2009	European	Adults	Questionnaire	Hospital based	602/7079	0.33

Note: ACE – angiotensin-converting enzyme; ATS – American Thoracic Society; HWE – Hardy–Weinberg equilibrium.

controls. If the included study did not carry a statement that the controls were from healthy subjects, we defined the control group as “normal controls.”

Quantitative Synthesis

The evaluation of association between ACE polymorphism and asthma risk was presented in Table 2. Overall, a statistically significant association of asthma risk and the D allele, compared with I allele (OR = 1.27, 95% CI = 1.10–1.46; $p = .008$, $I^2 = 59\%$ for heterogeneity), was found. The I/D polymorphism of ACE with increased asthma risk was also found under homozygote comparison (DD vs. II: OR = 1.59, 95% CI = 1.20–2.12; $p = .002$, $I^2 = 56\%$ for heterogeneity; Figure 1), dominant genetic model (DD/DI vs. II: OR = 1.15, 95% CI = 1.02–1.30; $p = .10$, $I^2 = 31\%$ for heterogeneity), and recessive genetic model (DD vs. ID/II: OR = 1.62, 95% CI = 1.24–2.10; $p < .0001$, $I^2 = 67\%$ for heterogeneity). However, no significant association was found under heterozygote comparison (ID vs. II: OR = 1.06, 95% CI = 0.93–1.20; $p = 0.25$, $I^2 = 17\%$ for heterogeneity).

In the stratified analysis by ethnicity, ACE polymorphism was associated with a significantly increased risk of asthma in both European and Asian populations under homozygote comparison and recessive genetic model. However, the risk of asthma associated with the D allele was significantly elevated among Europeans (OR = 1.28, 95% CI = 1.07–1.53; $p = .01$, $I^2 = 60\%$ for heterogeneity) but not Asians (OR = 1.28, 95% CI = 0.99–1.64; $p = .004$, $I^2 = 63\%$ for heterogeneity). In the stratified analysis by age, significant association between ACE polymorphism and asthma risk was found in four tested models (D vs. I; DD vs. II; DD vs. ID/II; DD/DI vs. II) among adults and two models (DD vs. II; DD vs. ID/II) among children. In the subgroup analysis by source of control, we found significant main effects for ACE polymorphism on asthma risk among population-based controls in four genetic models (D vs. I; DD vs. II; DD vs. ID/II; DD/DI vs. II), whereas these associations were not found in hospital-based controls in all tested models.

Test of Heterogeneity

There was significant heterogeneity for allelic frequency comparison ($p_{\text{heterogeneity}} = .0007$), homozygote comparison (DD vs. II: $p_{\text{heterogeneity}} = .002$), and recessive model comparison (DD vs. DI/II: $p_{\text{heterogeneity}} < .0001$), but not for heterozygote comparison (ID vs. II: $p_{\text{heterogeneity}} = .25$) nor dominant model comparison (DD/DI vs. II: $p_{\text{heterogeneity}} = .10$). We then assessed the source of heterogeneity for homozygote comparison by age, ethnicity, and source of controls. However, none of them (source of controls: $\chi^2 = 2.88$, $p = .24$; age: $\chi^2 = 0.85$, $p = .65$; ethnicity: $\chi^2 = 0.29$, $p = .59$) were found to contribute to substantial heterogeneity. Further meta-regression indicated that neither age, nor ethnicity, nor source of controls could explain the significant between-study heterogeneity.

Publication Bias

We used Funnel plot and Egger's regression asymmetry test to access the publication bias of literatures. The data

TABLE 2.—Total and stratified analyses of the ACE polymorphism on asthma risk.

Variables	Number ^a	Cases/Controls	D vs. I			DD vs. II			ID vs. II			DD/ID vs. II			DD vs. ID/II		
			OR (95% CI)	p^b	p	OR (95% CI)	p^b	p	OR (95% CI)	p^b	p	OR (95% CI)	p^b	p	OR (95% CI)	p^b	p
Total	16	2465/9432	1.27 (1.10,1.46)	.00 ^c	.00	1.59 (1.20,2.12)	.00 ^c	.00	1.06 (0.93,1.20)	.25	.39	1.15 (1.02,1.30)	.10	.02	1.62 (1.24,2.10)	.00 ^c	.00
Ethnicities																	
European	8	1382/8307	1.28 (1.07,1.53)	.01 ^c	.00	1.55 (1.08,2.22)	.02 ^c	.02	1.10 (0.83,1.46)	.09 ^c	.52	1.25 (0.94,1.66)	.06 ^c	.12	1.54 (1.12,2.11)	.00 ^c	.00
Asian	10	1083/1125	1.28 (0.99,1.64)	.00 ^c	.06	1.72 (1.04,2.85)	.00 ^c	.03	0.97 (0.79,1.20)	.60	.81	1.10 (0.91,1.34)	.31	.33	1.83 (1.10,3.04)	.00 ^c	.02
Age																	
Adults	11	1749/8085	1.32 (1.08,1.61)	.00 ^c	.00	1.31 (1.10,1.56)	.00 ^c	.00	1.15 (0.99,1.33)	.31	.07	1.21 (1.05,1.39)	.07 ^c	.00	1.26 (1.10,1.46)	.00 ^c	.00
Children	6	335/1005	1.22 (0.99,1.52)	.11	.07	1.69 (1.09,2.62)	.07 ^c	.02	0.86 (0.62,1.20)	.64	.37	1.07 (0.79,1.45)	.41	.68	1.67 (1.14,2.46)	.05 ^c	.00
Sources of controls																	
Population based	12	984/1516	1.47 (1.18,1.83)	.01 ^c	.00	2.27 (1.45,3.56)	.02 ^c	.00	1.23 (0.99,1.52)	.55	.07	1.43 (1.17,1.76)	.33	.00	2.06 (1.30,3.26)	.00 ^c	.00
Hospital based	2	681/7166	1.16 (0.89,1.50)	.19	.28	1.18 (0.93,1.49)	.57	.17	0.96 (0.53,1.76)	.15	.90	1.14 (0.94,1.38)	.57	.17	1.46 (0.67,3.16)	.02 ^c	.34

Notes: ^aNumber of studies; ^b p -value of Q -test for heterogeneity; ^crandom-effects model was used when p -value for heterogeneity test $< .10$, otherwise, fixed-effects model was used; .00 means value $< .01$.

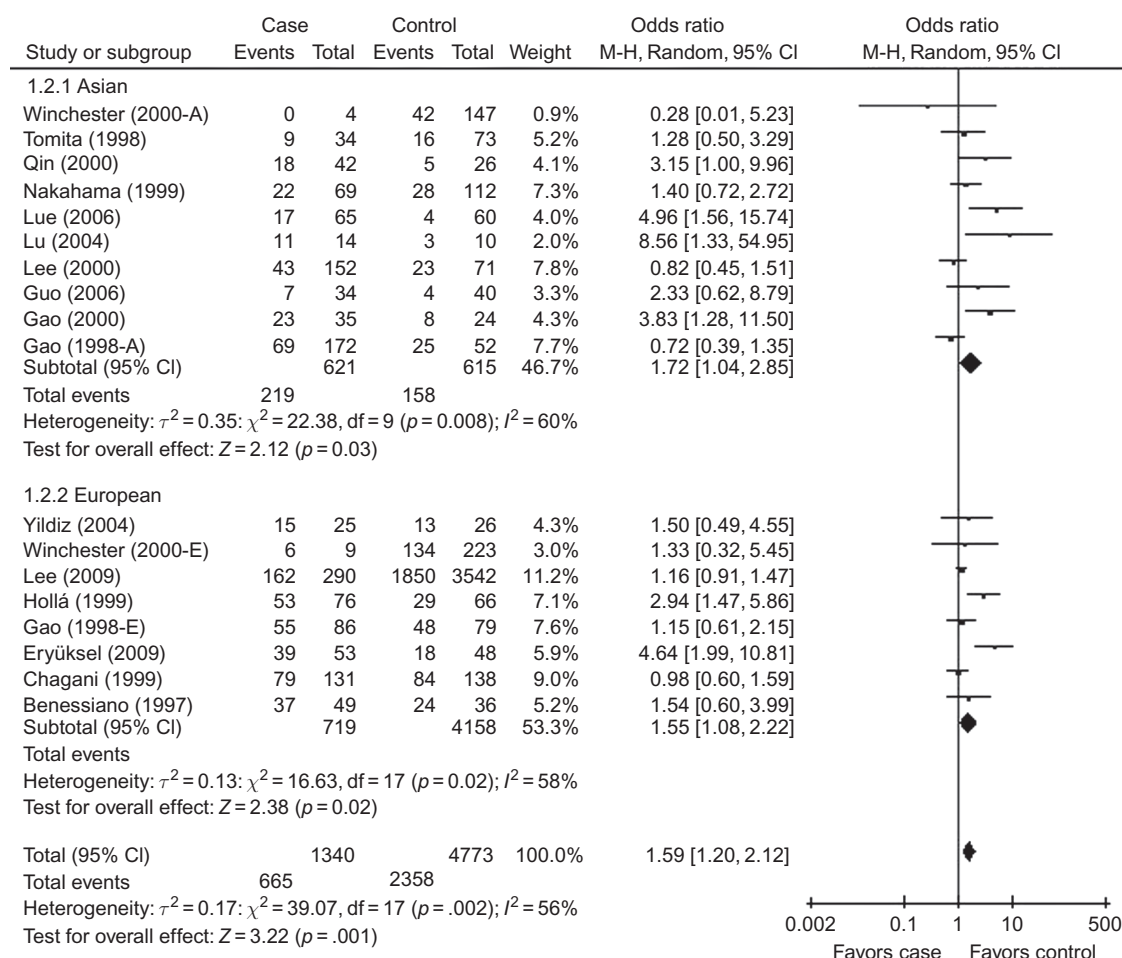


FIGURE 1.—Meta-analysis with a random-effects model for the ORs of asthma risk associated with ACE polymorphism (DD vs. II).

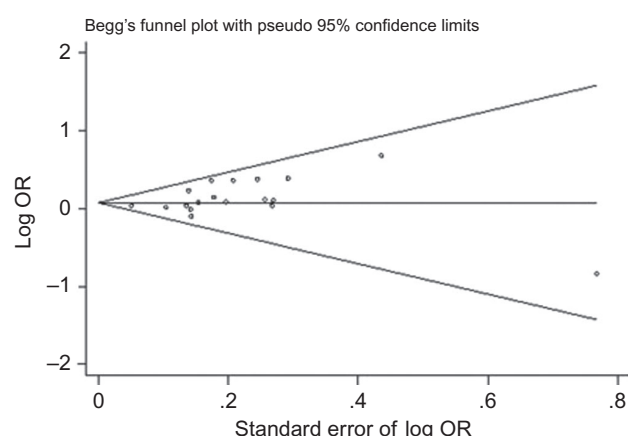


FIGURE 2.—Funnel plot for publication bias of the meta-analysis of asthma risk and ACE polymorphism in allelic frequency comparison.

suggested that there was no evidence of publication bias in allelic frequency comparison ($t = 1.78$, $p = .09$; Figure 2).

DISCUSSION

In this study, a meta-analysis was performed to examine the association between ACE I/D polymorphism and asthma

risk, by critically reviewing all eligible studies with a total of 11,897 subjects. Our results were partly inconsistent with a recently published meta-analysis, which was based on 4098 subjects (35). In the previous meta-analysis, two studies used the same population in the original article (16, 20), but the authors simply put them into different ethnic groups. At the same time, one study of both children and adults was left out of the meta-analysis when stratified according to age (7). Most importantly, the systematic review was incomplete as the largest published study was omitted in the previous meta-analysis (21). Therefore, there was insufficient power to support their conclusions especially in the subgroup analyses. In our study, more subjects were included to provide a more comprehensive result. In addition, stratified analyses were performed by source of controls to investigate the association between ACE polymorphism and asthma risk in our analysis.

Our study indicated that ACE polymorphism was associated with asthma risk, which is in agreement with most related studies. However, the exact mechanisms how ACE polymorphism affect asthma risk at the molecular level remain unknown. Given that ACE have detrimental effects on airway inflammation and remodeling in asthma, it is biologically plausible that the deletion mutation in the ACE gene leads to an increase in the circulating ACE level. On the contrary, ACE converts angiotensin I into

the vasoactive compound angiotensin II, which could contribute to the pathogenesis of asthma by causing proliferation and increased contractility of airway smooth muscle, thus favoring excessive airflow obstruction (36).

In stratified analyses, we observed that the association between ACE polymorphism and asthma risk remained significant in Europeans and Asians. Allele frequency might reflect the natural selection pressures or a balance by other related functional genetic variants and environmental exposures (37, 38). Thus, the association between ACE polymorphism and other ethnic groups needed further investigation. At the same time, it is worth emphasizing that ACE polymorphism contributed to an increase in asthma susceptibility in both adults and children. In addition, we found that the association between ACE polymorphism and asthma risk among studies using health controls was stronger than those with hospital-based controls. Study had shown that hospital-based controls might have inherent selection biases when controls were associated with the disease-related conditions (39). Thus, the choice of a representative population-based control subjects is very important in those genotype association studies.

Although we carefully conducted this meta-analysis, significant heterogeneity still existed in some comparisons. However, the reasons for heterogeneity were unclear. Although we assessed the source of heterogeneity for homozygote comparison by age, ethnicity, and source of controls, none of them were found to contribute to heterogeneity. It may be due to other factors, including the selection of methods, definition of cases, and sample sizes. The diverse genotyping methods that were used in different studies might lead to heterogeneity. Definition of asthma cases was not totally uniform, and the observed associations may simply be due to heterogeneity. In addition, the studies with small sample size appear to overestimate the true association due to the lack of sufficient power to detect such an association (40). Publication bias was also considered as a possible limitation in our study. First, only English and Chinese studies were included in this meta-analysis and this might therefore have led to publication bias. Second, inappropriate selection of controls is a major source of bias in case-control studies. Third, on account of different populations used in our analysis, population stratification bias may also occur.

CONCLUSION

Our meta-analysis suggests that ACE polymorphism is significantly associated with asthma risk. However, additional large studies are warranted to validate our findings. Future studies should include multi-ethnic groups and use standardized unbiased genotyping methods, different grades of asthma patients, and well-matched controls.

ACKNOWLEDGMENTS

The authors are extremely thankful to Julie Lee and Morten Dahl of Department of Clinical Biochemistry, Herlev

University Hospital, Denmark, for providing original data of their study. They also thank Prof. Andrew G. Hawthorn of Department of Business Studies and International Trade, Ningbo University of Technology, Ningbo, for his review and scientific editing of the manuscript.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

AUTHOR CONTRIBUTIONS

Qun-Li Ding and Shi-Fang Sun contributed equally to this study.

REFERENCES

1. Djukanović R, Roche WR, Wilson JW, Beasley CR, Twentyman OP, Howarth RH, Holgate ST. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990; 142:434–457.
2. Hubert C, Houot AM, Corvol P, Soubrier F. Structure of the angiotensin I-converting enzyme gene. Two alternate promoters correspond to evolutionary steps of a duplicated gene. *J Biol Chem* 1991; 266:15377–15383.
3. Erdos EG, Yang HY. An enzyme in microsomal fraction of kidney that inactivates bradykinin. *Life Sci* 1967; 6:569–574.
4. Cambien F, Alhenc-Gelas F, Herbeth B, Andre JL, Rakotovao R, Gonzales MF, Allegrini J, Bloch C. Familial resemblance of plasma angiotensin-converting enzyme level: the Nancy study. *Am J Hum Genet* 1988; 43:774–780.
5. Costerousse O, Allegrini J, Lopez M, Alhenc-Gelas F. Angiotensin I-converting enzyme in human circulating mononuclear cells: genetic polymorphism of expression in T-lymphocytes. *Biochem J* 1993; 290:33–40.
6. Benessiano J, Crestani B, Mestari F, Klouche W, Neukirch F, Hache-Bey S, Durand G, Aubier M. High frequency of a deletion polymorphism of the angiotensin-converting enzyme gene in asthma. *J Allergy Clin Immunol* 1997; 99:53–57.
7. Gao PS, Mao XQ, Kawai M, Enomoto T, Sasaki S, Shaldon SR, Dake Y, Kitano H, Coull P, Hagihara A, Shirakawa T, Hopkin JM. Lack of association between ACE gene polymorphisms and atopy and asthma in British and Japanese populations. *Clin Genet* 1998; 54:245–247.
8. Tomita H, Sato S, Matsuda R, Ogisu N, Mori T, Niimi T, Shimizu S. Genetic polymorphism of the angiotensin-converting enzyme (ACE) in asthmatic patients. *Respir Med* 1998; 92:1305–1310.
9. Hollá L, Váskú A, Znojil V, Sisková L, Vácha J. Association of 3 gene polymorphisms with atopic diseases. *J Allergy Clin Immunol* 1999; 103:702–708.
10. Nakahama H, Obata K, Nakajima T, Nakamura H, Kitada O, Sugita M, Fujita Y, Kawada N, Moriyama T. Renin-angiotensin system component gene polymorphism in Japanese bronchial asthma patients. *J Asthma* 1999; 36:187–193.
11. Chagani T, Paré PD, Zhu S, Weir TD, Bai TR, Behbehani NA, Fitzgerald JM, Sandford AJ. Prevalence of tumor necrosis factor- α and angiotensin converting enzyme polymorphisms in mild/moderate and fatal/near-fatal asthma. *Am J Respir Crit Care Med* 1999; 160:278–282.
12. Lee YC, Cheon KT, Lee HB, Kim W, Rhee YK, Kim DS. Gene polymorphisms of endothelial nitric oxide synthase and angiotensin-converting enzyme in patients with asthma. *Allergy* 2000; 55:959–963.
13. Winchester EC, Millwood IY, Rand L, Penny MA, Kessling AM. Association of the TNF- α -308 (G→A) polymorphism with self-reported history of childhood asthma. *Hum Genet* 2000; 107:591–596.
14. Qin JH, Wang LS. DD genotype of angiotensin-converting enzyme may be a risk factor for development of asthma in children (in Chinese). *Zhonghua Er Ke Za Zhi*. 2000; 38:487–489.

15. Gao J, Lin Y, Xiao Y, Xu K, Xu W, Zhu Y, Ma Y, Bai Y. Polymorphism of angiotensin-converting enzyme gene and genetic susceptibility to asthma with familial aggregation. *Chin Med Sci J* 2000; 15:24–28.
16. Yildiz P, Oflaz H, Cine N, Genchallac H, Erginel-Unaltuna N, Yildiz A, Yilmaz V. Endothelial dysfunction in patients with asthma: the role of polymorphisms of ACE and endothelial NOS genes. *J Asthma* 2004; 41:159–166.
17. Lu HM, Li LY. Polymorphism of angiotensin-converting enzyme gene and susceptibility to patients of asthma in Tianjin (in Chinese). *Shanxi Yi Yao Za Zhi* 2004; 33:1016–1017.
18. Guo YB, Lv Y, Cai HW, Chen YH, Cheng YS, Ye XF. Genetic polymorphism of angiotensin converting enzyme(ACE) gene in kidney-deficiency asthma from Guangdong population (in Chinese). *Zhongguo You Sheng Yu Yi Chuan Za Zhi* 2006; 14:20–22.
19. Lue KH, Ku MS, Li C, Sun HL, Lee HS, Chou MC. ACE gene polymorphism might disclose why some Taiwanese children with allergic rhinitis develop asthma symptoms but others do not. *Pediatr Allergy Immunol* 2006; 17:508–513.
20. Eryüksel E, Ceyhan BB, Bircan R, Avşar M, Cırakoğlu B. Angiotensin converting enzyme gene polymorphism in Turkish asthmatic patients. *J Asthma* 2009; 46:335–338.
21. Lee J, Nordestgaard BG, Elevated DM. ACE activity is not associated with asthma, COPD, and COPD co-morbidity. *Respir Med* 2009; 103:1286–1292.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557–560.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634.
24. Kim TH, Chang HS, Park SM, Nam BY, Park JS, Rhim T, Park HS, Kim MK, Choi IS, Cho SH, Chung IY, Park BL, Park CS, Shin HD. Association of angiotensin I-converting enzyme gene polymorphisms with aspirin intolerance in asthmatics. *Clin Exp Allergy* 2008; 38:1727–1737.
25. Kawakami Y, Munakata M, Yamaguchi E, Furuya K, Matsuda T. Molecular studies of bronchial asthma, sarcoidosis and angiotensin converting enzyme inhibitor-induced cough. *Respirology* 1998; 3:45–49.
26. Urhan M, Degirmenci I, Harmanci E, Gunes HV, Metintas M, Basaran A. High frequency of DD polymorphism of the angiotensin-converting enzyme gene in Turkish asthmatic patients. *Allergy Asthma Proc* 2004; 25:243–247.
27. Guo S, Zhang JH, Yan YD, Ding YF, Sheng JY. Association between renin-angiotensin system gene polymorphism and recurrent wheezing in Chinese children: a 4-year follow-up study. *J Int Med Res* 2009; 37:351–358.
28. Song LJ, Quan CS, Peng L, Fu WY. Correlation between asthma and polymorphism of angiotensin-converting enzyme gene with insertion or deletion in 108 Chinese northern children with asthma (in Chinese). *Lin Chuang Er Ke Za Zhi* 2001; 19:364–365.
29. Zhang JH, Ding YF, Tao H, Yan YD, Sheng JY. Gene polymorphisms and familial aggregation of the angiotensin converting enzyme in wheezy children (in Chinese). *Jiangsu Yi Yao* 2005; 31:401–403.
30. Zhang JH, Ding YF, Wu LX, Xu M, Wang M, Wang ZC, Sheng JY. Relationship between gene polymorphisms of angiotensin converting enzyme in the first wheezy children and wheeze relapse (in Chinese). *Shi Yong Er Ke Lin Chuang Za Zhi* 2007; 22:1223–1224.
31. Gao JM, Lin YG, Xiao Y. Polymorphism of angiotensin converting enzyme gene and susceptibility to asthma with familial aggregation (in Chinese). *Zhonghua Jie He He Hu Xi Za Zhi* 1999; 22:669–672.
32. Qin JH, Chu HY, Wang LS. Polymorphisms of angiotensin converting enzyme in children asthma (in Chinese). *Zhonghua Jian Yan Yi Xue Za Zhi* 2000; 23:366.
33. Qin JH, Chu HY, Wang LS. The I/D polymorphism of the angiotensin-converting enzyme gene in children asthma (in Chinese). *Zhongguo You Sheng Yu Yi Chuan Za Zhi* 2000; 8:19–20.
34. Jung SK, Ra J, Seo J, Jung HJ, Choi JY, Cho YJ, Hong MS, Chung JH, Kim J. An Angiotensin I Converting enzyme polymorphism is associated with clinical phenotype when using differentiation-syndrome to categorize Korean bronchial asthma patients. *Evid Based Complement Alternat Med* [Epub ahead of print].
35. Zhang YG, Li XB, Zhang J, Huang J, He C, Tian C, Deng Y, Wan H, Shrestha D, Yang YY, Fan H. The I/D polymorphism of angiotensin-converting enzyme gene and asthma risk: a meta-analysis. *Allergy* 2011; 66:197–205.
36. Erdős EG. Angiotensin I converting enzyme and the changes in our concepts through the years. Lewis K. Dahl memorial lecture. *Hypertension* 1990; 16:363–370.
37. Zhang YM, Cao C, Liang K. Genetic polymorphism of epidermal growth factor 61A>G and cancer risk: a meta-analysis. *Cancer Epidemiol* 2010; 34:150–156.
38. Cao C, Ying T, Fang JJ, Sun SF, Lv D, Chen ZB, Ma HY, Yu YM, Ding QL, Shu LH, Deng ZC. Polymorphism of vascular endothelial growth factor -2578C/A with cancer risk: evidence from 11263 subjects. *Med Oncol* 2011; 28:1169–1175.
39. Zhang Z, Xue H, Gong W, Wang M, Yuan L, Han S, Zhang Z. FAS promoter polymorphisms and cancer risk: a meta-analysis based on 34 case-control studies. *Carcinogenesis* 2009; 30:487–493.
40. Zhou C, Zhou Y, Li J, Zhang Y, Jiang L, Zeng X, Feng X, Wang Z. The Arg194Trp polymorphism in the X-ray repair cross-complementing group 1 gene as a potential risk factor of oral cancer: a meta-analysis. *Tohoku J Exp Med* 2009; 219:43–51.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.