

Angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to pediatric asthma: A meta-analysis

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Abstract

Objective: The correlation of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism with pediatric asthma risk was assessed in this meta-analysis.

Methods: PubMed, Web of Science, Embase and CNKI databases were systematically searched for relevant literature, followed by application of odds ratios (OR) along with 95% confidence interval (CI) for determining the strength of relationship.

Results: Seven articles with 802 cases and 632 controls fulfilled the inclusion criteria. As a result, the ACE I/D polymorphism was related to elevated pediatric asthma risk (D vs I: OR = 1.87, 95% CI = 1.59–2.20; dominant model: OR = 1.53, 95% CI = 1.28–1.81; recessive model: OR = 1.54, 95% CI = 1.28–1.85; DD vs II: OR = 2.95, 95% CI = 2.19–3.98; DI vs II: OR = 0.96, 95% CI = 0.78–1.19). Subgroup analysis stratified by race revealed significant interrelation in Asians.

Conclusion: This meta-analysis demonstrated that the ACE I/D polymorphism might be related to the risk of pediatric asthma.

Keywords

ACE gene, genetic variant, pediatric asthma

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Introduction

According to the Global Initiative for Asthma 2019, asthma is a common chronic allergic disorder that involves the respiratory tract and affects an estimated 300 million individuals worldwide. It is a serious global health problem affecting all age groups, with increasing prevalence in many developing countries, rising treatment costs, and a rising burden for patients and professionals. To be specific, asthma is highly heterogeneous and typically includes chronic inflammation of the airway with symptoms including shortness of breath, cough, chest tightness, wheezing and variably reduced expiratory airflow.² The complicated pathogenesis of asthma remains largely undefined. However, decreased lung function, allergic disorder, as well as bacterial and viral infections are considered the main risk factors for the persistence and progression of asthma.^{3–5} Additionally, variants of more than 40 genes have been reported to have a certain correlation with asthma.⁶ Moreover, parental asthma is a potent predictive

factor for pediatric asthma, implicating the potent genetic basis of pediatric asthma.⁷

Angiotensin-converting enzyme (ACE), a vital enzyme of the renin-angiotensin system, is mainly expressed in the lung, playing a critical part in asthma pathogenesis.⁸ Functionally, ACE is capable of converting angiotensin I to angiotensin II, possibly participating in asthma etiology by interaction with bronchial muscle. ACE can also inactivate various inflammatory peptides, such as substance P and bradykinin, the latter of which is generated in the lungs of patients with asthma.⁹ The location of the ACE

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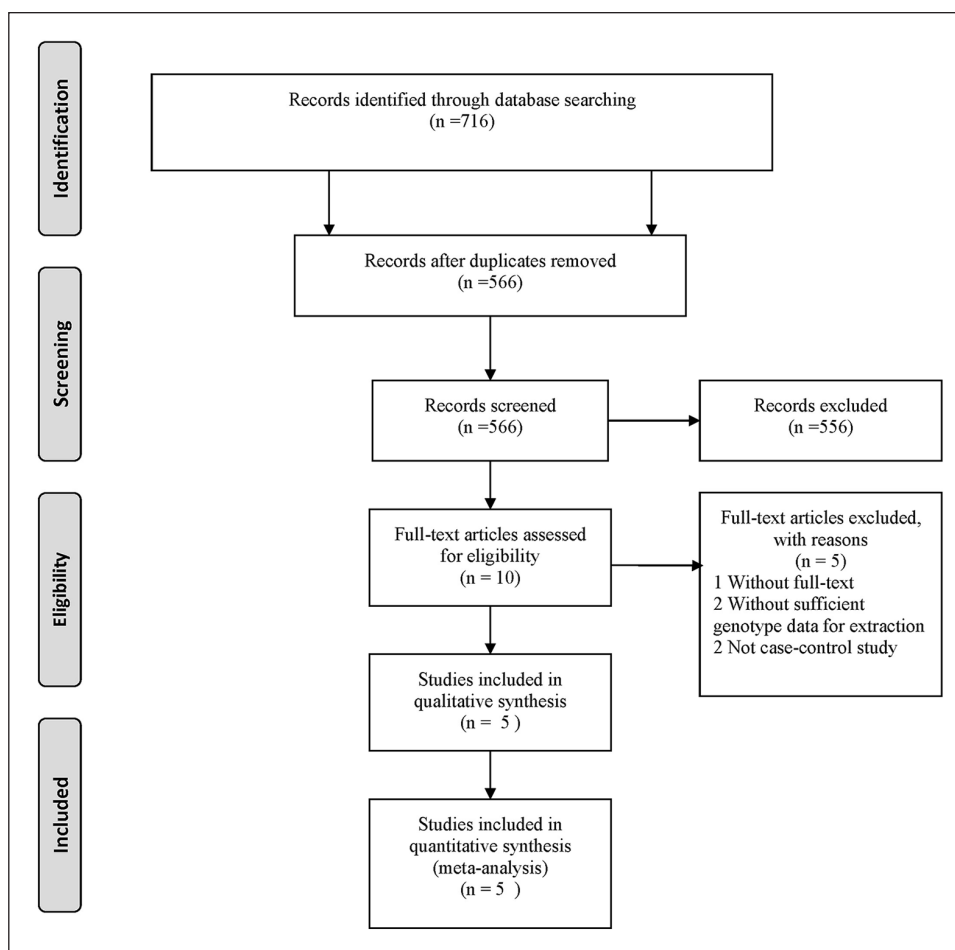


Figure 1. Flow diagram for selection of publication.

gene is on the long arm of chromosome 17. In addition, the *ACE* gene insertion/deletion (I/D) polymorphism is commonly found, with a 287-bp fragment within intron 16. In terms of the correlation with plasma ACE level, homozygous D allele is the highest, sequentially followed by heterozygous one (ID) and homozygous I allele.¹⁰ Previous meta-analysis showed that the *ACE* I/D polymorphism might enhance Henoch-Schönlein purpura risk.¹¹

In the past decade, the correlation of the *ACE* I/D polymorphism with pediatric asthma vulnerability has been examined in several studies, however, with great controversy. Insufficient power, false-positive outcomes and the mild impacts of the *ACE* I/D polymorphism on pediatric asthma risk might partially explain the inconsistency. Herein, we determined whether the *ACE* gene I/D polymorphism was related to pediatric asthma risk in the present meta-analysis.

Materials and methods

Search strategy for identification of studies

PubMed, Embase, Web of Science and CNKI databases were systematically searched for all articles written on the

correlation of the *ACE* I/D polymorphism with pediatric asthma risk (updated to August 2019) using search terms including *asthma* or *asthmatic* and *polymorphism* or *mutation* or *variant* and *angiotensin-converting enzyme* or *ACE*. Moreover, we manually reviewed the references from the retrieved articles to extract more eligible researches.

Inclusion and exclusion criteria

The abstracts were independently reviewed by two investigators to determine the inclusion or exclusion of the articles, and discrepancies were reached by discussion between the investigators. The inclusion criteria were shown in the following: (a) case-control research concerning pediatric asthma cases and normal controls; (b) research concerning the correlation of the *ACE* I/D polymorphism with pediatric asthma vulnerability and (c) research with adequate genotype information. The exclusion criteria were shown in the following: (a) not case-control research; (b) duplicates of previous research; (c) studies with inadequate data and (d) meta-analyses, editorials, reviews, letters or case reports.

Table 1. Characteristics of included studies for meta-analysis.

Study	Year	Area	Race	Cases/ Controls	Allele for cases		Allele for controls		Genotypes for cases			Genotypes for controls			HWE test
					D	I	D	I	DD	ID	II	DD	ID	II	
Qin ¹⁴	2000	China	Asian	52/40	46	58	24	56	18	10	24	5	14	21	0.29
Song ¹²	2001	China	Asian	108/56	127	89	47	65	41	22	45	9	18	29	0.04
Lue ¹³	2006	China	Asian	106/102	24	82	20	82	6	48	52	4	42	56	0.25
Guo ¹⁵	2009	China	Asian	149/165	178	120	122	208	71	36	42	41	40	84	0.00
Zheng ¹⁷	2012	China	Asian	198/110	190	206	81	139	75	40	83	15	51	44	0.97
Chen ¹⁸	2012	China	Asian	87/58	95	79	36	80	38	19	30	9	18	31	0.03
Bora ¹⁶	2013	Turkey	Caucasian	102/101	120	84	104	98	32	56	14	22	60	19	0.05

D: deletion; HWE: Hardy-Weinberg equilibrium; I: insertion.

Data extraction

Two authors extracted data from included articles independently, subsequently reaching consensus on all items. The following data were extracted from each article: last name of first author, race, country, publication date, numbers of genotyped controls and cases, and deviation from Hardy-Weinberg Equilibrium (HWE) of control group.

Statistical analysis

The strength of the relationship of the *ACE* I/D polymorphism with the susceptibility to pediatric asthma was evaluated by odds ratios (ORs) and their 95% confidence intervals (CIs). Specifically, the following genetic models were used: D vs I, recessive model (II + DI vs DD), dominant model (DD + DI vs II), heterozygote comparison (DI vs II) and homozygote comparison (DD vs II). P^2 test was employed for quantification of the effect of heterogeneity, ranging from 0% to 100% and reflecting the percentage of interstudy variability that was caused by heterogeneity rather than random chance. A value of $P^2 > 50\%$ implicated heterogeneity across studies and the subsequent application of a random-effects model. Otherwise, the fixed-effects model was employed. In addition, sensitivity analysis was conducted by removal of a single study and analysis of the remaining data. Finally, publication bias was assessed by Begg funnel plot. STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used for statistical analysis. A p value of less than 0.05 indicated statistical significance.

Results

Study characteristics

In total, 704 potentially relevant researches were retrieved, and seven case-control studies with full-text were finally enrolled in this meta-analysis after eliminating 697 researched according to the inclusion and exclusion criteria.^{12–18} The diagram for study selection

appears in Figure 1. The control population was mainly collected from healthy populations. The HWE test showed the consistency of genotype distribution with HWE in the controls except for studies by Song et al,¹² Guo and colleagues¹⁵ and Chen et al.¹⁸ Of these, one study focused on Caucasians and six studies focused on Asians. The study features are presented in Table 1.

Overall meta-analysis and further subgroup analysis

The combined data revealed that the *ACE* I/D polymorphism is related to elevated pediatric asthma risk in various genetic models, as indicated in Figure 2 and Table 2 (D vs I: OR = 1.87, 95% CI = 1.59–2.20; recessive model: OR = 1.54, 95% CI = 1.28–1.85; the dominant model: OR = 1.53, 95% CI = 1.28–1.81; DD vs II: OR = 2.95, 95% CI = 2.19–3.98; DI vs II: OR = 0.96, 95% CI = 0.78–1.19). Subgroup analysis by race showed a significant correlation in Asians (Figure 3), and subgroup analysis by HWE revealed a significant relationship in research consistent with HWE. Afterward, sensitivity analysis was conducted by evaluating the impact of each individual paper on the pooled OR via the deletion of one study each time, which revealed no single article affecting the pooled ORs, suggesting the stability of the outcomes (Figure 4).

Publication bias

The publication bias was assessed by Begg funnel plot (Figures 5 and 6). The shape of the funnel plot suggests no publication bias (all $p > .05$).

Discussion

Asthma is the most prevalent chronic pediatric disorder, with extremely complicated and largely undefined pathogenesis of asthma, despite several studies reporting various genetic loci and diverse environmental factors as important asthma determinants.¹⁹ The correlation of the

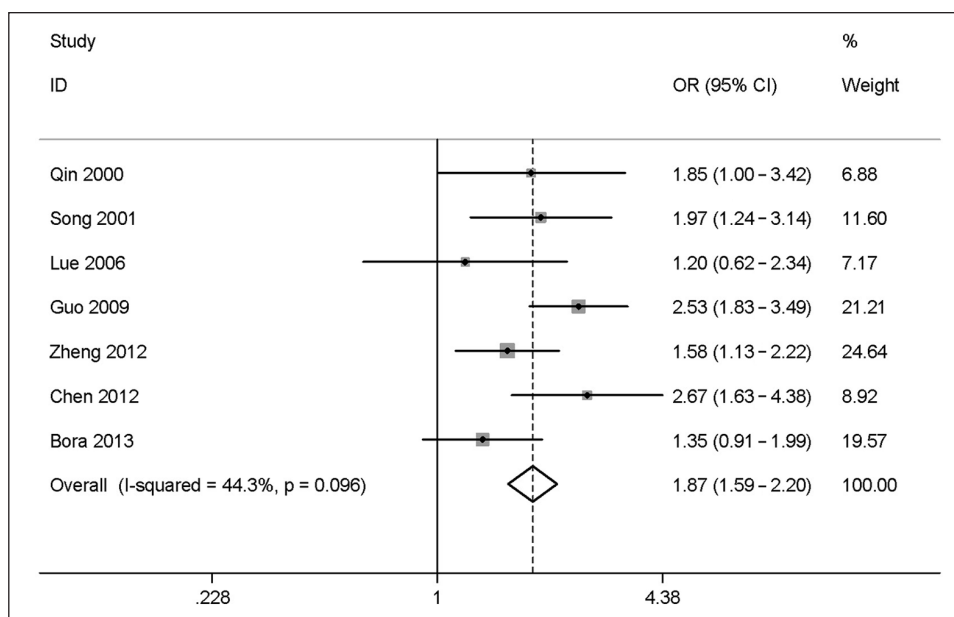


Figure 2. Forest plot of odds ratio (OR) for association between angiotensin-converting enzyme insertion/deletion (I/D) polymorphism and pediatric asthma under D vs I. ID: identification.

Table 2. Summary odds ratios and 95% CI of angiotensin-converting enzyme insertion/deletion polymorphism with pediatric asthma risk.

Variable	N ^a	D vs I	DD vs II	DI vs II	Dominant model	Recessive model
		OR (95% CI) Begg model	OR (95% CI) Begg model	OR (95%CI) Begg model	OR (95% CI) Begg model	OR (95% CI) Begg model
Total	7	1.87 (1.59–2.20) F 1.00	2.95 (2.19–3.98) F 1.00	0.96 (0.78–1.19) F 1.00	1.53 (1.28–1.81) F 1.00	1.54 (1.28–1.85) F 1.00
Ethnicity						
Asian	6	2.00 (1.68–2.38) F 1.00	3.11 (2.26–4.28) F 1.00	0.94 (0.65–1.35) R 1.00	1.61 (1.33–1.94) F 1.00	1.64 (1.33–2.01) F 1.00
Caucasian	1	–	–	–	–	–
HWE						
Yes	4	1.49 (1.19–1.86) F 1.00	2.39 (1.52–3.75) F 1.00	0.84 (0.56–1.26) R 1.00	1.21 (0.96–1.52) F 1.00	1.30 (1.02–1.65) F 1.00
No	3	2.41 (1.91–3.04) F 1.00	3.50 (2.34–5.25) F 1.00	1.23 (0.86–1.75) F 1.00	2.10 (1.61–2.74) F 1.00	1.98 (1.48–2.64) F 1.00

CI: confidence interval; D: deletion; F: fixed; HWE: Hardy-Weinberg equilibrium; I: insertion; OR: odds ratio; R: random.

^aNumber of comparisons.

ACE I/D polymorphism with pediatric asthma risk has been studied in several research studies, however, with controversial outcomes. This meta-analysis was designed to enhance sample size as well as statistical power by combining similar research for more authentic outcomes. Compared with the previous meta-analysis,^{20,21} the present study aimed at pediatric disorder specifically and conducted subgroup analysis.

In this meta-analysis, seven case-control research studies were included. As a result, the *ACE* I/D polymorphism

was related to pediatric asthma vulnerability. Nevertheless, subgroup analyses were further performed because of the potential impact of other confounding factors. To be specific, subgroup analysis by race revealed a significant relationship of pediatric asthma in Asians. Moreover, subgroup analysis stratified by HWE detected a significant correlation in studies consistent with HWE, indicating the authenticity of this meta-analysis. Additionally, sensitivity analysis along with publication bias validated the robustness of our findings.

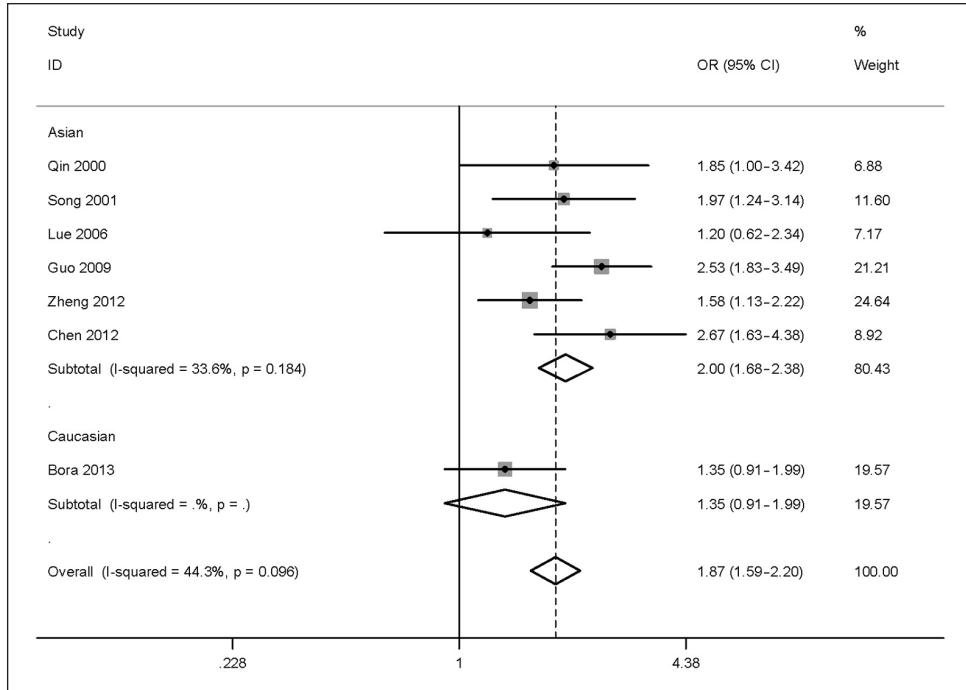


Figure 3. Forest plot of odds ratio (OR) for association between angiotensin-converting enzyme insertion/deletion (I/D) polymorphism and pediatric asthma in Asians under D vs I. ID: identification.

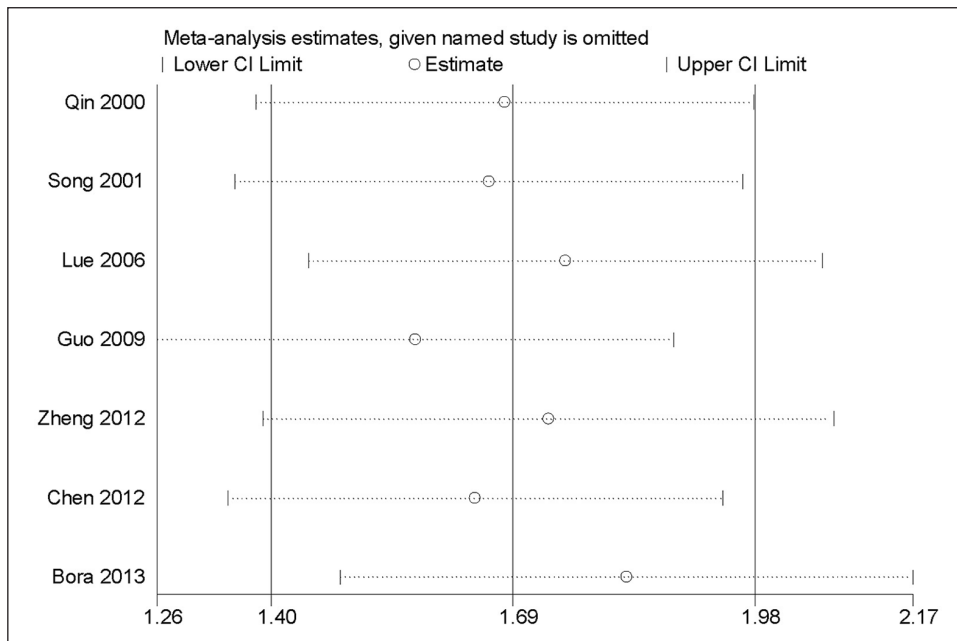


Figure 4. Sensitivity analysis of odds ratio (OR) for association between angiotensin-converting enzyme insertion/deletion (I/D) polymorphism and pediatric asthma.

The mechanism by which the *ACE* I/D polymorphism affects pediatric asthma risk is currently unclear.^{22,23} Typically, ACE plays a critical role in converting the renin-angiotensin system and angiotensin II, thereby increasing

the content of vascular smooth muscle cells, affecting aggregation and adhesion of platelets and monocytes, and smooth muscle cell proliferation. In addition, the location of the *ACE* I/D polymorphism is in an *ACE* gene intron,

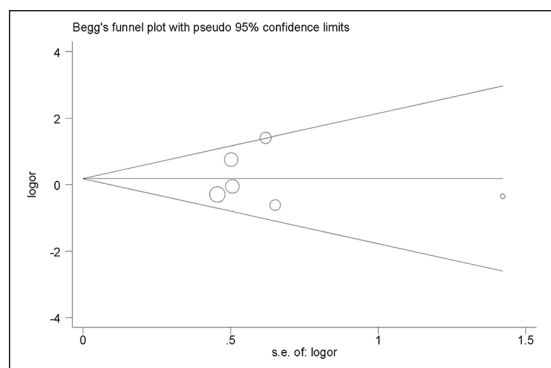


Figure 5. Begg funnel plot for association between angiotensin-converting enzyme insertion/deletion polymorphism and pediatric asthma.

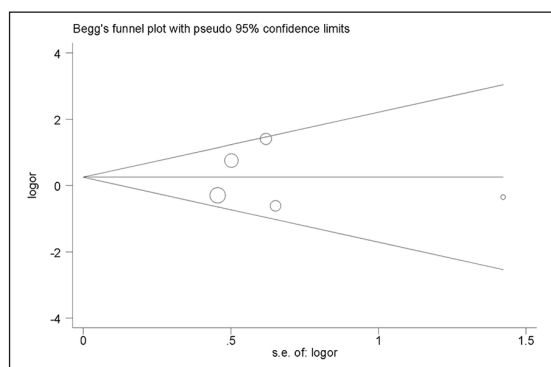


Figure 6. Begg funnel plot for association between angiotensin-converting enzyme insertion/deletion polymorphism and pediatric asthma in Asians.

accounting for about one-half of ACE plasma-level difference.¹⁰ Taken together, our results suggesting that the *ACE* I/D polymorphism may be a risk factor for developing asthma are biologically plausible.

Several limitations of this meta-analysis should be addressed. First, seven included studies were conducted mainly in Asian individuals, whereas only one study was conducted in Caucasians, all of which focused on the association of the *ACE* I/D polymorphism with pediatric asthma, limiting the statistical power. Thus, large-scale research with representative population is required to validate the present findings. Second, all the included studies are retrospective, possibly causing participant selection bias and subsequently influencing the reliability of final outcomes. Third, this meta-analysis enrolled only published literature, without any relevant unpublished ones, which might cause a potential publication bias.

In summary, we demonstrate that the *ACE* I/D polymorphism might have a correlation with pediatric asthma risk. In addition, large-scale case-control investigations are necessary to determine the potential gene-gene and gene-environment interaction on pediatric asthma risk.

Declaration of conflicting interests

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References

1. Global Initiative for Asthma. *Pocket guide for asthma management and prevention*. <https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/> (accessed 2020).
2. Tillie-Leblond I, Montani D, Crestani B, et al. Relation between inflammation and symptoms in asthma. *Allergy* 2009; 64: 354–367.
3. Alizadeh Z, Mortaz E, Adcock I, et al. Role of epigenetics in the pathogenesis of asthma. *Iran J Allergy Asthma Immunol* 2017; 16: 82–91.
4. von Mutius E. Gene-environment interactions in asthma. *J Allergy Clin Immunol* 2009; 123: 3–11.
5. Toskala E and Kennedy DW. Asthma risk factors. *Int Forum Allergy Rhinol* 2015; 5: S11–S16.
6. Purcell S, Neale B, Todd-Brown K, et al. PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007; 81: 559–575.
7. Litonjua AA, Carey VJ, Burge HA, et al. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998; 158: 176–181.
8. Lee YC, Cheon KT, Lee HB, et al. Gene polymorphisms of endothelial nitric oxide synthase and angiotensin-converting enzyme in patients with asthma. *Allergy* 2000; 55: 959–963.
9. Li X, Zhang Y, Zhang J, et al. Asthma susceptible genes in Chinese population: A meta-analysis. *Respir Res* 2010; 11: 129.
10. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990; 86: 1343–1346.
11. Zhang X, Wu L, Chai M, et al. Angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to Henoch-Schönlein purpura: A meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2019; 20: 1470320319836302.
12. Song LJ, Quan CS, Peng L, et al. Correlation between asthma and polymorphism of angiotensin-converting enzyme gene with insertion or deletion in 108 Chinese northern children with asthma (Chinese). *Lin Chuang Er Ke Za Zhi* 2001; 19: 364–365.
13. Lue KH, Ku MS, Li C, et al. *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.
14. Qin JH and Wang LS. DD genotype of angiotensin-converting enzyme may be a risk factor for development of asthma in children (Chinese). *Zhong Hua Er Ke Za Zhi* 2000; 38: 487–489.
 15. Guo S, Zhang JH, Yan YD, et al. 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.
 16. Bora E, Soyler R, Arıkan-Ayyıldız Z, et al. Plasminogen activator inhibitor-1 and angiotensin converting enzyme gene polymorphisms in Turkish asthmatic children. *Allergol Immunopathol (Madr)* 2013; 41: 11–16.
 17. Zheng BQ, Wang GL, Yang S, et al. Study of genetic susceptibility in 198 children with asthma (Chinese). *Zhongguo Dang Dai Er Ke Za Zhi* 2012; 14: 811–814.
 18. Chen X, Zhou L and Zhong WD. Preliminary study on gene polymorphism of angiotensin converting enzyme in asthma children (Chinese). *China Medical Herald* 2012; 9: 23–24.
 19. Lu YM, Cao LF, Li YQ, et al. *RANTES* gene polymorphisms and risk of pediatric asthma: A meta-analysis. *Exp Ther Med* 2012; 4: 918–922.
 20. Ding QL, Sun SF, Cao C, et al. Association between angiotensin-converting enzyme I/D polymorphism and asthma risk: A meta-analysis involving 11,897 subjects. *J Asthma* 2012; 49: 557–562.
 21. Zhang YG, Li XB, Zhang J, et al. The I/D polymorphism of angiotensin-converting enzyme gene and asthma risk: A meta-analysis. *Allergy* 2011; 66: 197–205.
 22. Ramsay SG, Dagg KD, McKay IC, et al. Investigations on the renin-angiotensin system in acute severe asthma. *Eur Respir J* 1997; 10: 2766–2771.
 23. Millar EA, Angus RM, Hulks G, et al. Activity of the renin-angiotensin system in acute severe asthma and the effect of angiotensin II on lung function. *Thorax* 1994; 49: 492–495.