

ACE polymorphisms and childhood asthma risk of East Asia

Angiotensin-converting enzyme gene polymorphisms might be associated with childhood asthma in East Asia

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Asthma is a common inflammatory disease of the airways characterized by intermittent and reversible airflow obstruction.[1] In recent years, the prevalence and mortality of asthma in children have increased.[2] However, the precise pathophysiology of this disease is complex and not fully understood. Some evidence suggests that it is caused by a combination of autoimmune, genetic, and environmental factors.[3,4] So far, a growing number of studies from East Asia have found that angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) variation may increase the risk of asthma in children.[5-7] However, several studies have failed to confirm this relationship.[8] In this study, we evaluated the association of ACE gene polymorphisms with childhood asthma susceptibility in East Asia using a meta-analysis.

Using Pubmed, Embase and Chinese databases such as CNKI, we carried out a systematic search. The key words were: angiotensin-converting enzyme OR ACE, allele(s) OR polymorphism(s) OR variation(s) OR genotype(s) AND asthma. All studies were updated to July of 2016. The study population was limited to children in East Asia. The original study was included if it met criteria as follows. (i) the study design had to be a case-control study on association between I/D polymorphism of ACE gene and susceptibility to asthma; (ii) the study should provide distribution frequencies of each genotype in case groups and control groups; (iii) genotype distribution in control group must comply with Hardy-Weinberg equilibrium (HWE).

Based on the selection criteria, two researchers independently screened the original studies and extracted the following information from each study, such as author name, date of

publication, ethnicity of the study population, genotype distributions of cases and controls. The STATA 12.0 (version 11.0; Stata Corp., College Station, TX, USA) was used to assess the association between ACE gene polymorphisms and childhood asthma. The decision to use a random-effects or fixed-effects model was based on the clinical heterogeneity between the included studies. We selected fixed-effect model if studies were considered homogeneous. Otherwise, random-effect model was chosen.

Finally, 9 studies met inclusion criteria that included 1041 cases with asthma and 828 controls.[5-13] Among them, 7 studies were from China, 1 from Taiwan and 1 from Japan (Table 1). Pooling the data from the included studies, we found that the genotype D/D may increase asthma risk in children (D/D vs others: OR =3.60, 95% CI 2.38-5.45, $p < 0.001$; DD vs II: OR =3.19, 95% CI 2.10-4.85, $p < 0.001$; D/D vs I/D: OR = 4.22, 95% CI 2.71-6.57, $p < 0.001$;Table 2), while I/D and I/I genotypes may decrease susceptibility to asthma (I/D vs others: OR = 0.52, 95% CI 0.39-0.69, $p < 0.001$; I/I vs others: OR = 0.75, 95% CI 0.59-0.94, $p = 0.014$;Table 2). When compared with I/D genotype, I/I may be a genetic risk factor of asthma (I/I vs I/D: OR = 1.33, 95% CI 1.05-1.69, $p = 0.019$;Table 2). Unfortunately, we could not find this significant association in a comparison between D allele and I allele. The results of Begger's funnel plot and Egger's linear regression test showed that the possibility of publication bias was low.

Previous studies found the ACE gene polymorphisms were related to the risk of asthma in Chinese children. However, Gao PS et al couldn't find this association in Japanese.[8] In this

study, we integrated the relevant data and suggested ACE D/D genotype may be associated with asthma susceptibility in East Asia.

We tried to explain the reason for this findings. ACE mediates the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). Then Ang II promotes the synthesis of inflammatory cytokines and induces intracellular ROS generation. ACE D/D carriers have higher ACE activity levels than those with I/D and I/I genotypes. Higher activity levels of ACE in D/D carriers probably contribute to the increasing of Ang II, which induces airway high reaction triggered by inflammatory response and oxidative stress.[14] Therefore, compared with other genotypes, genotype D/D may increase the risk of asthma. This is consistent with our results in children from East Asia. However, due to the differences in genetic background and environmental factors, this protective effect may only be observed in certain populations.

In conclusion, this study suggested that genotype D/D in ACE may increase the risk of childhood asthma from East Asia. However, there were some limitations. Because we only included 9 studies, this analysis could not involve more ethnicities. In the future, more studies with larger sample sizes are needed to confirm our results.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors are supported by grants from the National Natural Science Foundation of China (NSFC; Grant Number 81560502), the National Natural Science Foundation of Yunnan Province (Grant Numbers 2013FB044 and 2014FB008), the Education Department Fund of Yunnan Province (Grant Numbers 2014Y165, 2015Z082); Doctoral Graduate Academic Newcomer Award of Yunnan Province (2014) and Doctoral Innovation Fund (Grant Numbers 2016D02).

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Table 1. Distribution of angiotensin-converting enzyme genotype frequency in all included studies.

Author	Year	Country	Race	Cases			Controls		
				D/D	I/D	I/I	D/D	I/D	I/I
Gao PS	1998	Japan	Asian	27	41	32	25	48	27
Qin JH	2000	China	Asian	18	10	24	5	14	21
Song LJ	2001	China	Asian	41	22	45	9	18	29
Guo YB	2006	China	Asian	7	18	27	4	32	36
Lue KH	2006	Taiwan	Asian	17	40	48	4	42	56
Zheng BQ	2012	China	Asian	75	40	83	15	51	44
Chen X	2012	China	Asian	38	19	30	9	18	31
Rong JY	2014	China	Asian	99	44	61	26	89	77
Li Q	2014	China	Asian	55	46	34	10	48	40

Table 2. Meta-analysis of associations between angiotensin-converting enzyme gene polymorphisms and asthma risk in children.

Comparison	Effect model	Effect sizes			Heterogeneity	
		OR	95% CI	<i>p</i> value	<i>p</i> value	<i>I</i> ² , %
D/D vs others	R	3.6	2.38-5.45	<0.001	0.01	60.1
I/D vs others	R	0.52	0.39-0.69	<0.001	0.053	47.9
I/I vs others	F	0.75	0.59-0.94	0.014	0.186	29.1
D/D vs I/I	R	3.19	2.10-4.85	<0.001	0.026	54.1
D/D vs I/D	R	4.22	2.71-6.57	<0.001	0.018	56.8
I/I vs I/D	F	1.33	1.05-1.69	0.019	0.313	14.5
D vs I	R	1.1	0.77-1.57	0.589	<0.001	86.8

R, Random effect model; F, Fixed effect model.

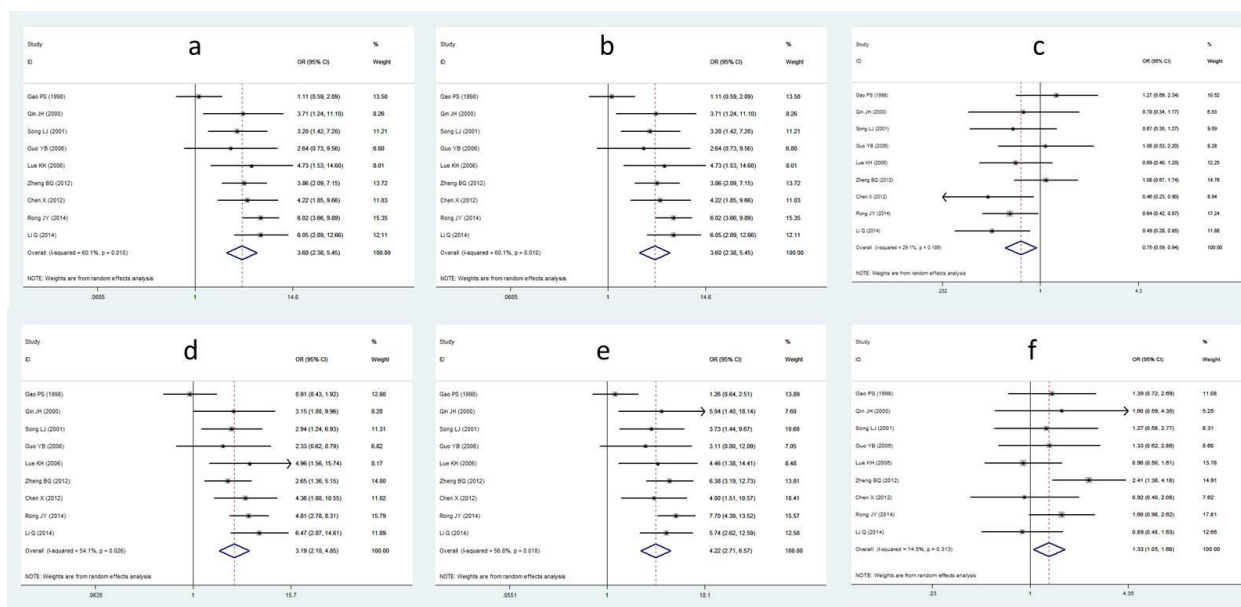


Figure 1. Forest plot of vitiligo associated with (a) angiotensin-converting enzyme (ACE) genotype (D/D vs. others); (b) ACE genotype (I/D vs. others);(c) ACE genotype (I/I vs. others); (d) ACE genotype (D/D vs I/I); (e) ACE genotype (D/D vs I/D); (f) ACE genotype (I/I vs I/D). The squares and horizontal lines correspond to the odds ratio and 95% CI. D, deletion; I, insertion.