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Angiotensin-converting enzyme gene insertion/deletion polymorphism and high-altitude pulmonary edema: An updated meta-analysis

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Abstract

Objective: The purpose of the study was to investigate the association between angiotensin-converting enzyme gene insertion/deletion polymorphism and high-altitude pulmonary edema.

Methods: A systematic search for relevant literature was performed in MEDLINE, CNKI, and EMBASE. The pooled odds ratios and their corresponding 95% confidence intervals were calculated in STATA 12.0 software.

Results: Seven studies, with a total of 304 patients and 564 controls, qualified for the inclusion in the analysis. There was no significant association between angiotensin-converting enzyme insertion/deletion polymorphism and high-altitude pulmonary edema risk in the total population (DD vs II: odds ratio=1.07, 95% confidence interval 0.52–2.24; DI vs II: odds ratio=1.12, 0.85–1.49; dominant model: odds ratio=1.07, 0.83–1.40; recessive model: odds ratio=0.96, 0.53–1.77). Subgroup analysis according to race also revealed no significant correlation between angiotensin-converting enzyme gene insertion/deletion polymorphism and high-altitude pulmonary edema.

Conclusions: Our findings suggest that angiotensin-converting enzyme insertion/deletion polymorphism does not contribute to the risk of high-altitude pulmonary edema. Larger, well-designed studies are required to further validate these results.

Keywords

Angiotensin-converting enzyme, high-altitude pulmonary edema, meta-analysis

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Introduction

High-altitude pulmonary edema (HAPE) is a potentially fatal disease that develops shortly after exposure to altitudes greater than 3000 m. The disease is initially caused by nonuniform hypoxic pulmonary vasoconstriction, leading to pulmonary capillary stress failure and a high-permeability pulmonary edema in the absence of infection with normal left atrial pressure.[1] Timely diagnosis and treatment of HAPE is required to counteract its harmful effects, which can lead to coma or even death.[2] Although hypoxia is a major trigger factor for HAPE, the exact pathogenesis remains unclear. A previous study showed that some individuals are more susceptible to HAPE than others when exposed to identical hypoxic conditions, suggesting that genetic susceptibility might contribute to an individual's risk of HAPE.[3]

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that converts angiotensin I to angiotensin II (vasoconstrictor) and degrades bradykinin (vasodilator), regulating blood pressure and cardiovascular homeostasis.[4] Approximately 90% of the physiological conversion of angiotensin I to angiotensin II takes place in the lungs. Peripheral blood ACE is thought to be identical to pulmonary ACE, and its level is proportional to blood oxygen concentration, suggesting that serum ACE activity is in good correlation with the enzyme level of the pulmonary tissue.[5]

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The human *ACE* gene is located on chromosome 17q23. A large number of *ACE* gene polymorphisms have been identified, including intron 16 insertion/deletion (I/D) polymorphism (rs4646994), which is characterized by the presence or absence of a 287 bp Alu repetitive sequence.[6] Homozygotes (DD) for the D allele have the highest plasma ACE levels, heterozygotes (ID) have intermediate levels, and homozygotes (II) for the I allele have the lowest levels.[7]

Many studies have investigated the relationships between *ACE* I/D polymorphism and HAPE, but the results have been inconsistent. The inconsistency has been attributed to inadequate statistical power due to small sample size and eco-geographical differences. Meta-analysis is a statistical tool that can overcome the limitations of individual research studies.[8] Therefore, we performed a meta-analysis to obtain a more accurate estimation of the association between *ACE* gene I/D polymorphism and HAPE risk. Notably, our meta-analysis includes twice as many articles as the previous one.[9]

Materials and methods

Search strategy for identification of studies

We searched electronic databases (MEDLINE, PubMed, ISI Web of Knowledge, CNKI, and EMBASE) for all published journal articles containing the terms "angiotensin-converting enzyme/ACE," "high altitude pulmonary edema/HAPE," "genetic polymorphism," and "single nucleotide polymorphism." The references of the included studies were manually searched to identify additional articles of interest. In cases of overlapping information, the publication with the most comprehensive data was included.

Inclusion and exclusion criteria

Studies were considered eligible if they met the following inclusion criteria: (a) the relationship between *ACE* gene I/D polymorphism and HAPE risk was assessed; (b) case-control design; and (c) genotype data was provided. The exclusion criteria were as follows: (a) studies not concerning HAPE; (b) reviews; (c) studies without accessible information; and (d) duplicate publications.

Data extraction

Two independent researchers read the relevant articles and extracted the data. In cases of controversy, the articles were assessed again by a third investigator. The following information was collected from each article: first author, year of publication, race, number of cases and controls, genotype frequencies in cases and controls, and evidence of Hardy-Weinberg equilibrium (HWE) in the controls.

Statistical analyses

Fisher's exact test was used to test HWE for distributions of genotypes among controls. The strength of the correlation between *ACE* gene I/D polymorphism and susceptibility to HAPE was estimated by the odds ratio (OR) and 95% confidence interval (CI) under a homozygote comparison (DD vs II), heterozygote comparison (DI vs II), dominant model (DD+DI vs II), and recessive model (II+DI vs DD). Inter-study heterogeneity was assessed with the I^2 test. In case of substantial inter-study heterogeneity (I^2 value$>$50%), the random effects model was used; otherwise, the fixed effects model was performed. A sensitivity analysis was conducted by omitting each article from the overall analysis in turn. If the point estimate of its omitted analysis was outside of the 95% CI of the pooled analysis, the study was suspected of excessive sensitivity. To assess the potential publication bias, Begg's funnel plot was visually inspected. All statistical tests were performed in Stata (version 12.0; Stata Corporation, College Station, Texas, USA).

Results

Study characteristics

As shown in Figure 1, 42 studies exploring the relationship between *ACE* gene I/D polymorphism and HAPE susceptibility were identified, out of which eight met the pre-set inclusion criteria. A total of 304 cases and 564 controls were included in the pooled analysis.[10–17] The study characteristics are summarized in Table 1. Genotype distribution was consistent with HWE in the controls of all studies. Seven studies were conducted in Asians and one in Caucasians.

Meta-analysis results

The main results of our meta-analysis are presented in Table 2 and Figure 2. There was no association between *ACE* I/D polymorphism and the risk of HAPE (DD vs II: OR=1.07, 95% CI= 0.52–2.24; DI vs II: OR=1.12, 95% CI= 0.85–1.49; dominant model: OR=1.07, 95% CI= 0.83-1.40; recessive model: OR=0.96, 95% CI= 0.53–1.77). When stratified according to race, no significant association was detected between *ACE* gene I/D polymorphism and HAPE risk in Asians (DD vs II: OR=1.10, 95% CI=0.48–2.52; DI vs II: OR=1.13, 95% CI=0.85–1.51; dominant model: OR=1.14, 95% CI=0.74–1.74; recessive model: OR=0.98, 95% CI=0.49–1.95).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by omitting each study from the overall analysis in turn. No single article was found to influence the pooled OR, which suggests that the results are stable (Figure 3).

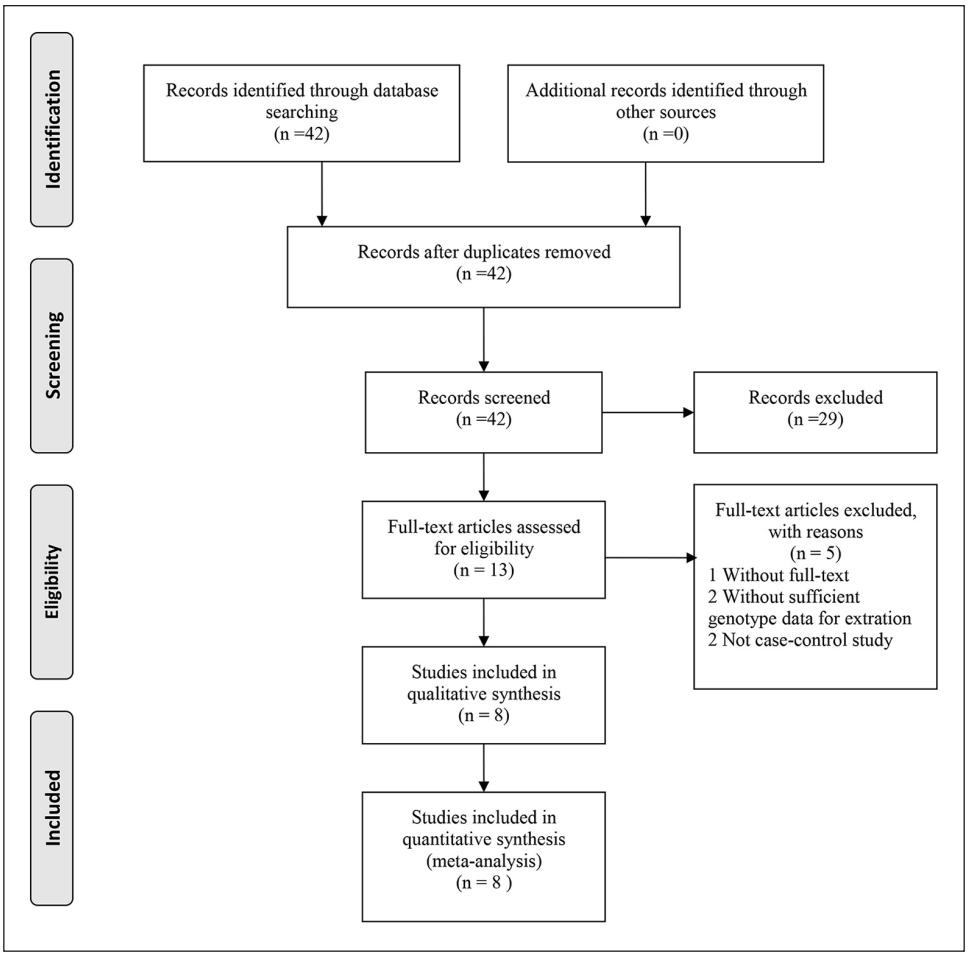

Figure 1. Flow diagram of included/excluded studies.

Table 1. Included studies of the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism with high-altitude pulmonary edema (HAPE).

First author et al., year	Country	Ethnicity	Cases/ controls	ACE I/D (case/control)			HWE test
				II	ID	DD	
Hotta et al., 2004[10]	Japan	Asian	49/55	22/26	19/25	8/4	0.54
Kumar et al., 2004[11]	India	Asian	19/20	8 /9	8 /9	3 /2	0.91
Charu et al., 2006[12]	India	Asian	64/53	18/23	34/21	12/9	0.28
Wang et al., 2013[13]	China	Asian	27/108	9/57	14/42	4/9	0.75
Yang et al., 2013[14]	China	Asian	147/193	64/83	69/86	14/24	0.81
Du et al., 2018[15]	China	Asian	30/30	14/17	13/11	3/2	0.90
Dehnert et al., 2002[16]	Germany	Caucasian	22/30	6/8	11/15	5/7	0.99
Bhagi et al., 2015[17]	India	Asian	79/75	26/12	43/34	10/29	0.70

HWE: Hardy-Weinberg equilibrium.

Publication bias

The funnel plot was inspected to assess for publication bias. No evidence of publication bias was found in the funnel plot (Figure 4), which suggests that our meta-analysis is not based on a biased sample of studies.

Discussion

HAPE, as a form of noncardiogenic pulmonary edema, is thought to be caused by an endothelial breakdown in the lungs secondary to unequal capillary pressure, and usually develops within 2–4 days of ascent above 3000 m. HAPE

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) of angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism with high-altitude pulmonary edema (HAPE) risk.

Variables	*n*[a]	DD vs II		DI vs II		Dominant model		Recessive model	
		OR (95% CI)	Model	OR (95% CI)	Model	OR (95% CI)	Model	OR (95% CI)	Model
Total	6	1.07 (0.52–2.24)	R	1.12 (0.85–1.49)	F	1.07 (0.83–1.40)	F	0.96 (0.53–1.77)	R
Country									
Asian	7	1.10 (0.48–2.52)	R	1.13 (0.85–1.51)	F	1.14 (0.74–1.74)	R	0.98 (0.49–1.95)	R
Caucasian	1	/		/		/		/	

[a]Number of comparisons.

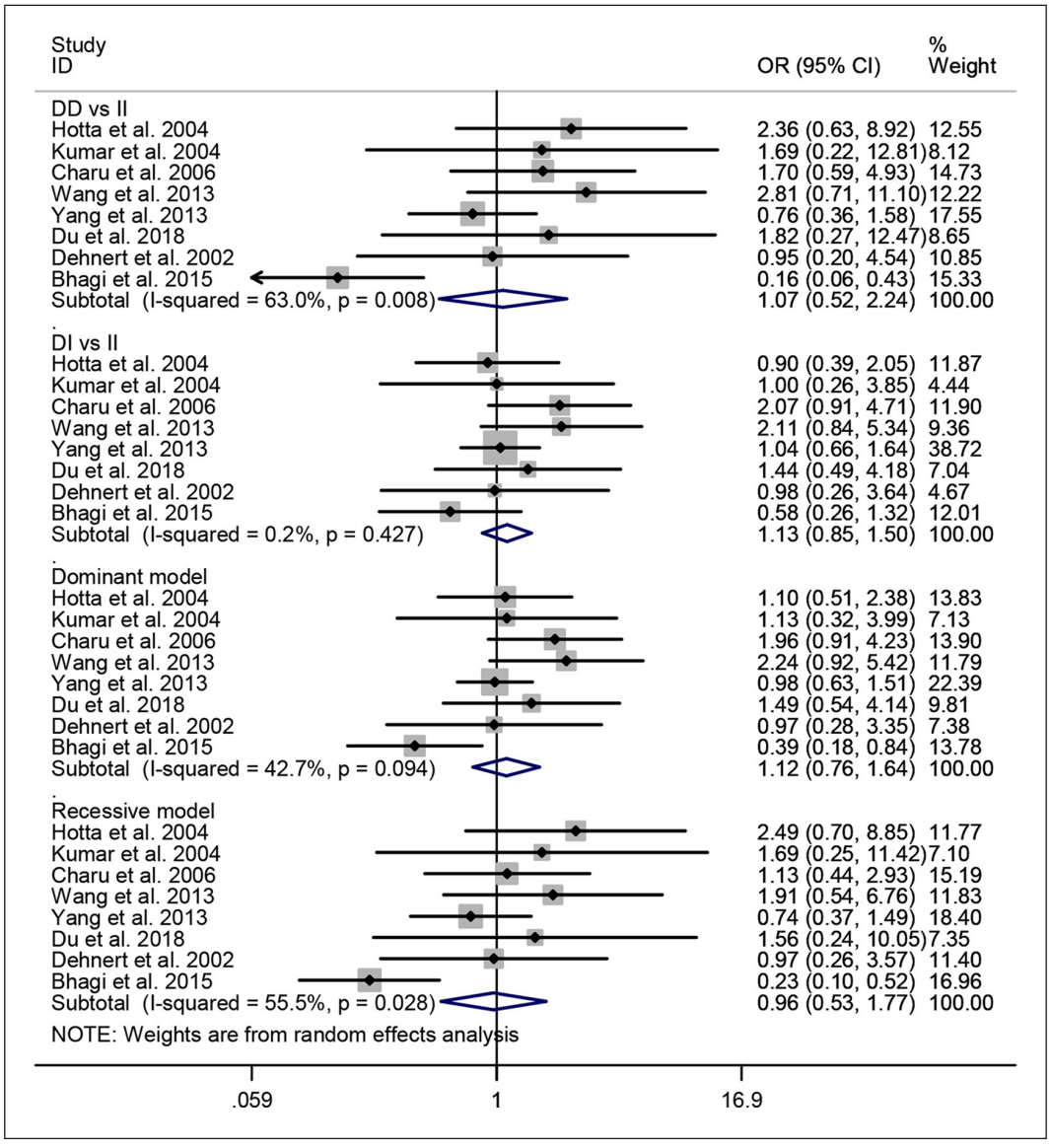

Figure 2. Forest plot for meta-analysis of the association between angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism and high-altitude pulmonary edema (HAPE) risk. CI: confidence interval; OR: odds ratio.

is associated with pulmonary hypertension and elevated capillary pressure,[18] although the exact pathogenesis remains to be established. It is known that HAPE is caused by a combination of genetic and environmental factors. Since Dehnert et al. (2002)[16] first examined the association between *ACE* I/D polymorphism and the risk of HAPE, a

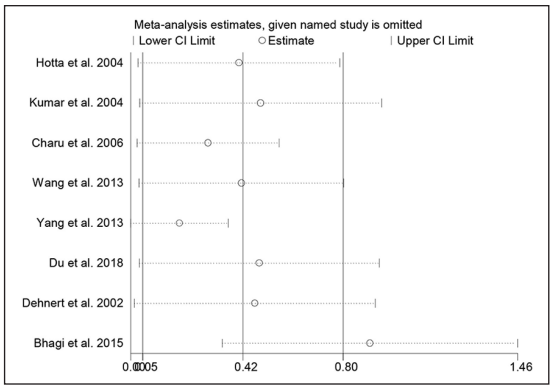

Figure 3. Sensitivity analysis of high-altitude pulmonary edema (HAPE) risk associated with angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism.
CI: confidence interval.

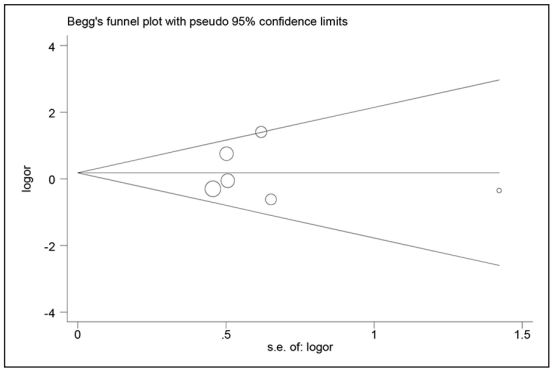

Figure 4. Funnel plot of the publication bias.

number of studies have been conducted to evaluate the role of I/D polymorphism in the *ACE* gene in HAPE development. However, the results remain inconclusive. To help resolve these conflicting results using as large a sample as possible, we conducted a meta-analysis of case-control studies analyzing potential associations between this polymorphism and risk of HAPE. Compared with the previous meta-analysis,[9] the present study is much larger, with almost twice as many articles.

Our results showed no significant association between *ACE* gene I/D polymorphism and risk of HAPE. Race-specific subgroup analysis, which was carried out to account for different genetic backgrounds and environmental factors, found no significant association in Asian populations. Since only one of the included studies was conducted in Caucasians, a stratified analysis could not be performed. Further studies are necessary to validate our findings in Caucasians. Sensitivity analysis and publication bias assessment confirmed the robustness of our results. The ACE is a complex physiological system involved in multiple components and genes that define its activity and its regulatory actions (e.g. on vascular growth or blood pressure); ACE system genes are highly polymorphic. The effects of any single polymorphism, and/or any single gene in the renin-angiotensin system (RAS), on HAPE might be less pronounced than originally anticipated. The failure to demonstrate a significant association between *ACE* gene I/D polymorphism and HAPE does not necessarily rule out the possibility that other gene variants, or combinations of alleles at multiple loci within the same gene, could be relevant to HAPE.[19] Systematically screening the genome for functional variants in ACE and other related genes in the RAS, and functional experiments to confirm the causal variants and epistatic interactions relevant to HAPE pathogenesis are warranted. High throughput genomic technologies should speed up the discovery of such variants. Further genetic association studies involving large numbers of cases and controls are needed to provide conclusive evidence on the effects of the *ACE* gene, and other genes within the RAS, on the risk of HAPE.

Certain limitations should be considered when interpreting the results of this meta-analysis. First, some relevant studies could not be included due to incomplete raw data provided or publication limitations. Second, since the random effects model was used in this meta-analysis, the results must be interpreted with caution. Additionally, genotype information stratified for the main confounding variables, such as age, sex, and other factors, was not available in the original studies, which could have introduced a confounding bias.

In conclusion, this meta-analysis suggests that *ACE* gene I/D polymorphism is not associated with HAPE risk. Larger, well-designed studies are required to further evaluate the influence of gene polymorphism on HAPE.

Declaration of conflicting interests

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