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Original Article

Meta-analysis of the association between angiotensin-converting enzyme I/D polymorphism and chronic obstructive pulmonary disease risk

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Abstract: Background: An insertion/deletion (I/D) polymorphism in intron 16 of the angiotensin-converting enzyme (ACE) gene accounts for most of the variability of serum ACE activity and is associated with the development of chronic obstructive pulmonary disease (COPD). However, the results are inconsistent. Therefore, we performed this meta-analysis. Methods: We conducted a systematic literature search in Google Scholar, PubMed and Web of Science databases (up to 30 Aug 2015) to accumulate all available studies. We assess the relevance between the ACE I/D polymorphism and COPD susceptibility by employing the odds ratios (ORs) with 95% confidence intervals (CIs). Results: In total, 14 relevant studies contained 2076 patients were enrolled. ACE I/D polymorphism was not associated with the susceptibility of COPD (OR=1.28; 95% CI, 0.88-1.86; *P*=0.19). When stratified by ethnicity, the significantly elevated COPD risk was observed in Asian (OR=2.99; 95% CI, 2.02-4.44; *P*<0.00001) but not in Caucasian (OR=0.92; 95% CI, 0.73-1.16; *P*=0.49). Conclusions: In conclusion, this meta-analysis indicated that ACE I/D polymorphism is a candidate for susceptibility to COPD in Asian.

Keywords: Chronic obstructive pulmonary disease, angiotensin-converting enzyme, meta-analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality throughout the world. It is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammation in the respiratory system [1]. It is expected that COPD will move from the sixth to the fourth cause of mortality and morbidity in the world [2]. Thus, it is important to detect which one has the high risk of developing COPD.

Angiotensin-converting enzyme (ACE) is a key enzyme of renin-angiotensin system (RAS), and plays an important part in maintaining the stabilization of water, electrolyte and internal environment in human body [3]. ACE can regulate the physiological function of blood vessel, for example, it can catalytically translate angiotensin I into angiotensin II shrinking blood vessel and secreting aldosterone, and also inactivate vasodilator bradykinin to affect neurotransmitter metabolism [4]. An insertion/deletion (I/D) polymorphism in intron 16 of the ACE gene accounts for most of the variability of serum ACE activity and is associated with the development of COPD [5-18]. However, the results are inconsistent. Therefore, we performed this meta-analysis.

Methods

Publication search

We conducted a systematic literature search in Google Scholar, PubMed and Web of Science databases (up to 30 Aug 2015) to accumulate all available studies on the association between polymorphisms of ACE I/D polymorphism and COPD susceptibility by following the search strategy: ("ACE" OR "Angiotensin-converting enzyme") AND ("polymorphism" OR "mutation" OR "variation") AND ("COPD" OR "Chronic obstructive pulmonary disease"). Studies were also searched manually on the reference lists of reviews and retrieved studies for extra eligible studies.

Table 1. Characteristics of the included studies

First author	Year	Country	Ethnicity	Age	Gender	Subjects (n)	HWE
Suylen	1999	Netherlander	Caucasian	65	Mixed	182	Yes
Wang	2000	China	Asian	68	Mixed	58	Yes
Jiang	2002	China	Asian	62	Mixed	60	Yes
Gu	2003	China	Asian	60	Mixed	281	Yes
Yildiz	2003	Turkey	Caucasian	62	Male	82	Yes
Ahsan	2004	India	Asian	NA	Male	93	Yes
Hopkinson	2004	UK	Caucasian	64	Mixed	204	Yes
Tkacova	2005	Slovakia	Caucasian	65	Mixed	184	Yes
Zhang	2008	China	Asian	63	Mixed	118	Yes
Pabst	2009	German	Caucasian	62	Mixed	310	Yes
Kuzubova	2013	Russia	Caucasian	60	Male	158	Yes
Simsek	2013	Turkey	Caucasian	61	Mixed	106	Yes
Ulasli	2013	Turkey	Caucasian	65	Mixed	129	Yes
Ayada	2014	Turkey	Caucasian	NA	NA	111	Yes

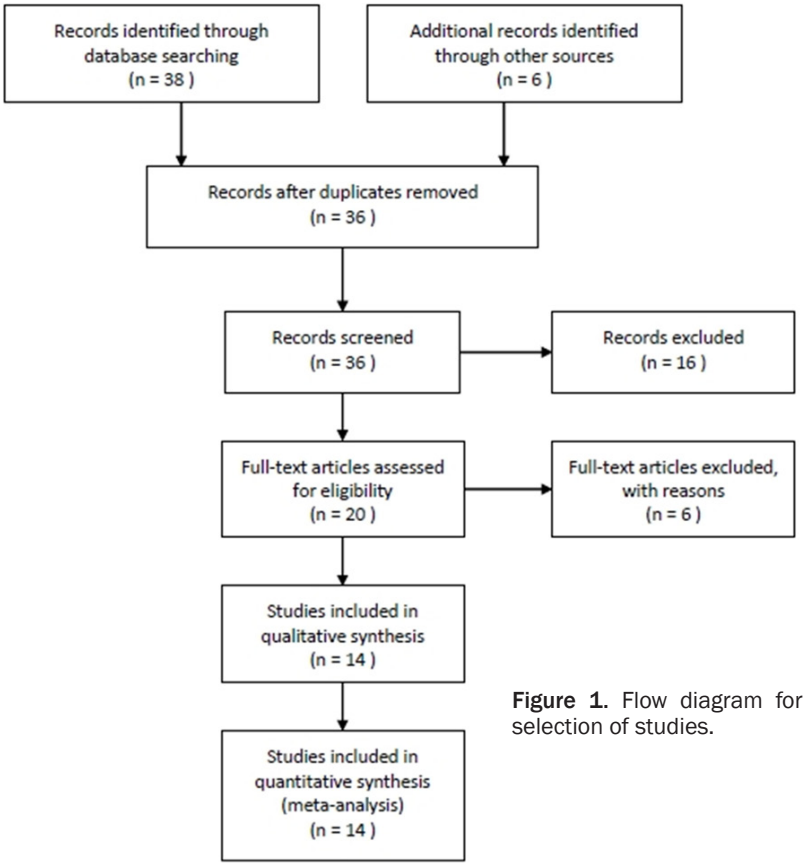

Figure 1. Flow diagram for selection of studies.

Inclusion and exclusion criteria

The articles enrolled in the present meta-analysis were consistent with the criteria: (a) the relationship between the polymorphisms in ACE I/D polymorphism and COPD susceptibility was identified in the studies; (b) study method should be case-control or cohort; (c) we can extract the ORs with 95% CIs of all the cases and controls. Studies were excluded when they were: (a) studies without sufficient raw data to evaluate ORs with 95% CIs; (b) case-only studies; (c) publications which were duplicated; (d) studies based on animals or families.

Data extraction

The data was extracted independently by two investigators. Data with discrepancies were discussed by all authors. The following data were collected: the name of first author, publication year, country of origin, ethnicity, age, gender, and total numbers of cases and control. Ethnic backgrounds were categorized as Asian and Caucasian.

Statistical analysis

We assess the relevance between the ACE I/D polymorphism and COPD susceptibility by employing the ORs and 95% CIs in the studies and conducted the pooled ORs on the recessive (DD vs. ID+ II) model. The *P* values of Hardye-Weinberg equilibrium (HWE) were calculated by χ^2 test for the genotype distribution in controls. The meta-analyses were conducted by operating the software STATA 12.0 (Stata Corporation, College Station, Texas). A chi-square based Q-statistic test was performed to evaluate the heterogeneity of studies in the

Table 2. Meta-analysis results and subgroup analyses

	$P_{heterogeneity}$	Model	OR (95% CI)	*P* value
Overall	<0.0001	R	1.28 (0.88-1.86)	0.19
Asian	0.14	F	2.99 (2.02-4.44)	<0.00001
Caucasian	0.25	F	0.92 (0.73-1.16)	0.49

R, random effects model; F, fixed effects model.

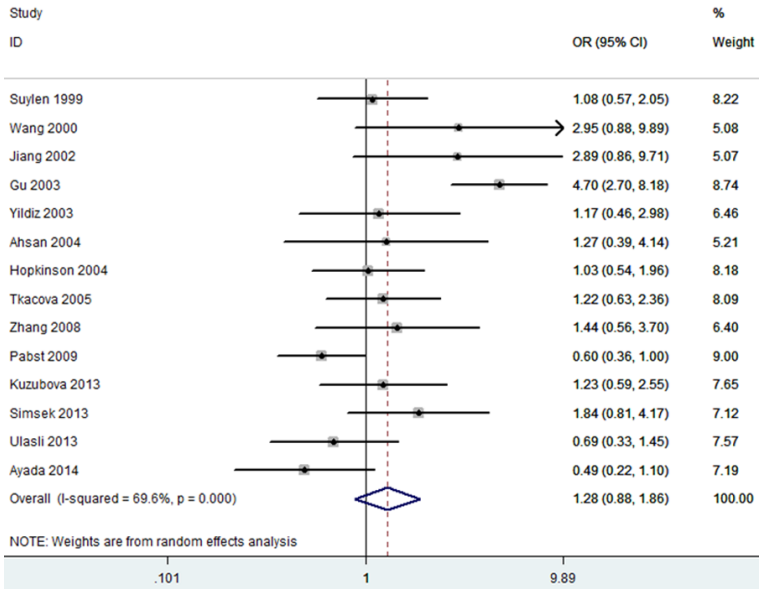

Figure 2. Meta-analysis of the association between the *ACE* I/D polymorphism and COPD risk.

case-control studies. If the Q test (P>0.1) indicated homogeneity within studies, the fixed effects model would be applied; Or else, we chose the random effects model. Stratification analyses were performed by ethnicity. We removed a single study each time to evaluate the stability of the results. Begg's funnel plot and Egger's test were adopted to assess the publication bias.

Results

Study characteristics

The main features of eligible studies were shown in **Table 1**. In total, 14 relevant studies contained 2076 patients were enrolled (**Figure 1**). Among them, participants in 5 studies were Asian and in the other 9 were Caucasian. Three studies only enrolled male subjects. All studies were in HWE.

Meta-analysis synthesis

The primary results of the present meta-analysis and the heterogeneity test were summarized in **Table 2**. By pooling ORs and 95% CIs, we discovered that ACE I/D polymorphism was not associated with the susceptibility of COPD (OR=1.28; 95% CI, 0.88-1.86; *P*=0.19; **Figure 2**). When stratified by ethnicity, the significantly elevated COPD risk was observed in Asian (OR=2.99; 95% CI, 2.02-4.44; *P*<0.00001) but not in Caucasian (OR=0.92; 95% CI, 0.73-1.16; *P*=0.49).

The sensitivity analyses were conducted by excluding one single case-control study and no separate study shown the influence on the pooled OR (**Figure 3**). Begg's funnel plot and Egger's test were performed to assess the risk of publication bias and no visual publication bias was shown (*P*=0.08; **Figure 4**).

Discussion

COPD is a major cause of morbidity and mortality worldwide. It is a prevalent disease. The epidemiology of COPD has been studied, but the result was insufficiency. This meta-analysis of 14 case-control studies aimed to investigate whether ACE I/D polymorphism has an impact on the risk of COPD. The results of the meta-analysis revealed that ACE DD genotype was significantly associated with an increased COPD risk. This result indicated that ACE I/D polymorphism may be implicated in the development and progression of COPD. In the subgroup analysis of race, ACE I/D polymorphism was significantly associated with COPD in Asian, but not in Caucasian. This result indicated that there was ethnic difference in the effects of ACE I/D polymorphism on COPD susceptibility.

Kanazawa et al. found that mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and lactate concentration after exercise with both placebo and captopril were higher in patients with the DD genotype than in those with the II or ID genotypes [19]. Mortensen et al. suggested that use of statins and ACE inhibitors prior to admission is associ-

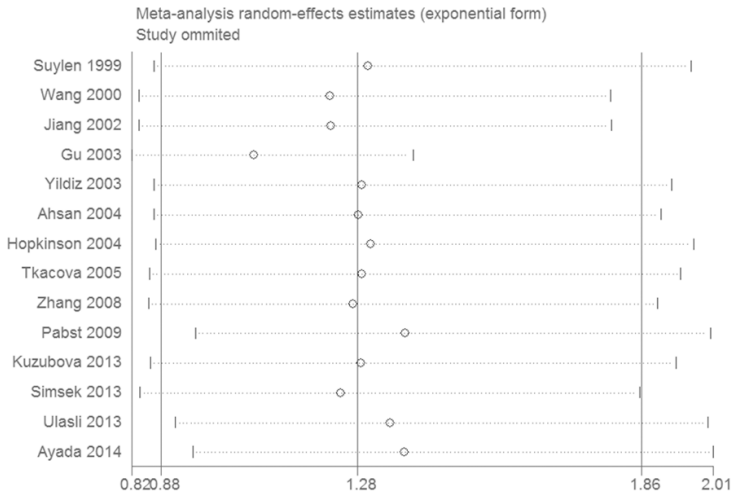

Figure 3. Sensitivity analysis for the *ACE* I/D polymorphism and COPD risk.

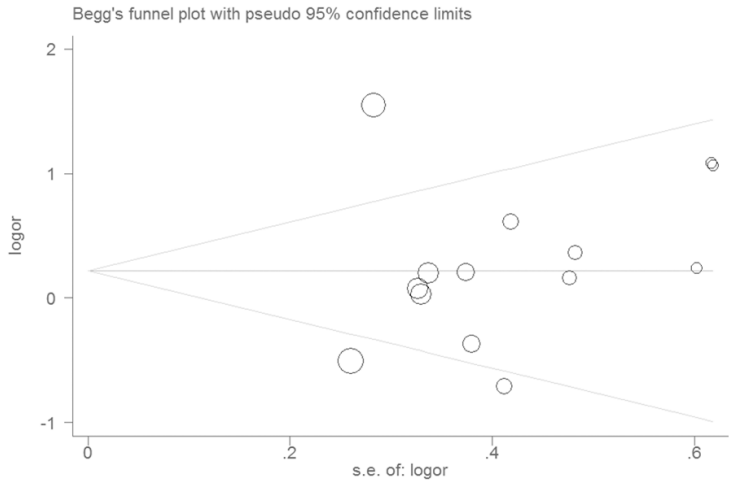

Figure 4. Funnel plot for the *ACE* I/D polymorphism and COPD risk.

ated with decreased mortality in subjects hospitalized with a COPD exacerbation [20]. Kuzubova and colleagues indicated that Detectable endothelial dysfunction in COPD patients was shown to correlate with high-producer D allele of ACE gene [15].

ACE I/D polymorphism also played an important role in other diseases. Zhao et al. indicated that the ACE I/D polymorphism may be a genetic susceptibility factor for IS, especially among Asians [21]. Huang et al. suggested that ACE I/D polymorphism was associated with aortic aneurysm risk [22]. Xie et al. suggested that the ACE I/D polymorphism might not be a common risk factor for overall cancer susceptibility, but might contribute to the susceptibility of prostate cancer [23]. Luo et al. suggested that ACE I/D polymorphism might be associated with the risk of hypertrophic cardiomyopathy [24].

The limitations in this meta-analysis that should be interpreted. First, there were only 5 studies investigated the association of ACE I/D polymorphism with COPD risk in Asians, and no study was published to assess this association in Africans. Therefore, more studies with large sample sizes are needed to further identify the association among Asians and Africans. Second, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between gene-to-gene and gene-to-environment may modulate COPD risk. These gene-to-gene and gene-to-environment interactions should be further evaluated. Third, due to the lack of sufficient and uniform information in original case-control studies, data were not stratified by other factors (e.g., smoking and other lifestyle factors).

In conclusion, this meta-analysis indicated that ACE I/D polymorphism is a candidate for susceptibility to COPD in Asians.

Disclosure of conflict of interest

None.

Abbreviations

OR, odds ratio; CI, confidential interval; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; RAS, renin-angiotensin system; HWE, Hardye-Weinberg equilibrium.

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