

## Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: A meta-analysis

Kazuaki Nishio, Shinji Kashiki, Hideaki Tachibana, Youichi Kobayashi

Kazuaki Nishio, Shinji Kashiki, Hideaki Tachibana, Matsui Hospital, The Department of Cardiology, Tokyo, 146-0082, Japan  
Kazuaki Nishio, Hideaki Tachibana, Youichi Kobayashi, The Third Department of Internal Medicine, School of Medicine Showa University, Tokyo 142-8666, Japan

Author contributions: Nishio K designed and performed the statistics; Kashiki S, Tachibana H and Kobayashi Y participate in selection of trials and data synthesis.

Correspondence to: **Kazuaki Nishio, MD, PhD**, The Third Department of Internal Medicine, School of Medicine Showa University, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan. [kazukun@jg7.so-net.ne.jp](mailto:kazukun@jg7.so-net.ne.jp)

Telephone: +81-3-37521111 Fax: +81-3-37521119

Received: February 9, 2011 Revised: July 22, 2011

Accepted: July 29, 2011

Published online: October 26, 2011

### Abstract

**AIM:** To evaluate the association between genetic polymorphisms and angiotensin converting enzyme inhibitor (ACEI)-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

**METHODS:** We conducted a search in PubMed, EMBASE, Cinahl, and the Cochrane Database without language limitation. A database of 11 studies on ACEI-related cough, with detailed information regarding *ACE I/D* or bradykinin B<sub>2</sub> receptor polymorphisms, was created. Eligible studies were synthesized using meta-analysis methods, including cumulative meta-analysis. A subgroup analysis was also performed using ethnicity.

**RESULTS:** Six studies were included on *ACE I/D* polymorphism (398 Caucasians, 723 East Asians), and three studies were included on bradykinin B<sub>2</sub> receptor polymorphism (300 East Asians). The distribution of ACE genotypes showed significant differences in the entire population ( $P = 0.004$ ) and in East Asians ( $P = 0.005$ )

but not in Caucasians ( $P = 0.23$ ). Allelic frequencies of ACE showed significant differences in East Asians [odds ratio (OR) = 1.49 (1.11-2.02)]. The meta-analysis with a random effects model showed a significant association between *ACE* allele *I/D* and ACEI-related cough [random effects (RE) OR = 1.49 (1.11-2.02),  $P = 0.009$ ] in East Asians, but not in Caucasians [RE OR = 0.90 (0.60-1.35)]. The allelic frequencies of the bradykinin B<sub>2</sub> receptor gene were significantly different [OR = 2.25 (1.42-3.57)]. The distributions of the T/C genotypes of the bradykinin B<sub>2</sub> receptor gene were significantly different ( $\chi^2 = 8.366$ ,  $P = 0.015$ ). The meta-analyses revealed that there was a significant association between the bradykinin B<sub>2</sub> receptor allele and ACEI-related cough in East Asians [RE OR = 2.29 (1.42-3.69),  $P = 0.001$ ].

**CONCLUSION:** *ACE I/D* and Bradykinin B<sub>2</sub> receptor polymorphisms contributed to the risk of ACEI-related cough in East Asians, but a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in Caucasians.

© 2011 Baishideng. All rights reserved.

**Key words:** Angiotensin converting enzyme inhibitor; Bradykinin; Cough; Genes; Polymorphism

**Peer reviewers:** Jacob Joseph, MBBS, MD, Associate Professor of Medicine, Boston University School of Medicine, VA Boston Healthcare, Cardiology Section, 1400 VFW Parkway, West Roxbury, MA 02132, United States; Folkert W Asselbergs, MD, PhD, Assistant Professor, Department of Cardiology, Division Heart and Lungs, E.03.809, PO Box 85500, 3508 GA Utrecht, The Netherlands

Nishio K, Kashiki S, Tachibana H, Kobayashi Y. Angiotensin-converting enzyme and bradykinin gene polymorphisms and cough: A meta-analysis. *World J Cardiol* 2011; 3(10): 329-336 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v3/i10/329.htm> DOI: <http://dx.doi.org/10.4330/wjc.v3.i10.329>

## INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEI) are widely used for the treatment of hypertension and congestive heart failure. The major adverse effect and the most frequent reason for withdrawal of the ACEI is a persistent, dry (nonproductive) cough<sup>[1,2]</sup>. The cause of the cough is reported to be intrinsic to the mechanism of action of ACEI, and so change to another ACEI is not recommended because of apparent cross-reactivity<sup>[2]</sup>. The accumulation of kinins has been suggested to play a major role in ACEI-related cough. This accumulation probably results from inhibition of the degradation of kinins, particularly bradykinin, in the airway, but the precise mechanism is still unknown. It seems reasonable to suspect that a primary, genetically determined characteristic resulting in an alteration of drug action or drug metabolism may be responsible<sup>[3]</sup>.

ACEI-related cough occurs in about 10%-20% of treated patients<sup>[4-6]</sup>. A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans<sup>[7-9]</sup>, among whom the population prevalence of the *I* allele is high<sup>[10]</sup>. Some studies showed the relationship between the *ACE I/D* genetic polymorphism and ACEI-related cough<sup>[11-13]</sup>. Furuya *et al.*<sup>[11]</sup> demonstrated that Japanese patients with *ACE* genotype *II* were most susceptible to cough. However, a significant difference was not observed in two genetic studies in French and British patients<sup>[12,13]</sup>. Other studies have also implied a genetic predetermination of ACEI-related cough caused by specifically implicated variants of the genes that encode ACE, chymase, and bradykinin B<sub>2</sub> receptors<sup>[14-16]</sup>. It is controversial whether genetic polymorphisms are associated with ACEI-related cough. There may be a race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy. The aim of this study was to evaluate the association between genetic polymorphisms and ACEI-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

## MATERIALS AND METHODS

### Selection of trials

We searched Medline, EMBASE, Cinahl, and the Cochrane Database from the earliest available date through September 2010. A search strategy using the Medical Subject Headings and text keywords “angiotensin converting enzyme inhibitor”, “cough”, “gene”, and “polymorphism” were used. The review included genetic association studies fulfilling the following inclusion criteria: (1) providing cases diagnosed with ACEI-related cough; (2) providing information on genotype frequency for *ACE I/D* or bradykinin B<sub>2</sub> receptor -58 T/C polymorphisms; and (3) using validated molecular methods for genotyping. The retrieved studies were manually screened to assess their appropriateness for this study. All references cited in the studies were also reviewed to identify

additional published articles not indexed in the database. Case reports, editorials and review articles were excluded. The search was not restricted by language.

### Data synthesis

Nineteen meta-analyses were performed to investigate the association between *ACE I/D* and ACEI-related cough for the allele contrast (*D vs I*), the recessive (*DD vs ID/II*), the dominant (*DD/ID vs II*), the additive (*DD vs II*) and the co-dominant (*ID vs DD/II*) models, and the association between bradykinin B<sub>2</sub> receptor -58T/C and ACEI-related cough. We calculated the overall odds ratio (OR) with the corresponding 95% confidence interval (CI) using the random effects (RE; DerSimonian and Laird) models. Statistical heterogeneity across the various studies was tested with the use of the *Q*-statistic<sup>[17]</sup>. A *P* value < 0.10 indicated a significant statistical heterogeneity across studies, allowing for the use of the RE model. A cumulative and recursive cumulative meta-analysis was also carried out<sup>[17,18]</sup>. Cumulative and recursive cumulative meta-analyses provide a framework for updating a genetic effect from all studies and a measure of how much the genetic effect changes as evidence accumulates. Thus, a cumulative meta-analysis indicates the trend in estimated risk effect and a recursive cumulative meta-analysis indicates the stability in risk effect. In the cumulative meta-analysis, studies were chronologically ordered by publication year, then, the pooled ORs were obtained at the end of each year, i.e. at each information step. In the recursive cumulative meta-analysis, the relative change in pooled OR in each information step (pooled OR in next year/pooled OR in current year) was calculated. In addition to the main (or overall) analysis which included all available data, a subgroup analysis for each “race” was also performed. “Racial” descent was categorized into Caucasian descents and East Asian descents<sup>[17]</sup>.

### Statistical analysis

OR and 95% CI for risk factors and significance level for  $\chi^2$  are given. Statistical heterogeneity was evaluated *via* the *Q* statistic. *P* < 0.01 was considered representative of significant statistical heterogeneity.

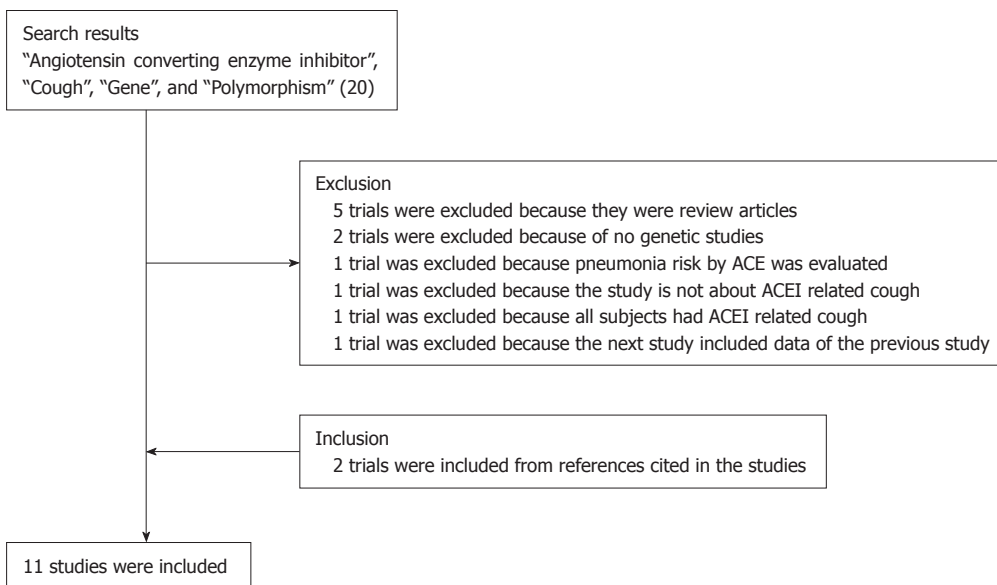
## RESULTS

### Eligible studies

Twenty citations identified through the literature search were independently screened by two investigators according to the inclusion criteria. Eleven articles were retrieved and evaluated against the same criteria. Data from 11 studies<sup>[11,13,19-26]</sup> met the meta-analysis eligibility criteria and were included in the context of the meta-analyses. Figure 1 represents a flow chart of retrieved studies and studies excluded, with specification of reasons. Six studies were included on the *ACE I/D* polymorphism (398 Caucasians, 723 East Asians), and three studies were included on bradykinin B<sub>2</sub> receptor polymorphism (300 East Asians, Table 1). 19 meta-analyses were conducted

**Table 1** Distribution of genotypes and allelic frequencies of ACE and bradykinin B<sub>2</sub> receptor polymorphisms in patients with or without cough

	Population	Studies		Genotype			$\chi^2$ test	Studies	Allele		Odds ratio (95% CI)
				I/I	I/D	D/D			I	D	
Angiotensin converting enzyme	All	11	Cough (-)	390 (32)	571 (48)	241 (20)	0.004	7	0.51	0.49	1.26
			Cough (+)	338 (39)	381 (44)	142 (17)			0.45	0.55	(0.99-1.61)
	Caucasians	3	Cough (-)	75 (24)	132 (43)	100 (33)	0.230	2	0.53	0.47	0.72
			Cough (+)	23 (19)	51 (41)	50 (40)			0.61	0.39	(0.46-61.4)
	East Asians	8	Cough (-)	315 (35)	439 (49)	141 (16)	0.005	5	0.49	0.51	1.49
			Cough (+)	315 (43)	330 (45)	92 (12)			0.39	0.61	(1.11-12.02)
B2 receptor B <sub>2</sub> receptor -58T/C	East Asians	3		T/T	T/C	C/C	0.015	2	C	T	
			Cough (-)	145 (26)	270 (50)	143 (24)			0.56	0.44	2.25
			Cough (+)	139 (30)	244 (52)	85 (18)			0.36	0.64	(1.42-23.57)

**Figure 1** Flow chart of retrieved studies and studies excluded, with specification of reasons.

for these 2 gene polymorphisms of angiotensin-converting enzyme *deletion/insertion* (ACE *D/I*) and bradykinin B<sub>2</sub> receptor -58T/C (Table 2, Figures 2 and 3).

### ACE *D/I*

Table 1 shows the distributions of the genotypes and the allelic frequencies of the polymorphisms of ACE and bradykinin B<sub>2</sub> receptor in subjects with or without cough. In the ACE gene, the distributions of genotypes showed significant differences in the entire population ( $P = 0.004$ ) and in East Asians ( $P = 0.005$ ) but not in Caucasians ( $P = 0.23$ ). Allelic frequencies of ACE showed significant differences in East Asians [OR = 1.49 (1.11-2.02)].

All studies investigating the association between ACE allele *I/D* and ACEI-related cough, were included in the meta-analysis. Table 2 shows OR and heterogeneity results for the genetic contrasts of ACE *I/D* and bradykinin B<sub>2</sub> receptor gene polymorphisms. The main analysis revealed no significant heterogeneity ( $pQ = 0.259$ ), and the random effects pooled OR was not significant [RE OR = 1.15 (0.87-1.52)] in the entire population. In the subgroup analysis by "race", Caucasians showed

lack of significant heterogeneity ( $pQ = 0.799$ ) and non-significant association [RE OR = 0.90 (0.60-1.35)] and East Asians revealed non-significant heterogeneity ( $pQ = 0.226$ ) and significant association [RE OR = 1.49 (1.11-2.02),  $P = 0.009$ ]. In contrast, there were significant heterogeneities for *DD vs DI* with *II* in the entire population ( $pQ = 0.005$ ) and in East Asians ( $pQ = 0.003$ ), and *II vs DD* with *DI* in East Asians ( $pQ = 0.027$ ), *DD vs II* in the entire population ( $pQ = 0.008$ ) and in East Asians ( $pQ = 0.006$ ) in the genetic models.

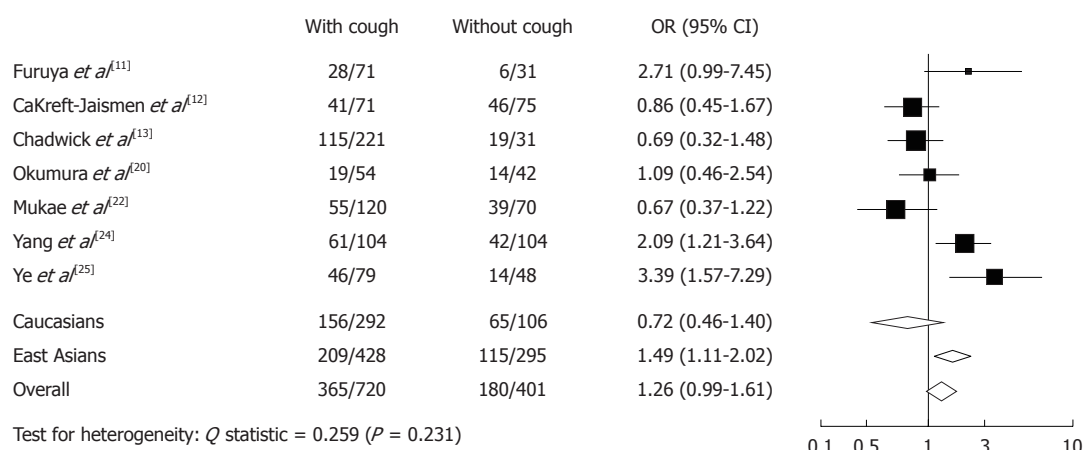
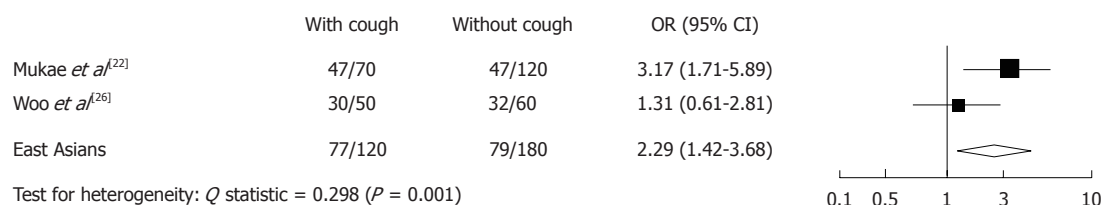
### Racial difference

In Caucasians, the genotype frequencies of ACE were 22.7% for *I/I*, 42.5% for *I/D*, and 34.8% for *D/D*. In East Asians, the genotype frequencies of ACE were 38.6% for *I/I*, 47.1% for *I/D*, and 14.3% for *D/D*. The distributions of genotypes in Caucasians and East Asians with ACEI-related cough differed significantly ( $\chi^2 = 103.299$ ,  $P < 0.01$ ).

Three studies demonstrated differences in the distributions of ACE genotypes by gender. The genotype frequencies of ACE were 44.4% for *I/I*, 46.3% for *I/D*,

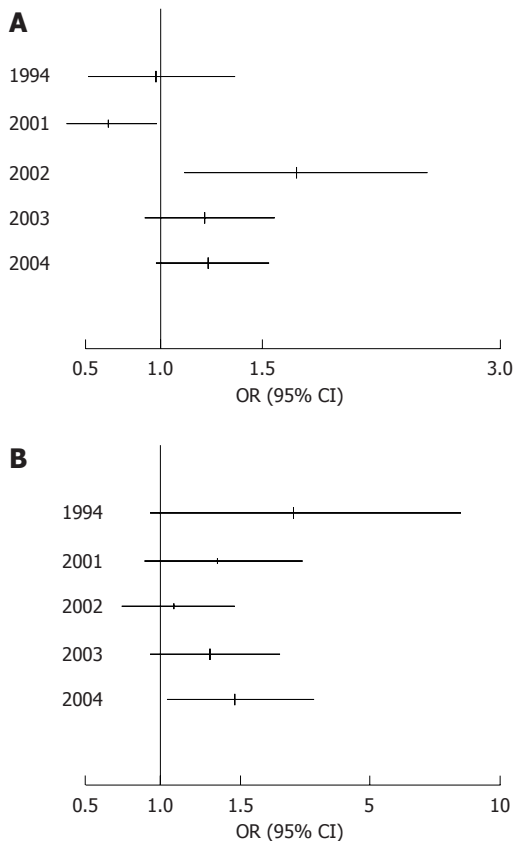
**Table 2 Odds ratios and heterogeneity results for the genetic contrasts of ACE I/D and bradykinin B<sub>2</sub> receptor gene polymorphisms**

	Genetic contrast	Population	Studies	Random effects [OR (95% CI)]	P value Q test	Z
Angiotensin converting enzyme	<i>D vs I</i>	All	7	1.15 (0.87-1.52)	0.259	0.231
		Caucasians	2	0.90 (0.60-1.35)	0.799	0.612
		East Asians	5	1.49 (1.11-2.02)	0.226	0.009
	<i>DD vs (DI + II)</i>	All	11	0.85 (0.67-1.06)	0.005	0.153
		Caucasians	3	1.14 (0.74-1.76)	0.716	0.563
		East Asians	8	0.76 (0.58-0.99)	0.003	0.042
	<i>(DD + II) vs II</i>	All	11	1.22 (0.91-1.64)	0.052	0.133
		Caucasians	3	0.84 (0.46-1.55)	0.560	0.553
		East Asians	8	1.35 (0.91-2.00)	0.027	0.075
	<i>DD vs II</i>	All	11	0.79 (0.62-1.01)	0.008	0.058
		Caucasians	3	1.12 (0.69-1.83)	0.614	0.626
		East Asians	8	0.70 (0.53-0.93)	0.006	0.013
	<i>ID vs (DD + II)</i>	All	11	0.95 (0.80-1.22)	0.936	0.354
		Caucasians	3	0.97 (0.63-1.50)	0.889	0.900
Bradykinin B <sub>2</sub> receptor -58T/C	<i>T vs C</i>	East Asians	8	0.94 (0.79-1.13)	0.786	0.342
		East Asians	2	2.29 (1.42-3.68)	0.298	0.001
		East Asians	3	1.47 (0.56-3.85)	0.002	0.467
	<i>CC vs (TC + TT)</i>	East Asians	3	0.90 (0.66-1.24)	0.661	0.507
	<i>TC vs (TT + CC)</i>	East Asians	3	1.08 (0.87-1.34)	0.947	0.477

**Figure 2 Random effects odds ratio estimates with the corresponding 95% confidence interval of the ACE allele contrast for ACEI-related cough.** The odds ratio (OR) estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The confidence intervals of pooled estimates are displayed as a horizontal line through the diamond. The horizontal axis is plotted on a log scale. OR greater than 1 indicates increased risk of ACEI-induced cough.**Figure 3 Random effects odds ratio estimates with the corresponding 95% confidence interval of the bradykinin B<sub>2</sub> receptor allele contrast for ACEI-related cough.** The odds ratio (OR) estimate of each study is marked with a solid black square. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The confidence intervals of pooled estimates are displayed as a horizontal line through the diamond. The horizontal axis is plotted on a log scale. OR greater than 1 indicates increased risk of ACEI-induced cough.

and 9.3% for *D/D* in male subjects without cough. The genotype frequencies of ACE were 43.3% for *I/I*, 47.2% for *I/D*, and 9.5% for *D/D* in male subjects with cough. These differences were not statistically significant ( $\chi^2 =$

0.074, *P* = 0.96). On the other hand, the genotype frequencies of ACE were 44.4% for *I/I*, 46.3% for *I/D*, and 9.3% for *D/D* in female subjects without cough. The genotype frequencies of ACE were 39.5% for *I/I*, 43.7%



**Figure 4** Cumulative meta-analysis of the ACE allele contrast for ACEI-related cough. A: Entire population; B: East Asians. The random effects pooled odds ratio (OR) with the corresponding 95% CI at the end of each year-information step is shown. OR greater than 1 indicates increased risk of ACEI-induced cough.

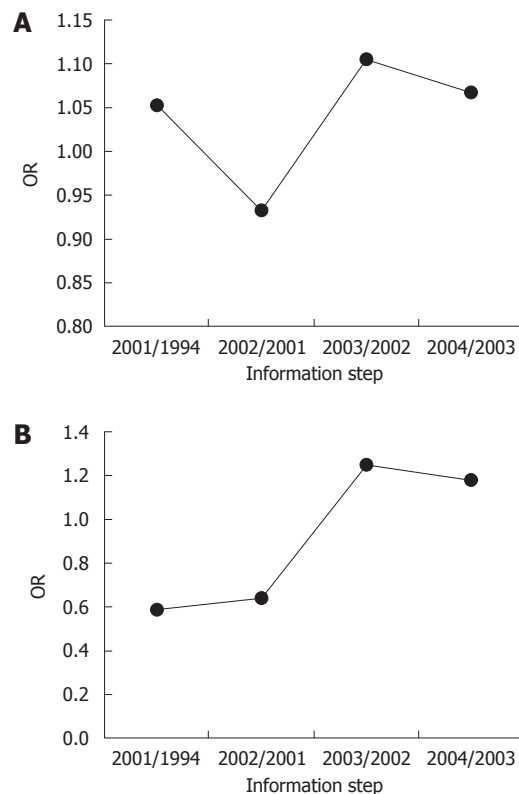
for *I/D*, and 16.7% for *D/D* in female subjects with cough. These differences were statistically significant ( $\chi^2 = 6.026$ ,  $P = 0.049$ ).

#### Potential bias

The cumulative meta-analysis of the allelic contrast for ACEI-related cough showed significant association as information accumulates in East Asians (Figure 4B) but not in all population (Figure 4A). In the recursive cumulative meta-analysis, the relative change in RE OR stabilized in a specific OR indicates that there is enough evidence to draw safe conclusions about the modifying effect of *ACE I/D* polymorphism in ACEI-related cough in East Asians (Figure 5B) but not in all population (Figure 5A).

#### Bradykinin B<sub>2</sub> receptor -58T/C

Bradykinin B<sub>2</sub> receptor -58T/C was investigated only in East Asians. The allelic frequencies of the bradykinin B<sub>2</sub> receptor gene were 0.56 for the C allele and 0.44 for the T allele in subjects without cough, and 0.36 and 0.64 in subjects with cough [OR = 2.25 (1.42-3.57)], respectively. The distributions of the T/C genotypes of the bradykinin B<sub>2</sub> receptor gene were 26% for CC, 50% for TC, and 24% for TT in the subjects without cough, and 30%,



**Figure 5** Recursive cumulative meta-analysis of the allele contrast (ACE *D* vs *I*) for ACEI-related cough. A: Entire population; B: East Asians. The relative change in random effects pooled odds ratio (OR) in each information step (OR in next year/OR in current year) for the allele contrast is shown.

52%, and 18% in the subjects with cough, respectively. The distributions of the T/C genotypes of the bradykinin B<sub>2</sub> receptor gene were significantly different ( $\chi^2 = 8.366$ ,  $P = 0.015$ ).

In the East Asians subgroup analysis, all studies investigating the association between bradykinin B<sub>2</sub> receptor -58T/C and ACEI-related cough, were included in the meta-analysis. The main analysis revealed no significant heterogeneity ( $pQ = 0.298$ ), and the random effects pooled OR was significant (RE OR = 2.29 (1.42-3.68)). There was significant heterogeneity for TT *vs* TC with TC ( $pQ = 0.002$ ). The distributions of the genotypes of the bradykinin B<sub>2</sub> receptor -58T/C polymorphism were 27% for TT, 52% for TC, and 21% for CC in men without cough, and 24% for TT, 53% for TC, and 23% for CC in men with cough. These values were 35% for TT, 46% for TC, and 19% for CC in women without cough, and 25% for TT, 52% for TC, and 23% for CC in women with cough. The distributions of the genotypes of the bradykinin B<sub>2</sub> receptor -58T/C polymorphism showed a trend for a significant difference in women ( $\chi^2 = 5.847$ ,  $P = 0.054$ ).

#### Assessment of publication bias

The funnel plot of the *ACE I/D* meta-analysis showed no asymmetry (Figure 6). This result suggested the absence of bias in the present meta-analysis.



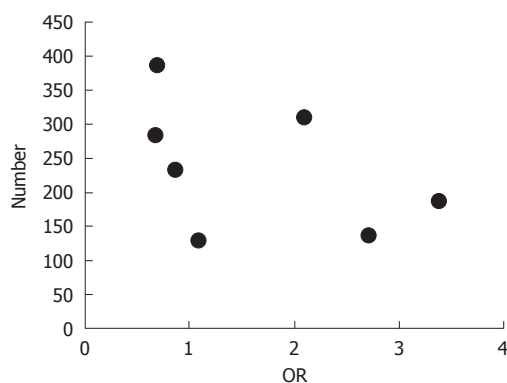


Figure 6 Funnel plot.

## DISCUSSION

In these meta-analyses, the studies offered inconclusive and in many cases contradictory results. The most widely investigated genetic polymorphisms were *ACE I/D* and bradykinin B<sub>2</sub> receptor T/C polymorphisms. Therefore, it is still controversial as to whether ACE and bradykinin polymorphisms are associated with ACEI-related cough. In our comprehensive meta-analysis, a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in the entire population and positive associations between ACE and bradykinin B<sub>2</sub> receptor polymorphisms and ACEI-related cough were observed in East Asians.

The specific mechanism by which ACEIs as a class cause cough is not firmly established. It is likely that increased levels of mediators outside the renin-angiotensin-aldosterone system cascade may be involved in the mechanism of cough. These mediators include kinins such as bradykinin, substance P, a neurotransmitter present in the respiratory tract, C-fibers and two bronchial inflammatory agents derived from arachidonic acid. Cough may be associated with ACE inhibition, not due to blockade of Ang II formation, but to inhibition of kinase II-related factors<sup>[27]</sup>.

A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans<sup>[7-9]</sup>. This symptom seems to be more prevalent in females than in males; in larger studies, two thirds of the affected patients were female<sup>[28]</sup>. Cough is also more common in nonsmokers than in smokers. Lee *et al.*<sup>[21]</sup> showed that ACEI-related cough mainly appeared in female patients with non-insulin dependent diabetes mellitus. Israili *et al.*<sup>[29]</sup> postulated that women have a low cough threshold and may report this adverse effect more often. Because cough is a class effect of ACEIs, and because its occurrence is not predicted by any external factors, it seems reasonable to suspect that a primary, genetically determined characteristic resulting in an alteration of drug action or drug metabolism may be responsible.

ACEI-related cough is thought to result from the interaction of multiple genetic factors. Since the *I/D* polymorphism is an intronic marker, it may be function-

ally neutral but is in strong linkage disequilibrium with another unobserved functional mutation within the ACE gene. A large majority of previous studies have shown a positive association between the *DD* genotype and an increased risk of myocardial infarction, but results in hypertension, left ventricular hypertension, cardiomyopathy and restenosis after percutaneous coronary intervention remain quite controversial. It was found that the frequency of genotype *II* in patients with cough was increased by 74% compared to patients without cough. It was suggested that a greater *I* allele frequency may increase genetic susceptibility to ACEI-related cough<sup>[11]</sup>. However, Kreft-Jais *et al.*<sup>[12]</sup> found no significant difference in *ACE* genotype. Chadwick *et al.*<sup>[13]</sup> demonstrated that the distribution of genotypes in British patients with ACEI-related cough and in Japanese patients with ACEI-related cough differed significantly. These results provide one possibility that East Asians experience more cough induced by ACEIs than Caucasians.

The risk of ACEI-related cough was consistent for the allele contrast, although the results showed significant heterogeneity. Heterogeneity may result from differences in sample selection, in genotyping methodology, or may be due to real differences in populations or due to interactions with other unknown risk factors<sup>[17]</sup>. The results of the meta-analysis were affected by population origin. East Asians showed statistically significant results under the *ACE* allele contrast, whereas Caucasians produced non-significant results. The link between ACEI-related cough and *I/D* polymorphism in the *ACE* gene suggests that ACEI-related cough is related to serum ACE concentration<sup>[24,30]</sup>. There was a lower frequency of the *DD* genotype in East Asians. Functional analyses of variation in the *ACE* gene have indicated that different loci control ACE levels in particular "racial" groups<sup>[31]</sup>. The *ACE I/D* polymorphism is associated with serum ACE activity, and patients with the *II* genotype have the lowest serum ACE levels compared with the *ID* and *DD* genotype; therefore the *II* genotype would be associated with an increased risk of developing cough<sup>[11]</sup>. The present study demonstrated that *ACE I/D* polymorphism showed a significant association with ACEI-related cough in East Asians, but not in the entire population or in Caucasians. The frequency of genotype *II* in patients with cough was significantly increased by 43% compared to patients without cough in East Asians. It is suggested there is a link between the *I* allele and an increased risk for ACEI-related cough in East Asians.

Bradykinins, a family of oligopeptides derived from the enzymatic action of kallikreins on kininogens, can promote all the major signs of inflammation, including hyperemia, leakage of plasma proteins, and pain<sup>[32-35]</sup>. Kinins act mainly as local hormones by activating specific receptors, known as B<sub>1</sub> and B<sub>2</sub> receptors, with most of the inflammatory and cardiovascular effects being mediated by the B<sub>2</sub> receptor<sup>[35,36]</sup>. Human bradykinin receptors are cell-surface G-protein-coupled receptors of the 7-transmembrane-domain superfamily<sup>[37]</sup>. The bradykinin

B<sub>2</sub> receptor gene has been implicated as one of the candidate genes involved in the complex genetic underpinnings of essential hypertension and cardiovascular diseases. Since B<sub>2</sub>-bradykinin receptor mediates most of the inflammatory actions of bradykinin and is widely present in most tissues<sup>[38,39]</sup>, a genetic defect of the bradykinin B<sub>2</sub> receptor may lead to altered biological activities of the functional protein.

Single nucleotide polymorphisms (SNPs) located in the coding or regulatory regions of genes are most likely to cause functional differences<sup>[40]</sup>. Although most SNPs have no effect on gene function, non-synonymous SNPs can serve as valuable markers<sup>[41]</sup>. Using promoter assay studies of genetic variants of the bradykinin receptor, -58T was found to have a higher transcriptional rate than that of -58C<sup>[42,43]</sup>, and it has been suggested that the transcriptional activity of the promoter might be involved in the appearance of ACEI-related cough<sup>[16]</sup>. The T/T genotype in the bradykinin B<sub>2</sub> receptor was the most sensitive compared to T/C and C/C, and this tendency was more prevalent among women<sup>[16]</sup>. The transcriptional activity of the bradykinin B<sub>2</sub> receptor promoter might be involved in the occurrence of ACEI-related cough, and high transcriptional activity of the bradykinin B<sub>2</sub> receptor promoter might induce ACEI-related cough<sup>[16]</sup>. The present study demonstrated that bradykinin T/C polymorphism showed a significant association with ACEI-related cough in East Asians.

In conclusion, many studies have tried to characterize the effects of *ACE I/D* and bradykinin B<sub>2</sub> receptor polymorphisms on ACEI-related cough. However, the reported results so far are discrepant and inconsistent. The relationship between *ACE* and bradykinin B<sub>2</sub> receptor genetic variation and ACEI-related cough remains an unresolved issue. In view of the available evidence, *ACE I/D* and bradykinin B<sub>2</sub> receptor polymorphisms contributed to the risk of ACEI-related cough in East Asians, but a negative association between *ACE I/D* polymorphism and ACEI-related cough was observed in Caucasians.

## COMMENTS

### Background

Studies in French or in British have not showed the relation between the angiotensin-converting enzyme genetic polymorphism and angiotensin-converting enzyme inhibitors (ACEI) related-cough. The role of genetic polymorphisms in ACEI-related cough remains controversial.

### Research frontiers

It is important to perform a worldwide trial in the whole world to evaluate this relation but it is impractical. The research have performed this meta-analysis to evaluate the association with genetic polymorphisms and ACEI-related cough, and the race- or ethnicity-related difference in the prevalence of cough attributed to ACEI therapy.

### Innovations and breakthroughs

This results proved the reason why a high incidence of cough has been reported in the Asians.

### Peer review

The current meta-analysis by Nishio *et al* investigates the relation between *ACE I/D* and Bradykinin SNP's on the development of cough in different ethnic populations. The subject of the meta-analysis is relevant for daily clinical practice as

cough is a major limitation of ACEi usage.

## REFERENCES

- Fuller RW, Choudry NB. Increased cough reflex associated with angiotensin converting enzyme inhibitor cough. *Br Med J (Clin Res Ed)* 1987; **295**: 1025-1026
- Bucknall CE, Neilly JB, Carter R, Stevenson RD, Semple PF. Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. *Br Med J (Clin Res Ed)* 1988; **296**: 86-88
- Yeo WW, Ramsay LE, Morice AH. ACE inhibitor cough: a genetic link? *Lancet* 1991; **337**: 187
- Andrejak M, Andrejak MT, Osterman G. Enalapril, captopril, and cough. *Arch Intern Med* 1988; **148**: 249
- Karpman L. Cough from ACE inhibitors. *Am Heart J* 1988; **116**: 1658
- McEwan JR, Choudry N, Street R, Fuller RW. Change in cough reflex after treatment with enalapril and ramipril. *BMJ* 1989; **299**: 13-16
- Chan WK, Chan TY, Luk WK, Leung VK, Li TH, Critchley JA. A high incidence of cough in Chinese subjects treated with angiotensin converting enzyme inhibitors. *Eur J Clin Pharmacol* 1993; **44**: 299-300
- Ding PY, Hu OY, Pool PE, Liao W. Does Chinese ethnicity affect the pharmacokinetics and pharmacodynamics of angiotensin-converting enzyme inhibitors? *J Hum Hypertens* 2000; **14**: 163-170
- Schelleman H, Klungel OH, van Duijn CM, Witteman JC, Hofman A, de Boer A, Stricker BH. Drug-gene interaction between the insertion/deletion polymorphism of the angiotensin-converting enzyme gene and antihypertensive therapy. *Ann Pharmacother* 2006; **40**: 212-218
- Lee EJ. Population genetics of the angiotensin-converting enzyme in Chinese. *Br J Clin Pharmacol* 1994; **37**: 212-214
- Furuya K, Yamaguchi E, Hirabayashi T, Itoh A, Hizawa N, Ohnuma N, Kawakami Y. Angiotensin-I-converting enzyme gene polymorphism and susceptibility to cough. *Lancet* 1994; **343**: 354
- Kreft-Jais C, Laforest L, Bonnardeaux A, Dumont C, Plouin PF, Jeunemaitre X. ACE inhibitors, cough, and genetics. *Lancet* 1994; **343**: 740
- Chadwick IG, Yeo WW, Higgins KS, Jackson PR, Ramsay LE, Morice AH. ACE inhibitors, cough, and genetics. *Lancet* 1994; **343**: 740-741
- Morice AH, Turley AJ, Linton TK. Human ACE gene polymorphism and distilled water induced cough. *Thorax* 1997; **52**: 111-113
- Zee RY, Rao VS, Paster RZ, Sweet CS, Lindpaintner K. Three candidate genes and angiotensin-converting enzyme inhibitor-related cough: a pharmacogenetic analysis. *Hypertension* 1998; **31**: 925-928
- Mukae S, Aoki S, Itoh S, Iwata T, Ueda H, Katagiri T. Bradykinin B(2) receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. *Hypertension* 2000; **36**: 127-131
- Zintzaras E, Lau J. Synthesis of genetic association studies for pertinent gene-disease associations requires appropriate methodological and statistical approaches. *J Clin Epidemiol* 2008; **61**: 634-645
- Zintzaras E, Raman G, Kitsios G, Lau J. Angiotensin-converting enzyme insertion/deletion gene polymorphic variant as a marker of coronary artery disease: a meta-analysis. *Arch Intern Med* 2008; **168**: 1077-1089
- Yeo WW, Higgins KS, Morice AH, Jackson PR, Peack JR, Ramsay LE. Investigation of the relation between ACE gene polymorphisms and ACE inhibition cough. *Br J Clin Pharmacol* 1993; **35**: 66P
- Okumura H, Nishimura E, Kariya S, Ohtani M, Uchino K, Fukatsu T, Odanaka J, Takahashi T, Watanabe K, Itoh T,

- Hashiguchi M, Echizen H, Rikihisa T. [No relation between angiotensin-converting enzyme (ACE) inhibitor-induced cough and ACE gene polymorphism, plasma bradykinin, substance P and ACE inhibitor concentration in Japanese patients]. *Yakugaku Zasshi* 2001; **121**: 253-257
- 21 Lee YJ, Tsai JC. Angiotensin-converting enzyme gene insertion/deletion, not bradykinin B2 receptor -58T/C gene polymorphism, associated with angiotensin-converting enzyme inhibitor-related cough in Chinese female patients with non-insulin-dependent diabetes mellitus. *Metabolism* 2001; **50**: 1346-1350
- 22 Mukae S, Itoh S, Aoki S, Iwata T, Nishio K, Sato R, Katagiri T. Association of polymorphisms of the renin-angiotensin system and bradykinin B2 receptor with ACE-inhibitor-related cough. *J Hum Hypertens* 2002; **16**: 857-863
- 23 Lu J, Li LM, Zhan SY, Yang HY, Li XH, Cao WH, Hu YH. Study on candidate genes of benazepril related cough in Chinese hypertensives. *Zhonghua Liuxingbingxue Zazhi* 2003; **24**: 498-502
- 24 Yang SM, He QY, Miao YD. [The relationship between polymorphism of angiotensin converting enzyme gene and cough caused by angiotensin converting enzyme inhibitors]. *Zhonghua Jiehe He Huxi Zazhi* 2003; **26**: 203-205
- 25 Ye RJ, He QY, Gai J, Shang Y. [A prospective study on the cough mechanism induced by angiotensin-converting enzyme inhibitors in patients with hypertension]. *Zhonghua Jiehe He Huxi Zazhi* 2004; **27**: 581-584
- 26 Woo SW, Bang S, Chung MW, Jin SK, Kim YS, Lee SH. Lack of association between ACE and bradykinin B2 receptor gene polymorphisms and ACE inhibitor-induced coughing in hypertensive Koreans. *J Clin Pharm Ther* 2009; **34**: 561-567
- 27 Lacourcière Y, Brunner H, Irwin R, Karlberg BE, Ramsay LE, Snavely DB, Dobbins TW, Faison EP, Nelson EB. Effects of modulators of the renin-angiotensin-aldosterone system on cough. Losartan Cough Study Group. *J Hypertens* 1994; **12**: 1387-1393
- 28 Stoller JK, Elghazawi A, Mehta AC, Vidt DG. Captopril-induced cough. *Chest* 1988; **93**: 659-661
- 29 Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992; **117**: 234-242
- 30 Takahashi T, Yamaguchi E, Furuya K, Kawakami Y. The ACE gene polymorphism and cough threshold for capsaicin after cilazapril usage. *Respir Med* 2001; **95**: 130-135
- 31 McKenzie CA, Abecasis GR, Keavney B, Forrester T, Ratcliffe PJ, Julier C, Connell JM, Bennett F, McFarlane-Anderson N, Lathrop GM, Cardon LR. Trans-ethnic fine mapping of a quantitative trait locus for circulating angiotensin I-converting enzyme (ACE). *Hum Mol Genet* 2001; **10**: 1077-1084
- 32 Dray A, Perkins M. Bradykinin and inflammatory pain. *Trends Neurosci* 1993; **16**: 99-104
- 33 Bhoola KD, Figueroa CD, Worthy K. Bioregulation of kinins: kallikreins, kininogens, and kininases. *Pharmacol Rev* 1992; **44**: 1-80
- 34 Regoli D, Barabé J. Pharmacology of bradykinin and related kinins. *Pharmacol Rev* 1980; **32**: 1-46
- 35 Burch RM, Kyle DJ. Recent developments in the understanding of bradykinin receptors. *Life Sci* 1992; **50**: 829-838
- 36 Regoli D, Rhaleb NE, Drapeau G, Dion S. Kinin receptor subtypes. *J Cardiovasc Pharmacol* 1990; **15** Suppl 6: S30-S38
- 37 Pesquero JB, Lindsey CJ, Zeh K, Paiva AC, Ganten D, Bader M. Molecular structure and expression of rat bradykinin B2 receptor gene. Evidence for alternative splicing. *J Biol Chem* 1994; **269**: 26920-26925
- 38 Braun A, Kammerer S, Böhme E, Müller B, Roscher AA. Identification of polymorphic sites of the human bradykinin B2 receptor gene. *Biochem Biophys Res Commun* 1995; **211**: 234-240
- 39 Lung CC, Chan EK, Zuraw BL. Analysis of an exon 1 polymorphism of the B2 bradykinin receptor gene and its transcript in normal subjects and patients with C1 inhibitor deficiency. *J Allergy Clin Immunol* 1997; **99**: 134-146
- 40 Brookes AJ. The essence of SNPs. *Gene* 1999; **234**: 177-186
- 41 Collins FS, Brooks LD, Chakravarti A. A DNA polymorphism discovery resource for research on human genetic variation. *Genome Res* 1998; **8**: 1229-1231
- 42 Kammerer S, Braun A, Arnold N, Roscher AA. The human bradykinin B2 receptor gene: full length cDNA, genomic organization and identification of the regulatory region. *Biochem Biophys Res Commun* 1995; **211**: 226-233
- 43 Braun A, Kammerer S, Maier E, Böhme E, Roscher AA. Polymorphisms in the gene for the human B2-bradykinin receptor. New tools in assessing a genetic risk for bradykinin-associated diseases. *Immunopharmacology* 1996; **33**: 32-35

S- Editor Cheng JX L- Editor Webster JR E- Editor Zheng XM