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

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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 B2 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 B2 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 B2 receptor gene were significantly different [OR = 2.25 (1.42-3.57)]. The distributions of the T/C genotypes of the bradykinin B2 receptor gene were significantly different (χ² = 8.366, P = 0.015). The meta-analyses revealed that there was a significant association between the bradykinin B2 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 B2 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.

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

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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\(^{[1,2]}\). 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\(^{[3]}\).

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\(^{[4]}\).

ACEI-related cough occurs in about 10%-20% of treated patients\(^{[4-6]}\). A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans\(^{[7,8]}\), among whom the population prevalence of the I allele is high\(^{[9]}\). Some studies showed the relationship between the ACE I/D genetic polymorphism and ACEI-related cough\(^{[10-12]}\). Furuya et al.\(^{[13]}\) 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\(^{[12,13]}\). 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\(_2\) receptors\(^{[14-16]}\). 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 associations 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\(_2\) 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 (DD vs DD/II) models, and the association between bradykinin B\(_2\) receptor -58 T/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\(^{[17]}\). 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\(^{[17,18]}\). 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\(^{[19]}\).

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\(^{[11,13,19-26]}\) 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\(_2\) receptor polymorphism (300 East Asians, Table 1). 19 meta-analyses were conducted...
for these 2 gene polymorphisms of angiotensin-convert-
ing enzyme deletion/insertion (ACE D/I) and bradykinin B2 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 ACE and bradykinin B2 receptor polymorphisms in patients 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)] and 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 (γ² = 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,
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% for

| Genetic contrast | Population | Studies | Random effects [OR (95% CI)] | $P$ value | Q test | Z |
|------------------|------------|---------|-----------------------------|-----------|--------|----|
| Angiotensin converting enzyme | D vs 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 |
| | DD vs (DI + II) | 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 |
| | (DD + I) vs II | 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 |
| | DD vs II | 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 |
| | ID vs (DD + II) | All | 11 | 0.95 (0.80-1.22) | 0.936 | 0.354 |
| | | Caucasians | 3 | 0.97 (0.63-1.50) | 0.889 | 0.900 |
| | | East Asians | 8 | 0.94 (0.79-1.13) | 0.786 | 0.342 |
| Bradykinin B-receptor -588T/C | T vs C | East Asians | 2 | 2.29 (1.42-3.68) | 0.298 | 0.001 |
| | TT vs (TC + CC) | East Asians | 3 | 1.47 (0.56-3.85) | 0.002 | 0.467 |
| | CC vs (TC + TT) | East Asians | 3 | 0.90 (0.66-1.24) | 0.661 | 0.507 |
| | TC vs (TT + CC) | 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-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% for
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 B2 receptor -58T/C**

Bradykinin B2 receptor -58T/C was investigated only in East Asians. The allelic frequencies of the bradykinin B2 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 B2 receptor gene were 26% for CC, 50% for TC, and 24% for TT in the subjects without cough, and 30%, 52%, and 18% in the subjects with cough, respectively. The distributions of the T/C genotypes of the bradykinin B2 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 B2 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 B2 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 B2 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.
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![Figure 6 Funnel plot.](image)

**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 B2 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 B2 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.

A high incidence of cough has been reported in the Chinese population compared to only 20% in Europeans. This symptom seems to be more prevalent in females than in males; in larger studies, two thirds of the affected patients were female. Cough is also more common in nonsmokers than in smokers. Lee et al. showed that ACEI-related cough mainly appeared in female patients with non-insulin dependent diabetes mellitus. Israilli et al. 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 functionally 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. However, Kreft-Jais et al. found no significant difference in ACE genotype. Chadwick et al. 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. 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. 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. 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. 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. Ki-nins act mainly as local hormones by activating specific receptors, known as B1 and B2 receptors, with most of the inflammatory and cardiovascular effects being mediated by the B2 receptor. Human bradykinin receptors are cell-surface G-protein-coupled receptors of the 7-transmembrane-domain superfamily. The bradykinin
B2 receptor gene has been implicated as one of the candidate genes involved in the complex genetic underpinnings of essential hypertension and cardiovascular diseases. Since B2-bradykinin receptor mediates most of the inflammatory actions of bradykinin and is widely present in most tissues, a genetic defect of the bradykinin B2 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. Although most SNPs have no effect on gene function, non-synonymous SNPs can serve as valuable markers. Using promoter assay studies of genetic variants of the bradykinin receptor, -58T was found to have a higher transcriptional rate than that of -58C, and it has been suggested that the transcriptional activity of the promoter might be involved in the appearance of ACEI-related cough. The T/T genotype in the bradykinin B2 receptor was the most sensitive compared to T/C and C/C, and this tendency was more prevalent among women. The transcriptional activity of the bradykinin B2 receptor promoter might be involved in the occurrence of ACEI-related cough, and high transcriptional activity of the bradykinin B2 receptor promoter might induce ACEI-related cough. 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 B2 receptor polymorphisms on ACEI-related cough. However, the reported results so far are discrepant and inconsistent. The relationship between ACE and bradykinin B2 receptor genetic variation and ACEI-related cough remains an unresolved issue. In view of the available evidence, ACE I/D and bradykinin B2 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.

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