Angiotensin-converting enzyme I/D polymorphism and aortic aneurysm risk: a meta-analysis

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Abstract

OBJECTIVES: Angiotensin-converting enzyme (ACE) I/D polymorphism has been implicated in aortic aneurysm risk, but individual published studies show inconclusive results. The aim of this study was to explore a more precise estimation of its relation with aortic aneurysm using meta-analysis.

METHODS: Electronic searches of PubMed and EMBASE databases were conducted for all publications through February 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to access the strength of this association in the random-effects model or fixed-effects model.

RESULTS: Fourteen case–control studies, including a total of 3938 cases and 5748 controls, were included. This meta-analysis showed a significant association between ACE I/D polymorphism and aortic aneurysm risk (OR = 1.53, 95% CI 1.26–1.87, P < 0.01). In the subgroup analysis by ethnicity, a statistically significant association was found in Caucasians (OR = 1.46, 95% CI 1.20–1.77, P < 0.01), but not in Asians. In the subgroup analysis by type of aortic aneurysm, this polymorphism was significantly associated with abdominal aortic aneurysm risk (OR = 1.38, 95% CI 1.10–1.74, P < 0.01), thoracic aortic aneurysm risk (OR = 1.59, 95% CI 1.11–2.29, P = 0.01) and aortic dissection risk (OR = 2.43, 95% CI 1.07–5.52, P = 0.03). Stratification by hypertension status showed that hypertensive patients with this polymorphism were associated with increased aortic aneurysm risk (OR = 1.47, 95% CI 1.03–2.09, P = 0.03), whereas normotensive individuals with this polymorphism did not have an increased aortic aneurysm risk.

CONCLUSIONS: This meta-analysis suggested that ACE I/D polymorphism was associated with aortic aneurysm risk.

Keywords: Angiotensin-converting enzyme • Polymorphism • Aortic aneurysm • Meta-analysis

INTRODUCTION

Aortic aneurysm is a serious disease that can lead to death if it ruptures. Thus, determining the high-risk population is urgently needed for preventive care and early detection. Hypertension, smoking, obesity and environmental risk factors have important roles in the development of aortic aneurysms. However, only a small percent of individuals exposed to the known risk factors develop aortic aneurysms, whereas many patients develop aortic aneurysms even without those risk factors, which suggests that genetic factors have an important role in aortic aneurysms.

Angiotensin-converting enzyme (ACE) is a key zinc metallopeptidase that catalyses the conversion of angiotensin I to angiotensin II. ACE is highly expressed in the aneurysmal vascular wall, in both human disease and animal models [1]. ACE inhibitors protected against aortic expansion and rupture in animal models of aortic aneurysm [2]. In addition, ACE inhibitors were associated with a decreased risk of aneurysm rupture in a clinical study [3]. Thus, ACE might be critical in aortic aneurysm development because of the relation between the renin–angiotensin system (RAS) and blood pressure, which is a known risk factor for aortic aneurysm.

The ACE gene is located in chromosome 17q23.3. In intron 16 of this gene, a polymorphism comprising an insertion (I) or a deletion (D) of a 287-bp Alu repeat sequence has been identified that results in three genotypes: homozygous DD, II and heterozygous ID [4]. This I/D polymorphism within the ACE gene has been associated with many diseases, such as myocardial infarction [5]. The ACE I/D polymorphism could account for approximately half of the observed variance in ACE levels [4]. Individuals who are homozygous for the D allele have the highest levels of ACE, those who are homozygous for the I allele have the lowest and heterozygous individuals have an intermediate level [4].

Many studies have evaluated the association between ACE I/D polymorphism and aortic aneurysm risk, but the results are conflicting [6–19]. Thus, the association between ACE I/D polymorphism and aortic aneurysm risk is still uncertain. Therefore, we conducted this meta-analysis.
METHODS

Publication search

PubMed and EMBASE were searched to identify relevant published articles. The keywords used were as follows: (’angiotensin-converting enzyme’ or ’ACE’) and (’aortic aneurysm’ or ’thoracic aortic aneurysm’ or ’aortic dissection’) and (’polymorphism’ or ’mutation’). The last search date was 12 February 2014. The language of the papers was not restricted. All references cited in these studies and previously published review articles were retrieved for additional eligible studies.

Study selection

Studies were included if all of the following conditions were met: (i) evaluation of the association of ACE I/D polymorphism and aortic aneurysm risk; (ii) a case-control study or cohort study; and (iii) an available genotype or allele frequency for estimating an odds ratio (OR) with a 95% confidence interval (CI). When authors reported two or more publications on possibly the same patient populations, only the most recent or complete study was included in the review to avoid overlap between the cohorts. The major reasons for exclusion of studies were as follows: (i) family studies; (ii) containing overlapping data; and (iii) review papers or abstracts.

Data extraction

Data were extracted by two investigators independently. The following data were extracted from each article: first author’s surname, publication year, ethnicity, age, type of aortic aneurysm, numbers of the cases and controls, hypertension status and adjustment.

RESULTS

Eligible studies

Fourteen case-control studies, including 3938 cases and 5748 controls, were included in this meta-analysis, [6–19]. One study reported three independent case-control studies; thus, a total of

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Age</th>
<th>Disease type</th>
<th>Hypertension</th>
<th>Case</th>
<th>Control</th>
<th>Adjustment</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamano</td>
<td>1999</td>
<td>Asian</td>
<td>69</td>
<td>AAA</td>
<td>Mixed</td>
<td>125</td>
<td>153</td>
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<td>Yes</td>
</tr>
<tr>
<td>Pola</td>
<td>2001</td>
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<td>73</td>
<td>AAA</td>
<td>Mixed</td>
<td>124</td>
<td>112</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fatini</td>
<td>2005</td>
<td>Caucasian</td>
<td>72</td>
<td>AAA</td>
<td>Mixed</td>
<td>250</td>
<td>250</td>
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<td>Yes</td>
</tr>
<tr>
<td>Jones 1</td>
<td>2008</td>
<td>Caucasian</td>
<td>70</td>
<td>AAA</td>
<td>Mixed</td>
<td>576</td>
<td>472</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jones 2</td>
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<td>72</td>
<td>AAA</td>
<td>Mixed</td>
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<td>77</td>
<td>AAA</td>
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<td>339</td>
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<td>57</td>
<td>AD</td>
<td>All</td>
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<td>AD</td>
<td>Mixed</td>
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<tr>
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<td>68</td>
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<td>Mixed</td>
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<td>544</td>
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<td>201</td>
<td>252</td>
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<tr>
<td>Obukofe</td>
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<td>65</td>
<td>AAA</td>
<td>Mixed</td>
<td>1155</td>
<td>996</td>
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<tr>
<td>Lesauskaite</td>
<td>2011</td>
<td>Caucasian</td>
<td>61</td>
<td>TAA</td>
<td>Mixed</td>
<td>103</td>
<td>773</td>
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<td>Foffa</td>
<td>2012</td>
<td>Caucasian</td>
<td>59</td>
<td>TAA</td>
<td>Mixed</td>
<td>216</td>
<td>300</td>
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<td>No</td>
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<tr>
<td>Fisano</td>
<td>2012</td>
<td>Caucasian</td>
<td>54</td>
<td>TAA</td>
<td>Mixed</td>
<td>24</td>
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<td>Yes</td>
</tr>
<tr>
<td>Balistri</td>
<td>2013</td>
<td>Caucasian</td>
<td>66</td>
<td>TAA</td>
<td>Mixed</td>
<td>110</td>
<td>128</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jing</td>
<td>2013</td>
<td>Asian</td>
<td>67</td>
<td>AD</td>
<td>Mixed</td>
<td>161</td>
<td>256</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


*AData of hypertension and normotensive patients can be extracted.

Statistical analysis

For each case–control study, the Hardy–Weinberg equilibrium (HWE) of genotypes in the control group was assessed by using a \( \chi^2 \) test. OR and 95% confidence intervals (CI) were applied to determine the strength of the association between I/D polymorphism and aortic aneurysm risk. Given that the ACE DD genotype is associated with the highest ACE levels, we calculated the odds ratio (OR) and respective 95% CI by comparing DD versus ID + II. We used the Q statistic to assess the degree of heterogeneity between the studies, and a \( P < 0.1 \) was interpreted as significant heterogeneity among the studies. In addition, the \( I^2 \) index expressing the percentage of the total variation across studies because of heterogeneity was also calculated to further assess the between-study heterogeneity. \( I^2 \) values of 25, 50 and 75% were used as evidence of low, moderate and high heterogeneity, respectively. If heterogeneity existed, the random-effects model (the DerSimonian and Laird method) was adopted to calculate the overall OR value. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used. Subgroup analyses were carried out by ethnicity, type of aortic aneurysm and hypertension status. We carried out a cumulative meta-analysis. Sensitivity analyses were carried out by omitting each study in turn. We also conducted the sensitivity analyses by excluding studies not in HWE, with small sample size (n < 200) and without adjusting confounding factors. To explore the source of the heterogeneity, Galbraith plots were used. A funnel plot was used to assess the evidence for potential publication bias. All statistical tests were performed by using the STATA 12.0 software (Stata Corporation, College Station, TX, USA).
16 case–control studies was included. Table 1 summarizes the main characteristics of the included studies. Most of the studies were performed in a Caucasian population, whereas only three studies were conducted in an Asian population. There were nine studies of abdominal aortic aneurysm (AAA), four studies of thoracic aortic aneurysm (TAA) and three studies of aortic dissection (AD). Detailed data of hypertension status could be extracted from four studies. Six studies reported adjusted ORs and 95% CIs. There was only one study not in HWE.

Meta-analysis

When all 16 studies were pooled into the meta-analysis, significant heterogeneity was observed ($I^2 = 64\%$, $P < 0.01$); thus, the random-effects model was used to pool the results. The pooled OR was 1.53 (95% CI 1.26–1.87, $P < 0.01$, Fig. 1). In the subgroup analysis by ethnicity, a statistically significant association was found in Caucasians (OR = 1.46, 95% CI 1.20–1.77, $P < 0.01$), but not in Asians (OR = 2.26, 95% CI 0.97–5.29, $P = 0.06$). In the subgroup analysis by type of aortic aneurysm, this polymorphism was significantly associated with AAA risk (OR = 1.38, 95% CI 1.10–1.74, $P < 0.01$), TAA risk (OR = 1.59, 95% CI 1.11–2.29, $P = 0.01$) and AD risk (OR = 2.43, 95% CI 1.07–5.52, $P = 0.03$). Stratification by hypertension status showed that hypertensive patients with this polymorphism were associated with an increased aortic aneurysm risk (OR = 1.47, 95% CI 1.03–2.09, $P = 0.03$), whereas normotensive individuals with this polymorphism did not have an increased aortic aneurysm risk (OR = 2.35, 95% CI 0.80–6.90, $P = 0.12$). Table 2 lists the main results of this meta-analysis.

As shown in Fig. 2, cumulative meta-analysis showed that the pooled ORs tended to be stable. Sensitivity analysis was used to evaluate the stability of the results. The results were not changed when each study was excluded, suggesting the robustness of the results (Fig. 3). When we limited the meta-analysis to studies that controlled for confounding factors, the result was still statistically significant (OR = 1.55, 95% CI 1.29–1.87, $P < 0.01$). In addition, no significantly altered result was shown when excluding the studies not in HWE (OR = 1.57, 95% CI 1.27–1.94, $P < 0.01$). In an analysis limited to studies with a large sample size, a significant association between ACE I/D polymorphism and increased aortic aneurysm risk remained (OR = 1.35, 95% CI 1.06–1.71, $P = 0.01$). Table 3 lists the main results of the sensitivity analysis.

There was significant heterogeneity ($I^2 = 64\%$, $P < 0.01$). The Galbraith plot was used to find the source of the heterogeneity. As shown in Fig. 4, five studies were the outliers [8, 11, 14, 18, 19]. When these five studies were excluded, the heterogeneity disappeared ($I^2 = 0\%$, $P = 0.54$). In addition, the result was still statistically significant (OR = 1.40, 95% CI 1.21–1.63, $P < 0.01$). The shape of the funnel plot did not show obvious asymmetry (Fig. 5).

**DISCUSSION**

In this meta-analysis, we investigated the association between ACE I/D polymorphism and aortic aneurysm risk, including 3938 cases and 5748 controls. We found that individuals with the DD genotype had an increased risk of aortic aneurysm. This result suggested that the DD genotype carriers had 53% increased aortic aneurysm risk compared with the ID or II genotype carriers. In the stratified
analysis by ethnicity, the significant association was observed in Caucasians but not in Asians. However, there were only three studies on Asians for this polymorphism. Therefore, it was possible that the observed ethnic difference might be the result of chance. Additionally, the main result was still significant after combining the adjusted ORs.

Functional disturbances of the RAS are associated with many cardiovascular disorders, including aortic aneurysm [23]. The most direct verification of a role of the RAS in aortic aneurysm is the demonstration of aneurysmal formation induced by subcutaneous infusion of angiotensin II into normal or obese C57BL/6 mice [24]. Liao et al. documented that, in an elastase-perfused AAA model in rats, ACE inhibitors reduced elastin degradation and decreased the AAA diameter [2]. In addition, Hackam et al. demonstrated that ACE inhibitors reduced the risk of rupture in AAA [3]. Infusion of angiotensin II also promoted pathologies that were localized to the thoracic aorta. This was first detected during angiotensin II infusion into normal C57BL/6 mice [25]. Dissections of the ascending aorta occurred within 6–10 days after initiating angiotensin II infusion. It was believed that the ACE I allele might have a silencing effect resulting in the production of angiotensin II with a dose-dependent effect [3]. Thus, all these observations could support a potential role of the ACE gene I/D polymorphism in the development of aortic aneurysm.

Sensitivity analysis and cumulative meta-analysis results revealed that our results were stable. Heterogeneity is one of the important issues when performing meta-analysis. Galbraith plots were applied to detect the sources of heterogeneity. The I² value was decreased when the outliers were excluded. This result suggested that these outliers are the major source of the heterogeneity. Additionally, the main result was still significant when the outliers were excluded. Funnel plots suggested that no significant publication bias was found. Taken together, the results of this meta-analysis were reliable.

There were some limitations in this meta-analysis. Firstly, we only included published articles in this meta-analysis. Thus, some relevant unpublished studies might have been missed. Secondly, we did not perform subgroup analyses by age, sex, obesity or other variables. This might have caused a serious confounding bias. Finally, we did not assess the potential gene–gene and

Table 2: Summary of results from meta-analysis and subgroup analysis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Subgroup</th>
<th>No. of studies</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD vs ID + II</td>
<td>Overall</td>
<td>16</td>
<td>1.53 (1.26–1.87)</td>
<td>&lt;0.01</td>
<td>64</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>Asian</td>
<td>3</td>
<td>2.26 (0.97–5.29)</td>
<td>0.06</td>
<td>78</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>Caucasian</td>
<td>13</td>
<td>1.46 (1.20–1.77)</td>
<td>&lt;0.01</td>
<td>59</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>AAA</td>
<td>9</td>
<td>1.38 (1.10–1.74)</td>
<td>&lt;0.01</td>
<td>60</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>TAA</td>
<td>4</td>
<td>1.59 (1.11–2.29)</td>
<td>0.01</td>
<td>53</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>AD</td>
<td>3</td>
<td>2.43 (1.07–5.52)</td>
<td>0.03</td>
<td>67</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>Hypertension</td>
<td>4</td>
<td>1.47 (1.03–2.09)</td>
<td>0.03</td>
<td>0</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>Normotensive</td>
<td>3</td>
<td>2.35 (0.80–6.90)</td>
<td>0.12</td>
<td>85</td>
</tr>
</tbody>
</table>

AAA: abdominal aortic aneurysm; AD: aortic dissection; TAA: thoracic aortic aneurysm; OR: odds ratio; CI: confidence interval.

Figure 2: Cumulative meta-analysis for the association between aortic aneurysm risk and the ACE I/D polymorphism. OR: odds ratio; 95% CI: 95% confidence interval.
Figure 3: Sensitivity analysis of the summary odds ratio coefficients on the association of ACE I/D polymorphism with aortic aneurysm risk.

Table 3: Summary of results from sensitivity analyses

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Characteristics</th>
<th>No. of studies</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>$i^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD vs ID + II</td>
<td>Adjustment</td>
<td>8</td>
<td>1.55 (1.29–1.87)</td>
<td>&lt;0.01</td>
<td>13</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>HWE</td>
<td>15</td>
<td>1.57 (1.27–1.94)</td>
<td>&lt;0.01</td>
<td>66</td>
</tr>
<tr>
<td>DD vs ID + II</td>
<td>$n \geq 200$</td>
<td>7</td>
<td>1.35 (1.06–1.71)</td>
<td>0.01</td>
<td>63</td>
</tr>
</tbody>
</table>

HWE: Hardy–Weinberg equilibrium; OR: odds ratio; 95% CI: 95% confidence interval.

Figure 4: Galbraith plot of aortic aneurysm risk and the ACE I/D polymorphism.
gene–environment interactions because of lack of sufficient information. Finally, all of the included studies were performed in Asians and Caucasians. Further studies in other ethnic groups, especially Africans and Hispanics, are needed to confirm the results of this meta-analysis.

In conclusion, this study suggested that ACE I/D polymorphism is associated with an increased risk of aortic aneurysm. More studies are warranted to validate this finding in different populations.

Conflict of interest: none declared.

REFERENCES


