Low Potentiality of Angiotensin-Converting Enzyme Gene Insertion/Deletion Polymorphism as a Useful Predictive Marker for Carotid Atherogenesis in a Large General Population of a Japanese City

The Suita Study

Toshifumi Mannami, MD, PhD; Tomohiro Katsuya, MD, PhD; Shunroku Baba, MD, PhD; Nozomu Inamoto, MD; Kazuhiko Ishikawa, MD, PhD; Jitsuo Higaki, MD, PhD; Toshio Ogihara, MD, PhD; Jun Ogata, MD, PhD

Background and Purpose—Some previous studies, almost all western, have investigated whether there is a relationship between the insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) and carotid atherosclerosis. The results, however, have not been consistently positive. Further, there have been few investigations based on a large, general population. Therefore, the present study aimed to clarify whether ACE gene deletion polymorphism was associated with carotid atherosclerosis in a large Japanese general population with a more homogeneous genetic background than Caucasian populations.

Methods—Subjects aged 30 to 86 years were randomly selected from Suita City, located in Osaka, the second largest urban area of Japan, and included 1894 men and 2137 women. With the aid of high-resolution ultrasonography, carotid atherosclerosis was evaluated using our atherosclerotic indexes of intimal-medial thickness (IMT), plaque number (PN), plaque score (PS), and percentage of stenosis of the carotid artery assessed using high-resolution B-mode ultrasonography. ACE gene I/D polymorphism was detected by polymerase chain reaction.

Results—There were no significant differences among the ACE genotypes for age and conventional cardiovascular risk factors, except for systolic blood pressure (SBP) and the percentage of hypertension in men. The values of IMT, PN, and PS as carotid atherosclerotic indexes were not significantly different among genotypes for either sex. After adjusting for age, body mass index, smoking habit, high-density lipoprotein cholesterol, triglycerides, presence of hypertension, presence of diabetes mellitus, and presence of hyperlipidemia, the estimated ORs for the presence of IMT ≥1.10 mm (defined as thickened IMT), according to ACE genotype (DD versus II, DD+ID versus II, and DD versus ID+II), for men were 0.80 (95% CI 0.60 to 1.23), 0.89 (0.62 to 1.29), and 0.89 (0.70 to 1.28), respectively. On the other hand, the ORs for women after the same adjustment were 0.92 (95% CI 0.58 to 1.35), 0.93 (0.59 to 1.45), and 0.91 (0.59 to 1.27), respectively.

Conclusions—Our present data suggest that ACE I/D polymorphism is not potentially a useful predictive marker for carotid atherosclerosis when investigated in a large and homogeneous general Japanese population of 4031 subjects, a finding similar to that in a Caucasian population study, the Perth Carotid Ultrasound Disease Assessment Study, an Australian study based on a general population using 1111 subjects. (Stroke. 2001;32:1250-1256.)

Key Words: angiotensins ■ carotid arteries ■ genetics ■ Japan ■ ultrasonography

Many previous studies have reported that carotid intimal-medial thickness (IMT) correlates with traditional cardiovascular risk factors. Also, it has been shown in some population-based and intervention studies that carotid IMT measured by B-mode ultrasound is a valid and reliable surrogate measure of generalized atherosclerosis, including coronary atherosclerosis. Recently, it has been reported that carotid IMT is a significant predictive value of prevalent and incident stroke as well as coronary heart disease. These findings are increasing the importance of ultrasound studies compared with studies in which the end point is defined only by the presence or absence of clinical disease, ie, stroke or myocardial infarction.
It is well known that atherosclerosis is a complicated disease influenced by genes and environmental factors, including diet, smoking, and high blood pressure. Certainly, ACE $I/D$ polymorphism has been examined as a candidate gene polymorphism for an increased risk of ischemic heart disease$^{20-26}$ or other cardiac end points$^{23,27-29}$ in previous studies. However, most of those investigations assessed the relationship between ACE genotypes and myocardial infarction risk or increasing risk of hypertension. As a result, few investigations thus far have focused on the relationship between carotid atherosclerosis and gene polymorphism, although several studies$^{30-35}$ with relatively small, and often selective, populations have investigated the association between ACE $I/D$ polymorphism and increased carotid IMT. In particular, no studies based on a large, general population have, to our knowledge, investigated this association, with the exception of one: an Australian study, the Perth Carotid Ultrasound Disease Assessment Study.$^{36}$ Further, these results were heterogeneous and were not consistently positive.

The present study aimed to examine the relationship between ACE $I/D$ polymorphism and carotid atherosclerosis, including carotid IMT, in a large and relatively genetically homogeneous general Japanese population.

### Subjects and Methods

#### Subject Population

The population for our present study was based on a random sample selected from the residents of Suita, a city located in the second largest urban area in Japan (Osaka). Participants between the ages of 30 and 79 years were arbitrarily selected from the municipality population registry, stratified by sex and age groups of 10 years. The sample consisted of 12,200 men and women, although 3000 men and women were added randomly in the same way in 1996 and 1997. The basic sampling of the population started in 1989 with a cohort study base.

The subjects have visited the National Cardiovascular Center between Tuesday and Thursday every 2 years since then for regular health checkups, and approximately 2500 subjects have been participating in the health checkups every year. In addition to performing a routine blood examination that included total serum cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose levels, blood pressure, and anthropometric measurements, a physician or nurse administered questionnaires covering personal and family history of cardiovascular and other diseases and smoking and drinking habits. In addition, DNA was extracted from an extra 5 mL of blood withdrawn from those who visited the National Cardiovascular Center between May 1996 and February 1998. All subjects were Japanese, and only those who gave informed consent for genetic analysis were enrolled in the present study. The carotid ultrasonic examinations were begun in April 1994, but the examinations were not done on the days when the regular health checkups were performed between Tuesday and Thursday because the examinations were performed by a single physician. As the result, the subjects in the present study included 1894 men and 2137 women, aged 30 to 89 years, who attended regular health checkups and were classified as current smokers if they smoked at least 1 cigarette per day, nonsmokers if they had never smoked, and past smokers if they had stopped smoking for ≥1 year. Subjects were defined as hypertensive if diastolic blood pressure (DBP) was ≥90 mm Hg and/or systolic blood pressure (SBP) was ≥140 mm Hg or if they were taking antihypertensive medication. Those subjects whose serum total cholesterol levels were ≥5.68 mmol/L (220 mg/dL) or who were taking antihypercholesterolemic medication were defined as having hypercholesterolemia. Those subjects whose fasting blood glucose (FBG) levels were ≥7.00 mmol/L (126 mg/dL) or who were taking antidiabetic medication were defined as diabetic. Subjects who had a history of coronary heart disease or cerebrovascular disease (103 men and 67 women) were excluded from the present analysis. The subjects’ blood was sampled after overnight fasting, which resulted in the exclusion of 91 men and 113 women because they did not meet this condition. In total, 194 men and 180 women among the present 4031 subjects were excluded from this analysis. Blood pressure was measured twice in the right arm with a mercury sphygmomanometer, with the subject in a sitting position after taking a short rest. The second measurement was used for the analysis. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

Blood samples drawn from the subjects after a fast of ≥12 hours were collected in EDTA-containing tubes. Total cholesterol and triglycerides levels were assayed enzymatically with a Toshiba TBA-80 mol/L biochemical discrete analyzer. Glucose was assayed enzymatically, and HDL cholesterol was measured after precipitation with heparin and calcium ions with a Toshiba TBA-20R biochemical discrete analyzer. The measurements of total cholesterol, HDL cholesterol, and triglyceride levels were all standardized in accordance with the protocol of the Centers for Disease Control and Prevention.

#### Carotid Ultrasound

The details of the carotid ultrasonic examination method have been already published.$^{37,38}$ The method used in our present study was the same. We used a high-resolution B-mode ultrasonic machine with 7.5-MHz transducers yielding an axial resolution of 0.2 mm. The

#### Table 1. Clinical Characteristics of the Present Subjects, by Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>1700</td>
<td>1957</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.7±12.1*</td>
<td>58.8±11.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.0±2.8*</td>
<td>22.3±3.3</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>128.1±19.3*</td>
<td>126.5±20.3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.7±10.9*</td>
<td>77.1±10.9</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>5.24±0.82*</td>
<td>5.58±0.86</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.41±0.37*</td>
<td>1.68±0.39</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.53±1.14*</td>
<td>1.17±0.75</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>5.66±1.24*</td>
<td>5.29±0.81</td>
</tr>
</tbody>
</table>

**Smoking**

- Never smoked, % | 26.6† | 88.9
- Past smoker, % | 30.0† | 2.2
- Current smoker, % | 43.4† | 8.9

**Alcohol use**

- Never, % | 31.5† | 72.2
- Current, % | 68.5† | 27.8

**Diabetes, %**

- 9.5† | 4.2

**Hypertension, %**

- 37.4 | 32.1

**Hypercholesterolemia, %**

- 30.3† | 48.3

*Hypertension indicates SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or antihypertensive medication; diabetes, FBG ≥7.00 mmol/L (126 mg/dL) and/or antidiabetic medication; and hypercholesterolemia, serum cholesterol level ≥5.68 mmol/L (220 mg/dL) or antihypercholesterolemic medication. Values are mean±SD.

†P<0.05 between men and women by Student t test.

‡P<0.05 between men and women by χ² test.
regions between 30 mm proximal from the beginning of the dilation of the bifurcation bulb and 15 mm distal from the flow divider of both common carotid arteries (CCAs) were scanned. All measurements were made at the time of scanning with the instrument’s electronic caliper and were recorded as photocopies. The IMT was measured on a longitudinal scan of the CCAs at a point 10 mm proximal from the beginning of the dilation of the bulb. We defined a plaque, a focal IMT thickening, as an area where IMT was \( \geq 1.10 \) mm and calculated the plaque number (PN) by counting the number of plaques in the bilateral carotid arteries in the scanning area. We also calculated the plaque score (PS) by totaling the maximum thickness of all the plaques in the same area. Finally, we defined stenosis as a condition in which a plaque occupied more than half of the luminal circumference of an artery on a cross-sectional scan, and the degree of stenosis was calculated as a percentage ratio of the area of the plaque to that of the lumen, with the following formula: (Lumen Area – Residual Lumen)/Lumen Area \( \times 100 \). Both areas were measured automatically by the system on a frozen transverse section at the maximal narrowing site.

Table 2. Clinical Characteristics by Sex and ACE Genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.8±11.8</td>
<td>60.5±11.9</td>
<td>60.5±12.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.2±2.9</td>
<td>23.0±2.8</td>
<td>23.0±2.8</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>131.1±19.9</td>
<td>128.3±18.9</td>
<td>127.0±19.4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80.8±11.3</td>
<td>79.8±10.9</td>
<td>79.3±10.8</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>5.19±0.86</td>
<td>5.25±0.84</td>
<td>5.24±0.80</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.38±0.38</td>
<td>1.42±0.38</td>
<td>1.42±0.36</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.50±0.99</td>
<td>1.60±1.30</td>
<td>1.45±0.96</td>
</tr>
<tr>
<td>FBG, mg/dl</td>
<td>5.56±1.09</td>
<td>5.66±1.17</td>
<td>5.71±1.36</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>39.5</td>
<td>45.0</td>
<td>42.8</td>
</tr>
<tr>
<td>Alcohol use, %</td>
<td>66.0</td>
<td>70.8</td>
<td>66.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>8.8</td>
<td>9.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>47.9</td>
<td>37.8</td>
<td>33.7</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>31.2</td>
<td>31.6</td>
<td>28.7</td>
</tr>
<tr>
<td>Percentage of IMT ≥ 1.10 mm defined as thickened IMT, %</td>
<td>7.4</td>
<td>9.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Hypertension indicates SBP \( \geq 140 \) mm Hg and/or DBP \( \geq 90 \) mm Hg or antihypertensive medication; diabetes, FBG \( \geq 7.00 \) mmol/L (126 mg/dL) and/or antidiabetic medication; and hypercholesterolemia, serum cholesterol level \( \geq 5.68 \) mmol/L (220 mg/dL) or antihypercholesterolemic medication. Values are mean±SD.

Determination of Genotype of ACE I/D Polymorphism

DNA was extracted from 200 µL of buffy coat separated from fresh blood with the use of a QIAamp Kit (QIAGEN). Template genomic DNA (100 ng) was amplified by polymerase chain reaction with a thermal cycle (Omni Gene; Hybrid). I/D polymorphism was determined by agarose gel electrophoresis with ethidium bromide staining, and the DD genotype was reconfirmed by insertion allele–specific amplification according to the Lindpainter’s protocol\(^\text{17}\) with a minor modification. This minor modification does not affect the results and is as follows: The DNA was amplified for 30 cycles with denaturation at 94°C for 1 minute, annealing at 55°C for 30 seconds, and extension at 72°C for 1 minute 30 seconds after initial denaturation at 94°C for 5 minutes.

Statistical Analysis

All statistical analysis were performed using the SAS statistical software system and the Statistical Package for the Social Sciences (SPSS Inc.). The mean levels of all the numerical values were tested by the Student t test. Those of almost all the categorical values were examined by \( \chi^2 \) analysis. However, the Fischer exact test was adopted instead of the \( \chi^2 \) test in case the number of subjects was \( \leq 5 \). The association between ACE I/D polymorphism and clinical variables, carotid atherosclerotic indices (ie, IMT, PN and PS), was tested by 1-way ANOVA. The quantitative effects of covariates for carotid atherosclerotic index, the presence of IMT \( \geq 1.10 \) mm defined as thickened IMT, were assessed by multiple logistic regression analysis with the aid of SAS. Values of \( P<0.05 \) were considered significant.

Results

Study Population

Table 1 shows the clinical characteristics of the present subjects by sex. Almost all variables (ie, age, BMI, SBP, DBP, triglycerides, FBG, percentage of current smokers, current alcohol users, diabetes, and hypertension) were significantly higher in men than in women. The levels of total serum cholesterol and HDL cholesterol were significantly higher in women.
Clinical Characteristics by Sex and ACE I/D Polymorphism

For men, there were significant differences (P<0.05) in SBP, triglycerides, and the percentage of hypertension among the 3 genotypes. Also, SBP and the percentage of hypertension were highest in the DD genotype (Table 2). On the other hand, for women, no significant differences were found among the 3 genotypes with respect to age, BMI, SBP, DBP, total serum cholesterol, HDL cholesterol, triglycerides, FBG, the percentage of smoking, alcohol use, diabetes, and hypertension (Table 2).

Genotype Distribution of ACE I/D Polymorphism

The frequencies of the D and I allele were 35.9% and 64.1% for men and 35.1% and 64.9% for women. There were no significant differences in genotype frequencies of ACE I/D polymorphism among age groups for either sex (Table 3). According to Hardy-Weinberg’s expectation, there was no significant deviation in ACE genotype distribution for men ($\chi^2=0.12$, $P=0.94$) for women ($\chi^2=2.23$, $P=0.33$), or for total subjects ($\chi^2=0.71$, $P=0.70$). In the present subjects, there was no significant difference in ACE genotype distribution ($\chi^2=3.64$, $P=0.16$) between men and women.

Carotid Atherosclerotic Indexes by Sex and ACE I/D Polymorphism

Figure 1 shows the mean IMT values of both sexes, by ACE I/D polymorphism, adjusted for age, pack-years of smoking, alcohol consumption, SBP, serum total cholesterol level, HDL cholesterol, triglycerides, and FBG. There were no significant differences among the 3 genotypes by 1-way ANOVA for either sex. Figures 2 and 3 show the mean values for PN and PS, adjusted for age, pack-years of smoking, alcohol consumption, SBP, serum total cholesterol level, HDL cholesterol, triglycerides, and fasting blood glucose. The results were roughly similar to those shown in Figure 1, and no significant differences were found among the 3 genotypes by 1-way ANOVA. Table 4 shows the distribution and percentage of 2 grades of stenosis (stenosis of 25% to <50% and stenosis ≥50%) by sex and ACE I/D polymorphism. There was no significant difference among the 3 genotypes with respect to the percentage of these 2 grades of stenosis for men. On the other hand, for women, the percentage of these 2 grades of stenosis of DD was lower, though not significantly, than that of ID and II by Fischers exact test.

Distribution of the Mean IMT Divided Into 6 Classes by Sex

The prevalence of IMT ≥1.10 mm, defined as thickened IMT, was significantly (P<0.05) higher in men than in women (9.5% for men and 4.9% for women; Figure 4).

Association Between Presence of IMT ≥1.10 mm and ACE I/D Polymorphism

After being adjusted for age, BMI, smoking habit, drinking habit, HDL-C, TG, presence of hypertension, presence of diabetes mellitus, and presence of hypercholesterolemia, the estimated odds ratios for the presence of IMT ≥1.10 mm (defined as thickened IMT), according to ACE genotype (DD

---

**TABLE 3. Genotype Frequency of ACE I/D Polymorphism by Sex and Age Group**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>DD, %</td>
<td>ID, %</td>
<td>II, %</td>
<td>DD, %</td>
<td>ID, %</td>
</tr>
<tr>
<td>30–44</td>
<td>204</td>
<td>9.8</td>
<td>47.1</td>
<td>43.1</td>
<td>254</td>
<td>14.2</td>
</tr>
<tr>
<td>45–54</td>
<td>313</td>
<td>14.1</td>
<td>44.4</td>
<td>41.5</td>
<td>444</td>
<td>13.7</td>
</tr>
<tr>
<td>55–64</td>
<td>476</td>
<td>10.5</td>
<td>48.9</td>
<td>40.5</td>
<td>594</td>
<td>13.3</td>
</tr>
<tr>
<td>65–74</td>
<td>472</td>
<td>13.6</td>
<td>48.7</td>
<td>37.7</td>
<td>483</td>
<td>12.2</td>
</tr>
<tr>
<td>75–89</td>
<td>235</td>
<td>15.7</td>
<td>39.6</td>
<td>44.7</td>
<td>182</td>
<td>14.8</td>
</tr>
<tr>
<td>Total</td>
<td>1700</td>
<td>12.6</td>
<td>46.5</td>
<td>40.8</td>
<td>1957</td>
<td>13.4</td>
</tr>
</tbody>
</table>

---

**Figure 1.** IMT values (±SE), by ACE polymorphism and sex, adjusted for age, pack-years of smoking, alcohol consumption, SBP, serum total cholesterol level, HDL cholesterol, triglycerides, and FBG. The differences of IMT values among genotypes were analyzed by 1-way ANOVA and Scheffé test. There were no significant differences among genotypes for either sex.

**Figure 2.** PN values (±SE), by ACE polymorphism and sex, adjusted for age, pack-years of smoking, alcohol consumption, SBP, serum total cholesterol level, HDL cholesterol, triglycerides, and FBG. Differences of PN values among genotypes were analyzed by 1-way ANOVA and Scheffé test. There were no significant differences among genotypes for either sex.
versus II, DD + ID versus II, and DD versus ID + II), for men were 0.80 (95% CI 0.60 to 1.23), 0.89 (0.62 to 1.29), and 0.89 (0.70 to 1.28), respectively. These odds ratios for women after the same adjustment were 0.92 (95% CI 0.58 to 1.35), 0.93 (0.59 to 1.45), and 0.91 (0.59 to 1.27), respectively (Figure 5). In other words, there was no association between the presence of IMT ≥1.10 mm (thickened IMT) and ACE I/D polymorphism in either sex.

### Discussion

Investigation of the effect of the D allele of ACE has thus far mainly focused on IHD. Furthermore, a recent meta-analysis of 15 studies showed that there was a positive, but weak, relationship between the D allele and increased risk of myocardial infarction, although it is necessary to bear in mind that most of these results were heterogeneous and drawn from smaller, positive case-control studies. However, a large case-referent study using the Copenhagen City Heart Study of 10150 subjects has recently reported that there was no significant association in the development of myocardial infarction or any other manifestations of IHD. Furthermore, according to a recent review of meta-analyses examining the cause and effect relation between ACE I/D polymorphism and cardiovascular-renal risk among 49 959 subjects, there was no significant association of ACE I/D polymorphism with hypertension, but there was potentiality of the ACE I/D polymorphism as a useful marker of atherosclerotic cardiovascular complications and diabetic nephropathy. However, there have been few studies that focused on the relationship between ACE I/D polymorphism and carotid IMT, early atherosclerotic changes, or the nearly established surrogate end point of generalized atherosclerosis. In particular, there have been few studies based on a large and homogeneous randomly sampled population, except for one, the Perth Carotid Ultrasound Disease Assessment Study. Even in this large study, which comprised 1111 subjects, the D allele was not found to be associated with either thickened IMT or carotid plaque formation, although some studies with small sample size or selection bias showed positive association. Also, there have been no studies showing a relationship between the D allele and carotid plaque or stenosis.

The present study, to our knowledge, is the first report to show the lack of a relationship between ACE I/D polymorphism and carotid IMT based on a large, homogeneous, randomly selected general population. Also, our present data showed that the D allele was not associated with the presence of IMT ≥1.10 mm (thickened IMT), irrespective of whether it was considered a dominant, codominant, or recessive gene polymorphism in either sex. Some studies found an association between asymptomatic extracranial carotid lesions and asymptomatic brain infarction, which is thought to be a risk factor for symptomatic brain infarction. From this evidence, there is little possibility that ACE I/D polymorphism is a risk factor for ischemic stroke in Japan, although a previous Japanese study with relatively small sample size (228 hypertensive and 104 normotensive individuals) showed that there was a close relationship between the ACE D allele and ischemic stroke in Japanese hypertensives and that the D allele may be an independent risk factor for the development of cerebrovascular disease in hypertensive patients.

It is also well known that the frequency of gene polymorphism is different among races. With regard to ACE I/D
polymorphism, the D allele frequency among the present Japanese subjects was significantly lower than that in the Caucasian individuals of the Copenhagen City Heart Study\textsuperscript{39} or the Perth Carotid Ultrasound Disease Assessment Study.\textsuperscript{36} The advantages of the present study are that the participants were randomly selected from urban Japanese residents, which resulted in an all-Japanese, homogeneous population. Our previous studies\textsuperscript{10,11} (the Suita Study) have already shown that there was a strong relationship between carotid IMT and various cardiovascular risk factors such as hypertension, smoking, and hypercholesterolemia. Thus, our previous and present data strongly suggest that the impact of exposure from traditional cardiovascular risk factors (such as age, hypertension, smoking, and hyperlipidemia) on carotid atherogenesis may be so much greater than that of gene polymorphisms, especially the ACE I/D polymorphism. However, the combination of some gene polymorphisms may be a risk factor for carotid atherogenesis, although this possibility should be further investigated.

In conclusion, our present data, based on a large, homogeneous general population of 4031 subjects, showed that there was little genetic influence of ACE I/D polymorphism on carotid atherogenesis and suggested that ACE I/D polymorphism might not be a potentially useful predictive marker for increased risk of carotid atherosclerosis of the Japanese. These results are similar to those of a Caucasian population study, the Perth Carotid Ultrasound Disease Assessment Study,\textsuperscript{36} an Australian study based on a large general population of 1111 subjects.

References


Figure 5. Multiple adjusted odds ratios for the presence of IMT ≥1.10 mm (thickened IMT) according to ACE genotype, codominant (DD versus II), dominant (DD/ID versus II), and recessive (DD versus ID/II). There were no significant differences among all the classified groups of genotypes in for either sex. Values in parentheses indicate confidence intervals.


Toshifumi Mannami, Tomohiro Katsuya, Shunroku Baba, Nozomu Inamoto, Kazuhiko Ishikawa, Jitsuo Higaki, Toshio Ogihara and Jun Ogata

Stroke. 2001;32:1250-1256
doi: 10.1161/01.STR.32.6.1250

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/6/1250

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/