DD Genotype of the Angiotensin-Converting Enzyme Gene Is a Risk Factor for Left Ventricular Hypertrophy

Naoharu Iwai, MD; Nobuyuki Ohmichi, MD; Yasuyuki Nakamura, MD; Masahiko Kinoshita, MD

**Background.** The cardiac renin-angiotensin system has been suggested to be involved in the development of left ventricular hypertrophy. In humans, a strong correlation has been found between plasma angiotensin I-converting enzyme (ACE) activity and the insertion/deletion (I/D) polymorphism of the ACE gene, which has been reported to be associated with myocardial infarction, ischemic and idiopathic dilated cardiomyopathy, sudden death in hypertrophic cardiomyopathy, and restenosis after percutaneous transluminal coronary angioplasty. In the present study, we examined the possibility that the genotype of the ACE gene might influence the development of left ventricular hypertrophy.

**Methods and Results.** The study population consisted of 268 subjects, left ventricular mass (LVM) was determined by echocardiogram. The genotype of the ACE gene was determined by the polymerase chain reaction. ANCOVA revealed that the genotype of the ACE gene had no effect on blood pressure. The percentage of the explained variance of LVM with variables including diastolic blood pressure (DBP, P = .0001), body mass index (BMI, P = .0001), sex (P = .0009), and the genotype of the ACE gene (P = .0017) was 34.61%. Significant differences in the effects of the genotype of the ACE gene on LVM were observed between the II and DD (P = .0004) and between the ID and DD (P = .0077) genotypes. The percentage of the explained variance of the LVM/ht ratio with variables including sex (P = .134), age (P = .365), the genotype of the ACE gene (P = .0014), BMI (P = .0001), and DBP (P = .0001) was 31.25%. Significant differences in the effects of the genotype of the ACE gene on LVM/ht were observed between the II and DD genotypes (P = .0003) and between the ID and DD genotypes (P = .0091).

**Conclusions.** In addition to BMI and DBP, the genotype of the ACE gene was a significant predictor of LVM and LVM/ht in our study population. (Circulation. 1994;90:2622-2628.)

**Key Words.** angiotensin • hypertrophy • genes

Increased left ventricular mass (LVM) is a powerful independent predictor of cardiovascular morbidity and mortality. Although high blood pressure is the leading cause of left ventricular hypertrophy (LVH), the correlation between the magnitude of high blood pressure and LVM is poor. One reason for this poor correlation may be that office blood pressure does not accurately reflect the hemodynamic load on the left ventricle. In fact, better correlations have been reported between LVM and either 24-hour ambulatory blood pressure or peak systolic blood pressure during exercise. Moreover, factors other than blood pressure are recognized to be important in the development of LVH, including humoral factors such as catecholamine and angiotensin II, the age at onset of high blood pressure, body size or obesity, insulin sensitivity, and genetic background.

Recent experimental and clinical studies have suggested that the cardiac renin-angiotensin system may be involved in the development of LVH. Various antihypertensive drugs are known to produce various degrees of regression or prevention of LVH despite their similar antihypertensive effects. Furthermore, converting enzyme inhibitors have been recognized as one of the most effective means to cause regression or prevent LVH. Some of the components of the renin-angiotensin system have been reported to be synthesized in the ventricle of the heart. Moreover, increased expression of these components in the hypertrophied ventricle has also been reported. These findings suggest that intracardiac formation of angiotensin II independent of the circulating renin-angiotensin system may play a key role in the development of LVH.

Angiotensin I-converting enzyme (ACE) is a zinc metallopeptidase, the primary known functions of which are to convert angiotensin I to angiotensin II and to inactivate bradykinin. Regulation of the ACE expression might play a role in various cardiovascular diseases, including hypertension, vascular hypertrophy and remodeling, and ventricular hypertrophy and remodeling. In humans, the plasma level of ACE is determined genetically. The ACE gene, which has been mapped to human chromosome 17q22, has insertion/deletion (I/D) polymorphism in intron 16. The ACE genotype with two deletion alleles (DD genotype) has been reported to be associated with higher plasma ACE activity, probably due to tight linkage to another locus that is important in regulation of this gene. Although this I/D polymorphism of the ACE gene is considered to play a small role in the pathogenesis of hypertension, the DD genotype might be a risk factor for myocardial infarction, ischemic and idiopathic dilated cardiomyopathy, sudden death in hypertrophic cardiomyopathy, and restenosis after percutaneous transluminal coronary angioplasty. These hypotheses are intriguing because it is tempting to speculate that individuals with the DD genotype may exhibit higher...
angiotensin II formation in cardiac and vascular tissues. In the present study, we explored the possibility that I/D polymorphism of the ACE gene may be related to the development of LVH.

**Methods**

**Subjects**

The subjects in the present study were selected randomly in our outpatient clinic. DNAs of 450 subjects between 20 and 75 years old were collected from April 1992 to October 1993. About 60% of the subjects had been hospitalized in our department for evaluation of possible cardiovascular diseases. Subjects with myocardial infarction, a history of symptomatic congestive heart failure, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, valvular diseases, congenital heart diseases, permanent atrial fibrillation, arrhythmogenic right ventricular dysplasia, sarcoidosis of cardiac involvement, or complete AV block were excluded from the present study. Moreover, subjects with treated hypertension, angina pectoris, or arrhythmia whose precise clinical data before the treatment were not available were also excluded. Diagnosis of hypertrophic cardiomyopathy was based on a histological examination (existence of disarray). Subjects with increased LVM and one or more abnormalities including giant negative T wave on ECG and asymmetrical septal hypertrophy were considered to have hypertrophic cardiomyopathy even though diagnostic disarray was not evident on histological examination. Diagnosis of idiopathic dilated cardiomyopathy was based on severe hypokinesis (fractional shortening $\leq 0.2$) and dilated left ventricular end-diastolic dimension (LVDd) (>65 mm) with normal coronary angiography. Angina pectoris was diagnosed with coronary angiography by identifying staticenosis ($\geq 75\%$) or vasospasm with ECG changes and chest pain or oppression by acetylcholine infusion. Almost all subjects suspected of having angina pectoris were hospitalized and evaluated by coronary angiography. The clinical data included in the analyses were sex, age, body mass index (BMI), cholesterol level, and systolic and diastolic blood pressure levels at the initial observation period before any type of intervention. The mean value of the blood pressures on two or more separate occasions at our outpatient clinic was used as the subject's blood pressure value.

Of 450 subjects, 268 were within the criteria described above. Of these 268 subjects, 142 had technically excellent echocardiograms either under no medication or within 2 weeks from the initiation of any kind of medication.

**Echocardiographic Methods**

LVM was calculated from M-mode echocardiographic measurements of the left ventricle with an SSH160A system with 3.75 MHz transducers (Toshiba). Two-dimensionally guided M-mode measurements of LVdD, end-diastolic interventricular septum thickness (IVS), and end-diastolic posterior wall thickness (LVPW) were performed at the left ventricular minor axis at the level of the chordae tendineae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography. Each measurement was made three times, and the average value was used to calculate LVM according to the formula of Devereux and Reichek: $LVM (g) = 1.04 \left( LVDd + IVS + LVPW \right) - 13.6$. LVM was corrected by dividing it by height in centimeters (LVMht) as previously recommended. All echocardiograms, performed by three experienced echocardiographers, were recorded on videotape, and the quality of the echocardiograms was verified by experts in echocardiography.

Echocardiographically determined LVH (ECG-LVH) was diagnosed according to the criteria of the point score system of Marquette Electronics, Inc. This system includes five categories for ECG-LVH: normal, minimal voltage criteria for LVH, moderate voltage criteria for LVH, voltage criteria for LVH, and LVH. In the present study, minimal voltage criteria for LVH and moderate voltage criteria for LVH were considered normal variants, and only voltage criteria for LVH and LVH were considered ECG-LVH.

**DNA Studies**

Genomic DNA was isolated from peripheral leukocytes as previously reported. The genotype of the ACE gene was determined by the polymerase chain reaction (PCR) according to Rigat et al. The sense oligonucleotide primer was 5'-CTG GAG ACC ACT CCC ATC CTG TCT-3', and the antisense primer was 5'-GAT GTG GCC ATC ACA TTC GTG AGA T-3'. These primers allowed detection of a genomic DNA segment with 490 bp corresponding to the insertion allele (I) as well as a segment with 190 bp corresponding to the deletion allele (D). Reactions were performed in a final volume of 25 μL containing 10 pmol of each primer, 2.5 mmol/L MgCl₂, 50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 8.4), 0.1 mg/mL gelatin, 0.2 mmol/L of each dNTP, and 0.5 U of Taq DNA polymerase (Toyobo). The amplification profile included an initial denaturation at 94°C for 60 seconds and 35 cycles of denaturation at 94°C for 60 seconds, annealing at 58°C for 60 seconds, and extension at 74°C for 120 seconds. The PCR products were resolved in 1.5% agarose gels and visualized with ethidium bromide staining.

**Statistical Analyses**

All statistical analyses were conducted by use of the SAS statistical package licensed to Kyoto University (site 0002436001, Kyoto, Japan). Summary data are expressed as the mean±SD. ANCOVA was performed to assess the effects of the genotype of the ACE gene on blood pressures, LVM, and LVMht. The genotype of the ACE gene was considered class level information. Sex (male=0, female=1), BMI, diastolic blood pressure, serum cholesterol level, and history of angina pectoris with (0, without=1) were considered independent variables. LVM, LVMht, and blood pressures were considered dependent variables. Stepwise regression analyses (a backward elimination procedure) were performed to identify variables for predicting systolic blood pressure, diastolic blood pressure, LVM, and LVMht. For blood pressures, BMI, age, cholesterol, sex (male=0, female=1), presence of angina pectoris (with=0, without=1), and the genotype of the ACE gene (II+ID=0, DD=1) were considered independent variables. For LVM and LVMht, BMI, systolic and diastolic blood pressures, sex, age, cholesterol, presence of angina pectoris, and the genotype of the ACE gene (II+ID=0, DD=1) were included as independent variables. Any variables with a partial F value of 4.0 or more were included in the regression, and any previously entered variables with a partial F value <4.0 were removed from the analysis. A multiple regression analysis was performed to predict LVM/ht by BMI, age, diastolic blood pressure, and the genotype of the ACE gene (II+ID=0, DD=1).

**Results**

**Study Population**

The characteristics of the 268 patients who met the criteria are summarized in Table 1, and the characteristics of the 142 patients who were successfully evaluated by echocardiography are summarized in Table 2. About 60% of these patients were followed in our outpatient clinic for essential hypertension, borderline hypertension, angina pectoris, atypical chest pain, and arrhythmias. The remaining 40% were temporarily followed in our outpatient clinic for evaluation for possible hypertension, arrhythmia, or angina pectoris.
Effects of ACE Gene Genotypes on Blood Pressure

The Figure shows a typical example of genotyping of the ACE gene. Diagnoses of the DD genotype of the ACE gene were confirmed with a second PCR. The I allele frequencies of the ACE gene in our study populations were 0.606 (268, Table 1) and 0.606 (142, Table 2), which were close to those reported in other Japanese populations.32-44 We had previously examined the genotype of the ACE gene in 64 medical students who were randomly selected in our university, and the I allele frequency in this population was 0.64, which was not significantly different from those in our study populations.

In the 268 patients, an ANCOVA was performed in which the genotype of the ACE gene, sex (male=0, female=1), BMI, age, presence of angina pectoris (with=0, without=1), and cholesterol were included as independent variables and systolic or diastolic blood pressure was considered to be a dependent variable. The genotype of the ACE was considered to be class level information. The percentage of the explained variance with these independent variables for systolic blood pressure was 8.9579% ($R^2=.89579$, $P=.001$), and that for diastolic blood pressure was 12.6838% ($R^2=.126838$, $P=.0001$). The genotype of the ACE gene apparently had no significant effects on blood pressure ($P=.247$ for systolic blood pressure, $P=.291$ for diastolic blood pressure). A stepwise multiple regression analysis identified only BMI as a predictor of systolic blood pressure and BMI and the presence of angina pectoris as predictors of diastolic blood pressure (Table 3). The presence of angina pectoris was negatively correlated with diastolic blood pressure. The 268 patients analyzed above included elderly patients and patients with hypertension of known causes, which may have obscured the effects of genetic factors. Thus, subjects who were >66 years old and 9 subjects with hypertension of known causes were excluded to reassess the effects of the genotype of the ACE gene on blood pressure. However, even in this group (222 patients), the genotype of the ACE gene had no significant effect on blood pressure ($P=.2455$ for systolic blood pressure, $P=.3734$ for diastolic blood pressure). A stepwise multiple regression analysis identified only BMI as a predictor of systolic blood pressure and BMI and age as predictors of diastolic blood pressure (Table 4). Age was negatively correlated with diastolic blood pressure.

Stepwise and multiple regression analyses indicated that the genotype of the ACE gene had no significant effect on blood pressure in the 142 echocardiographically evaluated subjects (data not shown).

Among the 268 patients, 128 patients were categorized as having hypertension based on a diastolic blood pressure >90 mm Hg. In this hypertensive group, the prevalence of ECG-LVH was compared among the groups

### TABLE 2. Characteristics of the Patients Evaluated by Echocardiography

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>II</strong></td>
<td><strong>ID</strong></td>
<td><strong>DD</strong></td>
<td><strong>P</strong></td>
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<tr>
<td><strong>Age, y</strong></td>
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<td>27</td>
<td>17</td>
<td>.89</td>
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<tr>
<td>BMI, kg/m²</td>
<td>23.1±3.5</td>
<td>23.6±3.6</td>
<td>23.4±3.4</td>
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</tr>
<tr>
<td>Cho, mg/dL</td>
<td>196±33</td>
<td>217±54</td>
<td>199±28</td>
<td>.11</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>146±27</td>
<td>156±33</td>
<td>145±25</td>
<td>.35</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>86±16</td>
<td>88±16</td>
<td>87±15</td>
<td>.86</td>
</tr>
<tr>
<td>AP</td>
<td>9/36</td>
<td>4/27</td>
<td>4/17</td>
<td>.60</td>
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<tr>
<td>LVM, g</td>
<td>186±44</td>
<td>210±56</td>
<td>236±77</td>
<td>.01*</td>
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<tr>
<td>LVM/h, g/cm²</td>
<td>1.13±0.26</td>
<td>1.28±0.35</td>
<td>1.43±0.47</td>
<td>.01*</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Cho, cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; AP, angina pectoris; LVM, left ventricular mass.

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**TABLE 1. Characteristics of Patients**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Male</th>
<th></th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>II</strong></td>
<td><strong>ID</strong></td>
<td><strong>DD</strong></td>
<td><strong>P</strong></td>
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<tr>
<td><strong>Age, y</strong></td>
<td>57</td>
<td>59</td>
<td>27</td>
<td>.57</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.9±3.3</td>
<td>23.0±3.4</td>
<td>23.2±3.3</td>
<td>.93</td>
</tr>
<tr>
<td>Cho, mg/dL</td>
<td>193±30</td>
<td>213±49</td>
<td>197±26</td>
<td>.02*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>143±29</td>
<td>152±27</td>
<td>143±26</td>
<td>.18</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85±17</td>
<td>88±14</td>
<td>85±17</td>
<td>.55</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>17/57</td>
<td>25/59</td>
<td>12/27</td>
<td>.28</td>
</tr>
<tr>
<td>AP</td>
<td>10/57</td>
<td>8/59</td>
<td>4/27</td>
<td>.81</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Cho, cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG-LVH, electrocardiographic criteria for left ventricular hypertrophy; and AP, angina pectoris. One-way ANOVA or $\chi^2$ (2×3 contingency table) analysis is used to assess various phenotypic values or frequency.

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**TABLE 2. Characteristics of the Patients Evaluated by Echocardiography**
with different genotypes of the ACE gene. As shown in Table 5, the frequency of the D allele was significantly higher in hypertensive patients with ECG-LVH than in those without ECG-LVH. No significant difference in blood pressure was observed among the subgroups with different genotypes in this hypertensive group.

**Effects of ACE Gene Genotypes on LVM and LVM/ht**

The above observation suggested that the genotype of the ACE gene may affect the development of LVH. Therefore, we assessed the effects of the genotype of the ACE gene on LVM as assessed by echocardiogram.

An ANCOVA was performed in the 142 patients, in which the genotype of the ACE gene, sex (male=0, female=1), presence of angina (with=0, without=1), age, BMI, and diastolic blood pressure were included as independent variables and LVM was considered to be a dependent variable. The genotype of the ACE gene was considered to be class level information. The percentage of the explained variance of LVM with these variables was 34.6125% \( (R^2=0.346125, P=0.0001) \). Diastolic blood pressure \( (P=0.0001) \), BMI \( (P=0.0001) \), the genotype of the ACE \( (P=0.0017) \), and sex \( (P=0.0009) \) were significantly correlated with LVM. Significant differences in the effects of the genotype of the ACE gene on LVM were observed between the DD and II \( (P=0.0004) \) and between the DD and ID genotypes \( (P=0.0077) \) but not between the ID and II genotypes \( (P=0.293) \). A stepwise multiple regression analysis indicated that the genotype of the ACE gene had no effect on blood pressure in this echocardiographically assessed group (as described above).

When LVM was corrected for height (LVM/ht), the genotype of the ACE gene, BMI, and diastolic blood pressure were significantly correlated with LVM/ht. Correction of LVM for height eliminated sex as a significant predictor. The percentage of the explained variance of the LVM/ht with sex, age, the genotype of the ACE gene, BMI, and diastolic blood pressure was 31.2448% \( (R^2=0.312488, P=0.0001) \). Diastolic blood pressure \( (P=0.0001) \), BMI \( (P=0.0001) \), and the genotype of the ACE gene \( (P=0.0014) \) were identified as significant predictors for LVM/ht (Table 6). Significant differences in the effects of the genotypes of the ACE gene on LVM/ht were observed between the DD genotype and the II genotype \( (P=0.003) \) and between the DD genotype and the ID genotype \( (P=0.0091) \) but not between the II genotype and the ID genotype \( (P=0.2453) \). A stepwise multiple regression analysis revealed that BMI, diastolic blood pressure, age, and the genotype of the ACE gene \( (II+ID=0, DD=1) \) were significant predictors for LVM/ht (Table 7). Since no significant difference in the effects of the genotype of the ACE gene on LVM/ht was observed between the II and ID genotypes, the II and ID genotypes were categorized into one group in this multiple regression analysis.

**Discussion**

The major finding in the present study is that the genotype of the ACE gene, in addition to blood pressure and BMI, is an independent predictor of the development of LVH. Our present findings also support other evidence that the renin-angiotensin system may play an important role in the pathophysiology of cardiac hypertrophy and remodeling and that the genotype of the ACE gene is a risk factor for myocardial infarction and heart failure.

**Table 3. Multiple Regression Analysis of BP**

<table>
<thead>
<tr>
<th></th>
<th>( \beta )</th>
<th>SEM</th>
<th>Partial F</th>
<th>( P )</th>
</tr>
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<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression ( df=1, F=11.826, P=0.0007 )</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.606</td>
<td>0.468</td>
<td>11.826</td>
<td>.0007</td>
</tr>
<tr>
<td>Intercept</td>
<td>112.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R^2 )</td>
<td>.043</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
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<td></td>
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<tr>
<td>Regression ( df=2, F=14.244, P=0.0001 )</td>
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</tr>
<tr>
<td>BMI</td>
<td>1.096</td>
<td>0.240</td>
<td>20.906</td>
<td>.0001</td>
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<td>AP</td>
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<tr>
<td>Intercept</td>
<td>45.958</td>
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<tr>
<td>( R^2 )</td>
<td>.097</td>
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</table>

BP indicates blood pressure; BMI, body mass index; and AP, angina pectoris.
Association Between the Genotype of the ACE Gene and Blood Pressure

In our female study population, patients with the II genotype tended to have a slightly higher blood pressure (Table 1). However, the mean BMI and the mean age of female subjects with the II genotype were higher, although not significantly so, than those of the subjects with either the DD or ID genotype. Considering the effects of age and BMI on blood pressure, no significant effect of the genotype of the ACE gene was found by ANCOVA.

This lack of association between I/D polymorphism of the ACE gene and blood pressure in our study population is consistent with previous studies in Caucasian and Japanese populations.

Study Population

The subjects analyzed in the present study were all selected from our outpatient clinic, which treats predominantly cardiovascular diseases. Therefore, our study population was not representative of the general population in Japan. For example, because of the relatively high prevalence of hypertension in our younger patients, we tended to observe a negative association between age and diastolic blood pressure (Table 4).

One of the major concerns in the analysis of work-site populations is a spurious association due to population substructuring. If individuals with the DD genotype had more symptoms related to cardiovascular abnormality than individuals with the II genotype, the frequency of the D allele in our study population would be greater than that in the general population. However, the frequencies of the I and D alleles in our study populations were very similar to those reported in other Japanese populations and in our randomly selected medical students.

The frequency of the I allele in our study population (0.606) was almost equal to that of the echocardiographically assessed population (0.606), which was a subpopulation of our total study population. In this subpopulation, no significant effect of the genotype of the ACE gene on blood pressure was observed, which negates a possibility that subjects with hypertension and the DD genotype might be selectively included in this subpopulation. However, a large cross-sectional study in the general population may be necessary for a definitive confirmation of the present results.

<table>
<thead>
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<th>Genotype</th>
<th>Allele Frequency</th>
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</tr>
<tr>
<td>LVH(+)</td>
<td>20</td>
</tr>
<tr>
<td>LVH(−)</td>
<td>34</td>
</tr>
</tbody>
</table>

χ² = 4.24, P < .05

<table>
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<th>Genotype</th>
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<tr>
<td>Group</td>
</tr>
<tr>
<td>LVH(+)</td>
</tr>
<tr>
<td>LVH(−)</td>
</tr>
</tbody>
</table>

ECG-LVH indicates electrocardiographic criteria for left ventricular hypertrophy; ACE, angiotensin-converting enzyme.

A. The numbers of subjects with ECG-LVH [LVH(+)] or without ECG-LVH [LVH(−)] are described according to the genotypes of the ACE gene.

B. The mean blood pressure values (systolic/diastolic, in mm Hg) are described according to the subgroups defined above.
Speculation of Possible Mechanism

After the report by Cambien et al.\textsuperscript{33} that the DD genotype of the ACE gene was associated with an increased risk of myocardial infarction, numerous studies have shown that the DD genotype is disadvantageous. Studies in a large population have supported the hypothesis that the DD genotype is a risk factor for myocardial infarction.\textsuperscript{34} The DD genotype has been reported to be associated with excess deaths from ischemic heart disease in parents.\textsuperscript{34} An increased frequency of the DD genotype has been noted in patients undergoing cardiac transplantation for ischemic or idiopathic dilated cardiomyopathy.\textsuperscript{36} Moreover, an association has been observed between the DD genotype and hypertrophic cardiomyopathy with sudden death.\textsuperscript{37} The DD genotype has also been implicated in restenosis after percutaneous transluminal coronary angioplasty.\textsuperscript{38} Our present study suggests that the DD genotype is an independent predictor of the development of LVH, which is consistent with a preliminary report that the DD genotype is a strong risk factor for ECG-LVH.\textsuperscript{46}

Since LVH is an independent risk factor for myocardial infarction and heart failure,\textsuperscript{1,2} our present results strongly support previous findings that the DD genotype is a risk factor for myocardial infarction and heart failure. All of these clinical observations may be interpreted on the basis that the DD genotype is associated with increased plasma ACE, if not directly then as a result of tight linkage to another locus that is important in regulation of this gene.\textsuperscript{28} Unfortunately, no information is available regarding the expression levels of ACE in cardiac and vascular tissues according to I/D polymorphism of the ACE gene. However, ACE activity on T cells from individuals with the DD genotype is reportedly higher than that from individuals with the II or ID genotype.\textsuperscript{47} Therefore, it is tempting to speculate that ACE activity in cardiac tissues and vascular tissues might be higher in the DD genotype than in the II or ID genotype, and higher ACE activity might lead to higher angiotensin II formation in situ, which might facilitate cellular hypertrophy, extracellular matrix formation,\textsuperscript{23,48} and sympathetic neurotransmission.\textsuperscript{49}

Several studies have suggested that tissue ACE plays an important role in regulating angiotensin II production in peripheral tissues. During the chronic phase of two-kidney, one-clip renovascular hypertension in the rat (non-renin-dependent phase), increased expression of ACE activity\textsuperscript{25} and ACE mRNA\textsuperscript{50} has been reported. Increased vascular ACE leads to a parallel increase in vascular angiotensin II formation from angiotensin I.\textsuperscript{25} Likewise, increased expression of ACE and its mRNA was reported in the coarctation model for ventricular hypertrophy.\textsuperscript{19} This increase results in an increased intramyocardial conversion of angiotensin I to angiotensin II.\textsuperscript{19} Although plasma renin activity was not elevated in the chronic phase in this model, converting enzyme inhibitors are effective in preventing ventricular hypertrophy.\textsuperscript{22,51} Thus, modulation of tissue ACE expression seems to control angiotensin II production in the tissues. The effectiveness of converting enzyme inhibitors in the regression of LVH is also well known in clinical settings.\textsuperscript{16} Nevertheless, there is no direct evidence that plasma renin activity affects the development of LVH.\textsuperscript{52} This also suggests that tissue ACE may affect the development of LVH. Assessment of the expression levels of ACE in cardiac tissue according to the genotypes of the ACE gene should provide further insight into this hypothesis.

Acknowledgments

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References

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52. Devereux RB, Savage DD, Drayer JIM, Laragh JH. Left ventricular hypertrophy and function in high, normal, and low-renin forms of essential hypertension. Hypertension. 1982;4:524-531.
DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy.
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