Differences in Frequency of the Deletion Polymorphism of the Angiotensin-Converting Enzyme Gene in Different Ethnic Groups

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Differences in Frequency of the Deletion Polymorphism of the Angiotensin-Converting Enzyme Gene in Different Ethnic Groups

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A polymorphism characterized by the insertion or deletion of a 287-bp Alu repeat sequence in intron 16 of the angiotensin-converting enzyme gene determines about half the serum angiotensin-converting enzyme level variability among individuals. The deletion polymorphism is associated with higher levels of angiotensin-converting enzyme and perhaps with a greater risk of cardiovascular diseases. The relative frequency of this genetic polymorphism in different ethnic groups is not known. The objective of this study was to compare the frequency of angiotensin-converting enzyme gene insertion/deletion polymorphism in different ethnic groups. Angiotensin-converting enzyme genotype was determined in middle-aged healthy hospital workers of three different ethnic origins (African Americans, whites, and Indians). There were 142 African Americans, 136 Indians, and 82 whites. The distribution of the deletion-deletion, insertion-deletion, and insertion-insertion genotypes in African Americans (29%, 60%, and 11%, respectively), Indians (19%, 50%, and 31%, respectively) and whites (29%, 40%, and 31%, respectively) was significantly different ($p = < 0.005$). The frequency of the deletion allele among African Americans, Indians, and whites (0.59, 0.49, and 0.44, respectively) was also significantly different ($p = 0.05$). African Americans had the highest frequency of deletion allele and the lowest frequency of the insertion-insertion genotype among the three groups. The frequency of the deletion polymorphism of the angiotensin-converting enzyme gene is different among African Americans, whites, and Indians. This may be important in relation to the high risk of cardiovascular morbidity and mortality in African Americans and may be relevant in explaining differences in cardiovascular diseases in different populations. This finding also emphasizes the importance of studying angiotensin-converting enzyme gene polymorphism in genetically homogenous populations. Because of the small size of this study, however, these findings need further confirmation.

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Introduction

The epidemiologic features of ischemic heart disease vary in different populations.[1,2] Whereas differences in the prevalence and impact of risk factors, other diseases in the community, and socioeconomic factors may all be important in this regard, differences in genetic predisposition and susceptibility to diseases cannot be excluded.

African Americans seem to have a lower prevalence of angiographic coronary artery disease than whites.[3,4] Despite this fact, African Americans have a similar or higher risk of cardiovascular morbidity and mortality, and sudden cardiac death compared with findings in whites.[4] Factors other than angiographic coronary artery disease may, therefore, be involved in the risk of cardiovascular disease and sudden cardiac death in African Americans.

Left ventricular hypertrophy (LVH) is an independent predictor of mortality[5] and is more common in African Americans than in whites.[4,6] Coronary artery disease and systemic hypertension can lead to the development of LVH. Neurohormonal factors can also promote the development of LVH. One important neurohormonal factor that causes LVH is angiotensin II.

Angiotensin II is formed by the action of angiotensin-converting enzymes (ACE) on angiotensin I. A polymorphism characterized by insertion (I) or deletion (D) of a 287-bp Alu repeat sequence in intron 16 of human ACE gene is responsible for about half of the ACE level variability among individuals.[7] The D polymorphism is associated with a higher level of ACE. The D polymorphism has been reported to be associated with an increased risk of LVH and myocardial infarction in certain populations.[8,9] There are no data on the frequency of ACE gene polymorphism in African Americans or in persons of Indian origin. The objective of this study was to compare

Table I. Clinical characteristics of African Americans, whites and Indians.

Characteristic	African Americans n = 142	Whites n = 82	Indians n = 136
Age*†	45 ±13	36 ±11	36 ±10
Height†	64 ±6.2	67.5 ±4.8	65 ±4.7
Weight*†	168 ±37	167 ±33.6	152 ±25.5
Systolic BP†	128 ±17	120 ±13	118 ±12
Diastolic BP†	78 ±12	76 ±9	75 ±8
Men,* n (%)	52 (36.6)	50 (60.9)	83 (61)
Hypertension,* n (%)	39 (27.4)	6 (7.3)	10 (7.3)
Diabetes mellitus, n (%)	15 (10.5)	4 (4.8)	10 (7.3)
Angina, n (%)	11 (7.7)	4 (4.8)	4 (2.9)
Coronary artery disease,‡ n (%)	8 (5.6)	2 (2.4)	4 (2.9)
Stroke, n (%)	3 (2.1)	0 (0)	1 (0.7)
Heart failure, n (%)	3 (2.1)	0 (0)	0 (0)
Myocardial infarction or sudden death in 1st-degree relatives, n (%)	20 (14)	18 (21.9)	22 (16.1)

*$p = < 0.01$ by chi-square test for overall difference among the three groups. †Mean ± SD.
‡History of myocardial infarction, angiographic coronary disease, or positive stress test.

the distribution of the ACE genotypes in persons of three ethnic groups: African Americans, whites in the United States, and persons of origin in the Indian subcontinent.

Methods

The study subjects were employees at the Cook County Hospital in Chicago, IL. Apparently healthy persons 20 to 55 years of age were eligible to participate. The volunteers completed a questionnaire. The investigators measured the blood pressure and heart rate. African Americans were defined as self-identified Americans of African origin excluding first-generation immigrants. White Americans of European origin were identified as whites. Since persons of Indian or Pakistani origin living in the United States have a common ethnic ancestry, they are defined as Indians.

The ACE genotype was determined by polymerase chain reaction (PCR) analysis on DNA isolated from peripheral blood mononuclear cells. The PCR products were separated by electrophoresis on 2% agarose gel and identified by ethidium bromide staining. Individuals with the insertion-insertion (II) genotype had 490-bp PCR products, individuals with the deletion-deletion (DD) genotype had 190-bp PCR product, and individuals with the insertion-deletion (ID) genotype had both 490- and 190-bp PCR products.[7]

Clinical variables and genotypes among the three ethnic groups were compared. Clinical variables in subjects with ID/DD genotype vs those in subjects with the II genotype within each ethnic group were also compared; $p \leq 0.05$ by chi-square test for discrete variables and *t* test for continuous variables were considered statistically significant. The institutional review board of Cook County Hospital approved the study. The participants gave informed consent.

Results

Table I shows the clinical variables of the study subjects. There were 142 African Americans, 82 whites, and 136 Indians. Height, weight, and systolic blood pressure were significantly different among the three ethnic groups ($p \leq 0.05$ for overall difference among the three ethnic groups for each of these variables). There were no significant differences in the frequency of other variables in the three groups.

Table II shows the genotypes in the three ethnic groups. The distribution of the genotypes was significantly different among the three groups ($p < 0.005$). African Americans had the lowest frequency of the II genotype ($p < 0.003$ for the overall difference among the three ethnic groups). African Americans also had the highest frequency of the D allele among the three groups ($p = 0.05$). The difference in the frequency of D

Table II. ACE genotype in African Americans, whites and Indians.

Genotype*	African Americans, n (%) n = 142	whites, n (%) n = 82	Indians, n (%) n = 136
DD	44 (30.9)	24 (29.2)	26 (19.1)
ID	80 (56.3)	35 (42.6)	72 (52.9)
II	18 (12.6)	23 (28.0)	38 (27.9)
Frequency of D allele†	0.59	0.50	0.45

*$p < 0.005$ for the distribution of the genotype among the three groups.
†$p = 0.05$ by chi-square test for the difference in the frequency of the D allele among the three groups.

allele was statistically significant between African Americans and Indians ($p < 0.001$) and between whites and Indians ($p < 0.03$), but not between African Americans and whites ($p < 0.08$). There were no statistically significant differences in the frequency of clinical variables in persons with the ID/DD genotype compared with persons of the II genotype within any ethnic group (analysis not shown).

Discussion

This study shows that the distribution of ACE genotypes is different among African Americans, whites, and Indians. Therefore, it is important that studies of gene polymorphism in general and of ACE gene polymorphism in particular be conducted in genetically homogenous populations. The differences in the distribution of ACE genotype may be an important factor in the relative risk of cardiovascular morbidity and mortality in different populations.

The higher frequency of the D polymorphism seen in African Americans in this study is not related to the higher systolic blood pressure in this group because previous studies have shown that there is no correlation between ACE gene polymorphism and blood pressure.[10] It is known that African Americans have a greater prevalence of LVH and a higher proportion of sudden cardiac death despite a lower prevalence of angiographic coronary artery disease compared with whites.[4] The D polymorphism of the ACE gene has been reported to be associated with an increased risk of LVH by electrocardiography.[8] There is, however, contradictory evidence for its association with echocardiographic LVH.[11,12] The greater frequency of the D polymorphism of ACE gene may have an important role in the pathogenesis of LVH and high risk of cardiovascular morbidity and mortality in African Americans.

Angiotensin-converting enzyme catalyzes the synthesis of angiotensin II as well as the degradation of bradykinin. Angiotensin II is a powerful vasoconstrictor and acts as a growth factor for both the myocardium and the vascular smooth muscle cells.[7] On the other hand, bradykinin is a potent vasodilator.[7] The D polymorphism of the ACE gene is associated with higher levels of ACE in the plasma and in T lymphocytes[13] as well as in the myocardium.[14] The increased risk of LVH and other cardiovascular diseases associated with the D polymorphism of the ACE gene may, therefore, be mediated through an increased production of angiotensin II or through an enhanced degradation of bradykinin.[15]

The main limitation of the study is its relatively small size. Compared with previous reports,[7,8,12] the white subjects in our study had a lower frequency of the D allele. This may be because the whites in different studies are not genetically homogenous. Alternatively, it may be because estimates of the frequency of alleles from small sample sizes may not be reliable. Furthermore, the study did not have adequate power to detect differences in clinical events in persons of different ACE genotypes within each ethnic group.

Conclusion

The distribution of the ACE genotypes is different in African Americans, whites, and Indians. These findings emphasize the importance of studying ACE gene polymorphism in genetically homogenous populations. Angiotensin-converting enzyme gene polymorphism may be a relevant factor in differences in the epidemiologic features of ischemic heart disease in different populations. African Americans seem to have a higher frequency of the D polymorphism compared with the other ethnic groups. This may be an important factor in the high risk of cardiovascular morbidity and mortality in African Americans. Because of the small size of the study, however, these findings need further confirmation.

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