Angiotensin converting enzyme insertion/deletion polymorphism: association with ethnic origin

Jacqueline Barley, Alison Blackwood*, Nicholas D. Carter, Douglas E. Crews†, J. Kennedy Cruickshank‡, Stephen Jeffery, Afolabi O. Ogunlesi** and Giuseppe A. Sagnella*

Objective: To determine the distribution of the insertion/deletion (*I/D*) polymorphism of the angiotensin converting enzyme (ACE) gene in several ethnic groups: Caucasian Europeans, Black Nigerians, Samoan Polynesians and Yanomami Indians.

Results: The ratio of the frequencies of the *II*, *ID* and *DD* genotypes were 1 : 2 : 1 in the Europeans, but there was a tendency towards a higher frequency of the *D* allele in the Nigerians. In contrast, the Samoans and the Yanomami Indians displayed a much higher frequency of the *I* allele than of the *D* allele.

Conclusion: The relationship between ACE genotype and disease in these latter groups is still not known, but the present results clearly suggest that ethnic origin should be carefully considered in the increasing number of studies on the association between *I/D* ACE genotype and disease aetiology.

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Introduction

Genetic studies in the stroke-prone spontaneously hypertensive rat have demonstrated that a locus linked to the angiotensin converting enzyme (ACE) gene is strongly associated with blood pressure [1]. Rigat and co-workers [2,3] identified an insertion/deletion (*I/D*) polymorphism in intron 16 of the ACE gene in humans and demonstrated that this polymorphism was associated with serum ACE levels. More recently, the presence of the *D* (deletion) allele of this polymorphism has been found to be strongly associated with an increased risk of heart attack independent of other risk factors [4].

Although the pathophysiology and genetics of the renin–angiotensin system are well known, with lower activity in Black populations [5], the effect of ethnicity on variation in the ACE gene polymorphism has received relatively little attention. Hence, in the present study we investigated the distribution of this *I/D* polymorphism of the ACE gene in material from several different populations.

Subjects and methods

The frequency distribution of the *I/D* ACE genotype was measured in four ethnic groups. Caucasian Europeans; a sample (n = 186) of Caucasian subjects visiting or working at a major London hospital as detailed previously [6]. Nigerian Blacks; a sample (n = 80) of Black Nigerians randomly sampled from a working population (largely bank workers) in Ibadan, Nigeria. Samoans; samples were collected from a group of 58 Samoans as part of an anthropological study of the Samoan population; details of sampling and blood collection have been described previously [7]. Yanomami Indians; this group consisted of 49 native Yanomami Indians living along

From the Medical Genetics Unit and the *Blood Pressure Unit, St George's Hospital Medical School, London, the †Department of Anthropology, Ohio State University, Columbus, Ohio, USA, the ‡Clinical Epidemiology Unit, University of Manchester Medical School, Manchester, UK, and the **Department of Medicine, University College Hospital, Ibadan, Nigeria.

Requests for reprints to: Professor N. Carter, Medical Genetics Unit, St George's Hospital Medical School, London SW17 0RE, UK.

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the border between Brazil and Venezuela; full details of blood sampling were reported previously [8].

DNA analysis for angiotensin converting enzyme (*I/D*) genotype

Genomic DNA was isolated from blood leucocytes by the standard proteinase K–phenol method. The *I/D* ACE polymorphism was identified using polymerase chain reaction as reported previously [4]. The reaction products were analysed by agarose gel electrophoresis and two alleles were identified: a 190-b.p. fragment *D* (in the absence of the insertion) and a 490-b.p. fragment *I* (in the presence of the insertion).

Statistical analysis

Significant differences in frequency distributions were assessed using χ^2-tests.

Results

The distributions of the *II*, *ID* and *DD* genotypes in the four ethnic groups are shown in Fig. 1. The frequency distribution in the Caucasian European group (24.7, 48.4 and 26.9% for the *II*, *ID* and *DD* genotypes, respectively) was essentially as reported previously in European populations [3,9]; within the Black Nigerians the frequencies were slightly different; 16.2, 48.8 and 35.0% ($\chi^2=3.1$, $P=0.08$). In contrast, there were marked differences in the Samoan (82.8, 15.5 and 1.7%; $\chi^2=63.2$, $P<0.001$) and Yanomami (71.4, 26.5 and 2.0%; $\chi^2=40.4$, $P<0.001$) groups compared with the Caucasian Europeans. In these populations the frequency distribution of the *D* allele was considerably lower and that of the *I* considerably greater than those found in either the Caucasian Europeans or the Black Nigerians. There was no significant difference in the frequency distribution between the Samoans and the Yanomami groups.

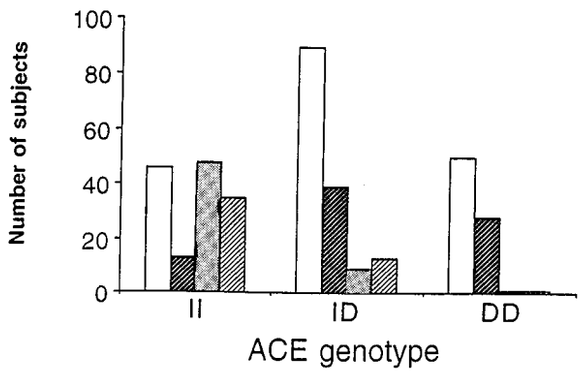

Fig. 1. Distribution of *II*, *ID* and *DD* genotypes among the four populations: □, Caucasians; ▩, Nigerians; ▒, Samoans; ▨, Yanomami Indians.

Discussion

Recent work on the *I/D* ACE polymorphism has demonstrated that the *DD* genotype is associated with increased risk of cardiovascular disease, especially in those without other risk factors [4], excess deaths from ischaemic heart disease in parents of those with the *DD* genotype [10], dilated or hypertrophic cardiomyopathy and sudden death [11,12], and restenosis [13].

However, little attention has been given to the impact of race or ethnic origin on this polymorphism. The major objectives of the present work were to establish the frequency distribution of the ACE gene *I/D* polymorphism with respect to ethnic origin. In several groups of subjects sampled from populations living within the London area, the frequency distribution of this polymorphism in the Caucasian European group was similar to that found in previous studies in European populations. The distribution was essentially 1 : 2 : 1, which is consistent with a Hardy–Weinberg equilibrium (as were the other genotype frequencies reported here).

A more novel aspect of the present work is the demonstration of significant ethnic differences. For comparison, the frequency of the *I/D* genotype has been estimated not only in Caucasian subjects of European descent but also in Black Nigerians, in a Polynesian sample (Samoans) and in South American natives (Yanomami Indians). The results demonstrate a small difference in the frequency distribution of the genotypes between Caucasians and Blacks, with the *D* allele tending to be more frequent in the Nigerians. In contrast, there was a striking preponderance of the *I* allele in the Samoans and Yanomami. The reason for this may be based on genetic drift related to common founder populations, as is found for many other polymorphisms such as blood groups, and we cannot exclude completely the influence of some unknown sampling bias. A more intriguing possibility is that some selective mechanism has increased the frequency of the *I* allele (the gene with low risk of myocardial infarction) in the Yanomami and Samoan populations. To test this hypothesis, a more detailed cross-sectional study of cardiac patients is necessary to evaluate whether the *D* allele is a similar risk factor in these as in Caucasian Europeans. Although coronary disease rates are just beginning to rise in the Samoan population, this group are more noted for their high levels of obesity and high prevalence of, and mortality rates from, diabetes [7]. The significance of the high frequency of the *I* allele in relation to diabetes and obesity remains to be resolved.

An interesting observation is that the Yanomami Indians also had a very high frequency of the *II* genotype compared with the *DD* genotype. Cardiovascular disease is still uncommon in this population, though they are known to be a low-salt culture and earlier studies have demonstrated that their blood pressure does not increase with age [14,15]. A recent study describes significantly increased *D* alleles in an elderly French population aged

approximately 100 years [16]. Thus, the longevity effect on *D* allele frequency also needs to be considered with different ethnic groups.

In conclusion, the differences demonstrated between these ethnic groups in the frequency distribution of the ACE genotypes emphasize the importance of using homologous populations in studies comparing ACE gene polymorphisms with predisposition to cardiovascular diseases.

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