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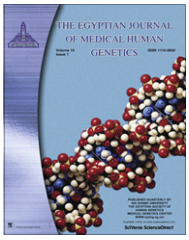

ORIGINAL ARTICLE

A study of the M235T variant of the angiotensinogen gene and hypertension in a sample population of Calabar and Uyo, Nigeria

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Abstract A common molecular variant of the angiotensinogen gene had been reported to predispose some ethnic groups to hypertension. This case–control study was designed to determine the frequency and association of the angiotensinogen M235T allele with hypertension in residents of Calabar and Uyo cities, south–south Nigeria.

The study involved 1308 subjects, 612 patients and 696 controls. The M235T variant was investigated using an allele specific polymerase chain reaction and enzymatic digestion to determine allele frequencies. Hypertensinogenic factors such as dietary habits, physical activity, smoking and drinking habits were assessed using questionnaires. Descriptive statistics, chi-square and multiple regression analysis were used to analyze the data obtained.

The M235T allele frequency was high (0.94 for hypertensives and 0.96 for controls) though it was not associated with hypertension status. The odds ratio for hypertension was 0.64 (95% confidence interval: 0.39–1.06) there were no significant differences between the genotype frequency of hypertensives and controls. By multiple regression, Hypertension was observed to be associated with age and was a predictor for systolic blood pressure in both patient $r^2 = 0.359$; $p < 0.05$ and control groups $r^2 = 0.26$.

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Age and body mass index were predictors for diastolic blood pressure in the control group, $r^2 = 0.28$.

Although the frequency of the M235T variant was high, it was not a significant risk factor for hypertension in the study population.

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1. Introduction

Hypertension is a multifactorial disorder because of the interaction of many risk genes such as molecular variants of the angiotensinogen gene, angiotensin converting enzyme gene, angiotensin II receptor I gene and the corin gene [1–4], and environmental factors such as obesity, body mass index (BMI), dietary salt intake, alcohol consumption, stress and high-density lipid (HDL)–cholesterol levels. Genes determine approximately 20–60% of the variability in blood pressure in different populations [4,1].

Most studies so far have focused on the genes of the renin–angiotensin–aldosterone system such as the *M235T* variant in the angiotensinogen gene, which has been associated with increased circulating angiotensinogen levels and blood pressure in many distinct populations [5–7] and a common variant in the angiotensin-converting enzyme (ACE) gene that has been associated in some studies with blood pressure variation in men [8,9]. However, these variants seem to only modestly affect blood pressure, and other candidate genes have not shown consistent and reproducible associations with blood pressure or hypertension in larger populations [10] thus, demonstration of common genetic causes of hypertension in the general population remains elusive [6,11,12].

The renin–angiotensin (R–A) system is a powerful pressure system which influences salt and water homeostasis. Angiotensinogen (AGT) is a key component of this system, it is cleaved by renin to yield angiotensinogen 1 (AGT 1), which is cleaved by angiotensinogen converting enzyme (ACE) to yield angiotensinogen II (AGT II), responsible for carrying out a range of functions that include prompting the constriction of blood vessels causing a rise in blood pressure, ensuring the release of aldosterone which induces an increase in the re-absorption of sodium by the Kidneys [13].

Many research groups have reported that among the two important molecular variants of AGT characterized so far, the M235T allele is the predominant allele in Blacks accounting for a frequency between 80% and 93% in the population. Most of the studies carried out so far in Nigeria have been concentrated in individuals and population in the South Western part of the country. Little is found in literature on hypertension in other geographical and ethnic areas of Nigeria, and its genetic epidemiology, especially since variations in the dietary intake, culture (way of life) etc. exist in these places. In Blacks, differences have been observed in the expression of risk factors such as level of circulating angiotensinogen, urbanization, dietary factors and metabolic disorder for hypertension depending on the environment [14–16].

The aim of this study was to determine the frequency of the M235T allele of the angiotensinogen gene and its association with hypertension status in the study population.

2. Subjects and methods

Venous blood (3 ml) was collected from each participant after they had given informed consent, into bottles containing anticoagulant EDTA. Plasma was obtained by centrifugation of blood samples. Blood and plasma were kept frozen in the freezer/cold room, then transported to the Department of Zoology University of Ibadan where samples were kept at −70 °C. Samples were then transported to freezers in the International Institute of Tropical Agriculture, Ibadan for subsequent lab investigations. DNA was extracted from blood for angiotensinogen (AGT) genotyping. For some participants who refused blood collection from the upper arm, blood was obtained from thumb pricks and blotted onto a filter (Whatman, No. 3) paper, allowed to dry at room temperature and preserved in plastic bags prior to DNA extraction.

Participants included in the study gave informed consent and ethical approval for the study was obtained from the joint UI/UCH Ethics Review Committee and each of the health establishment concerned – University Teaching Hospital Calabar, University of Uyo Teaching Hospital and the General Hospital, Calabar.

The wall in the collection centre was calibrated in meters. Individuals stood without foot or head wear facing the investigator, looking straight ahead and the investigator placed a ruler on top of the head of the individual and the reading in meters was recorded. Using the conventional weight scale, weight was measured in kilograms.

Blood pressure readings were taken using a sphygmomanometer in millimeters of mercury systolic and diastolic BP values were recorded. Before taking the measurement, the respondent was advised to sit quietly for 5 min, with the legs uncrossed and the right hand free from clothing. The right hand was placed on the table with the palm facing upward. The appropriate cuff size was selected and the cuff wrapped and fastened securely. The cuff was kept at the same level as the heart during measurement. The upper reading, the systolic blood pressure (SBP) and lower reading the diastolic blood pressure (DBP) were recorded, the first and second readings were taken twice and the average of the two used for the analysis.

2.1. DNA extraction

DNA was extracted according to the method developed by Dellaporta et al. [17] with a little modification. The DNA was re-suspended in 50 μl of Tris–EDTA buffer and stored in the freezer as stock solution.

An aliquot of the DNA stock solution was run on agarose gel electrophoresis to check the quantity of DNA. Each sample of genomic DNA (5 μl) was mixed with 2 μl of loading dye and transferred into the wells of the gel. A voltage of 110 V was applied for about 45 min. The samples were scored +, 2+,

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