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Aldosterone Synthase Promoter Polymorphism and Cardiovascular Phenotypes in a Large, Multiethnic Population-Based Study

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Abstract

Background—A single-nucleotide polymorphism in the aldosterone synthase gene (CYP11B2) promoter [–344c/t, rs1799998] has been reported to associate with cardiovascular phenotypes.

Methods—The Dallas Heart Study is a large, multiethnic cohort with a high prevalence of hypertension. We genotyped 3452 Dallas Heart Study participants for –344C/T. Generalized linear models were used to assess whether variation at –344C/T associated with plasma aldosterone concentration (PAC), systolic and diastolic blood pressure (SBP and DBP), plasma glucose (in persons with no diabetes), HOMA IR (Homeostasis Model Assessment as an Index of Insulin Resistance), and left ventricular (LV) mass indexed to height. Systolic blood pressure and DBP were significantly higher in blacks compared with whites ($P < 0.001$ for SBP and for DBP) and Hispanics ($P < 0.001$ for SBP and for DBP). Log-transformed body mass index was also significantly higher in blacks compared with whites ($P < 0.001$), but not Hispanics ($P = 0.10$). Log-transformed PAC was higher in whites compared with blacks ($P < 0.001$), but did not differ significantly in whites compared with Hispanics ($P = 0.73$). In univariate and multivariable analysis, –344C/T was not significantly associated with PAC within any ethnicity. In univariate and multivariable analysis, –344C/T was not associated with SBP or DBP within any ethnicity. After adjustment for multiple testing, univariate and multivariable analyses revealed no association between –344C/T and plasma glucose in patients with no diabetes, HOMA IR, or LV mass indexed to height.

Conclusions—We were unable to reproduce previously reported associations between –344C/T and PAC, blood pressure, plasma glucose, or LV mass. Methodological differences might explain the differences between our findings and those previously reported

Keywords

aldosterone; hypertension; genetics; glucose; left ventricular mass

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A single-nucleotide polymorphism (SNP) in the promoter region of the gene encoding aldosterone synthase (*CYP11B2*) has been reported to associate with a spectrum of human diseases and intermediate phenotypes.¹⁻¹⁸ Aldosterone production has been reported to associate with variation at this locus [-344C/T, rs1799998].¹ Moreover, clinically overt phenotypes that may be mediated by aldosterone have been linked to this SNP. For example, left ventricular (LV) morphology,¹⁷ blood glucose,¹⁸ congestive heart failure outcome,⁷ and hypertension¹ have been reported to associate with -344C/T.

Candidate gene studies have been criticized for failing to produce replicable results.¹⁹ Indeed, a number of the reported associations with -344C/T have not been verified in other studies. We and others have reported a lack of association between -344C/T and hypertension^{17,20} and LV morphology^{20,21} Because studies of -344C/T have been conducted primarily in lone, ethnically homogeneous populations, the conflicting findings might indicate that the -344C/T polymorphism is not the causal variant itself, but is rather a marker in linkage disequilibrium with a nearby causal variant. Different patterns of linkage disequilibrium in different ancestry groups might explain the presence of association in one group and absence in another. Alternatively, differences in methods could account for the variable findings. Therefore, we assessed for evidence of association of the aldosterone synthase promoter polymorphism with cardiovascular phenotypes within 3 ethnicities ascertained in a single cohort study.

The Dallas Heart Study (DHS) is a large multiethnic population-based study with a high prevalence of hypertension. Owing to its internally consistent methods and multiethnic population, the DHS is a unique resource for evaluating whether a genotype-phenotype association is dependent on genetic admixture. Accordingly, we used data from this study to evaluate persistent questions about associations between -344C/T and cardiovascular phenotypes.

Materials and Methods

Study Population

Participants were a subset of the DHS, which has been described in detail previously.²² Data are cross-sectional in nature and were gathered in 2007 to 2008, during DHS phase 1. Adults between the ages of 18 and 65 years were selected using a probability-based algorithm designed to ascertain equal numbers of African American and non-African American study participants. Up to 3 study visits were conducted the first of which was in the home. Self-assigned ethnicity was recorded as “non-Hispanic black,” “non-Hispanic white,” “Hispanic,” or “other ethnicity” during the first study visit. The small group of patients whose ethnicity was self-assigned as “other” (n = 75 with genotype data) was excluded to avoid confounding by hidden population stratification. The study was approved by the University of Texas Southwestern Medical Center at Dallas institutional review board. Written informed consent was obtained from all participants.

Anthropometric and Clinical Laboratory Evaluation

Anthropometric characterization included height, weight, and waist and hip circumferences. In addition, body composition was determined in a subset of patients (n = 2904) using dual-energy x-ray absorptiometry (DXA). Percent body fat was calculated as the total body fat mass divided by total body mass $\times$ 100. In addition, LV morphology and function were determined by cardiac MRI in a subset of patients (n = 2726). Study participants between the ages of 30 and 65 years were invited to a second home visit (patients aged <30 years having been invited during an earlier portion of the study). During the second study visit, a fasting venous blood sample and first morning urine were collected. These samples were maintained on ice during transport to the medical center. Plasma and serum were isolated, aliquoted and stored for future assays.

Blood Pressure Measurement

During each study visit, blood pressure (BP) and heart rate were measured 5 times in the seated position with a Series 52000 automatic oscillometric BP cuff (Welch Allyn, Skaneateles Falls, NY). To minimize the impact of the alerting response,²³ the mean of the last 3 measurements was recorded. Study personnel were trained to use the device and to choose an appropriate cuff size.

Genotyping

DNA was isolated from leukocytes, and the TaqMan assay system (Applied Biosystems, Foster City, CA) was used to perform the genotyping.

Statistical Methods

Analyses were performed using R version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22 (IBM, Armonk, NY). Hardy-Weinberg equilibrium (HWE) calculations were performed using the exact test²⁴ as implemented in the R package *HardyWeinberg*. Comparisons of continuous and categorical baseline characteristics were performed with 1-way analysis of variance (ANOVA) and χ^2 test, respectively. Continuous data are represented as mean $\pm$ SD. One-way ANOVA and generalized linear models adjusted for ethnicity were used to assess whether variation at –344C/T associated with quantitative phenotypes. Moreover, ethnicity-stratified generalized linear models were used to test for association under 5 different genetic models (codominant, dominant, recessive, additive, and log-additive; R package *SNPAssoc*).

Within each ethnicity, we assessed for association between –344C/T genotype and quantitative phenotypes, including plasma aldosterone concentration (PAC), systolic (SBP) and diastolic BP (DBP), plasma glucose in patients with no diabetes, HOMA IR (Homeostasis Model Assessment as an Index of Insulin Resistance), and LV mass indexed to height. The multivariable model for association between –344C/T and PAC included ethnicity, age, and sex. The ethnicity-stratified model was identical, except for the removal of ethnicity from the model. Values below the limit of detection of the PAC assay were taken to be 2.5 ng/dL, the value half-way between the limit of detection and 0. Because of nonnormality as assessed by QQ plot, PAC, HOMA IR, and LV mass indexed to height were natural log transformed. Logistic regression was used to evaluate the possibility that an

association between genotype and aldosterone was obscured because of the nonnormality of the PAC distribution.

The multivariable model for association between genotype and SBP or DBP included ethnicity, age at time of visit 1, sex, and body fat percentage by DXA scan. In addition, we assessed the relationship between genotype and BP, stratified by ethnicity and adjusted for age, sex, and body fat percentage. We used the mean of nonmissing SBP and DBP values from 3 study visits as the dependent variables in these BP models. Multivariable regression models, described below, were used to assess the relationship between genotype and plasma glucose in patients with no diabetes, HOMA IR, and LV mass indexed to height. $P < 0.05$ was considered statistically significant.

Results

Study Population Characteristics

We genotyped 3452 DHS participants for $-344C/T$. The characteristics of these study participants are shown in Table 1. Of the characteristics assessed, only serum potassium did not differ significantly between the 3 ethnic groups. For example, SBP and DBP were significantly higher in blacks compared with whites ($P < 0.001$ for SBP and DBP) and Hispanics ($P < 0.001$ for SBP and DBP). Log-transformed body mass index was also significantly higher in blacks compared with whites ($P < 0.001$), but not Hispanics ($P = 0.10$). Log-transformed PAC was higher in whites compared with blacks ($P < 0.001$), but did not differ significantly in whites compared with Hispanics ($P = 0.73$).

Genotyping Results

Table 2 shows the overall genotype frequencies for the 3 ethnicities. Genotypes were in HWE among Hispanics ($P = 0.31$) and non-Hispanic whites ($P = 0.22$), but departed marginally from HWE in non-Hispanic blacks ($P = 0.03$, not statistically significant if adjusted for multiple testing in 3 ethnicities). The C allele frequency was significantly lower in blacks compared with whites ($P < 0.001$) and Hispanics ($P < 0.001$).

Tests of Genetic Association

In univariate analysis, genotype did not associate with ln-transformed PAC within any ethnicity (1-way ANOVA, $P = 0.19$ for non-Hispanic blacks, $P = 0.96$ for Hispanics, $P = 0.22$ for non-Hispanic whites; Fig. 1). A C allele–dominant model similarly showed no significant association within any ethnicity ($P = 0.50$ for non-Hispanic blacks, $P = 0.79$ for Hispanics, $P = 0.18$ for non-Hispanic whites). In multivariable analysis adjusted for ethnicity, age, and sex, there was no significant association between genotype and ln-transformed PAC ($P = 0.13$). In ethnicity-stratified multivariable analysis adjusting for age and sex, there was no association between genotype and ln-transformed PAC ($P = 0.11$ for non-Hispanic blacks, $P = 0.94$ for Hispanics, $P = 0.31$ for non-Hispanic whites). Moreover, $-344C/T$ was not significant in multivariable dominant, recessive, overdominant, and log-additive models of association with ln-transformed PAC. In a multivariable logistic regression model adjusted for $-344C/T$ genotype, sex, age, and ethnicity, genotype was not associated with an undetectable ln-transformed PAC ($P = 0.89$).

In univariate analysis, CYP11B2 promoter polymorphism genotype was not associated with SBP within any ethnicity (1-way ANOVA, $P=0.06$ for non-Hispanic blacks, $P=0.99$ for Hispanics, and $P=0.23$ for non-Hispanic white; Fig. 1). Likewise, there was no association between genotype and DBP by 1-way ANOVA ($P=0.27$ for non-Hispanic blacks, $P=0.85$ for Hispanics, $P=0.48$ for non-Hispanic whites). Presence of a C allele was not associated with SBP or DBP within any ethnic group (Student t test, $P>0.05$ for SBP and DBP in all ethnic groups). In multivariable linear regression adjusting for ethnicity, age, sex, and percent body fat, genotype was not associated with SBP ($P=0.08$) or DBP ($P=0.28$). In an ethnicity-stratified multivariable linear regression model adjusting for age, sex, and percent body fat, genotype was not significantly associated (after correction for multiple testing) with mean SBP within any ethnicity (uncorrected $P=0.02$ for non-Hispanic blacks, $P=0.94$ for Hispanics, $P=0.22$ for non-Hispanic whites). In an ethnicity-stratified multivariable model adjusting for the same factors, genotype did not associate with mean DBP over 3 visits within any ethnicity ($P=0.12$ for non-Hispanic blacks, $P=0.60$ for Hispanics, $P=0.50$ for non-Hispanic whites).

In univariate analysis corrected for multiple testing, $-344C/T$ genotype did not associate with glucose in patients with no diabetes (1-way ANOVA, $P=0.22$ for non-Hispanic blacks, $P=0.02$ for Hispanics, $P=0.12$ for non-Hispanic whites, prior to correction for multiple testing) or ln-transformed HOMA IR ($P=0.93$ for non-Hispanic blacks, $P=0.53$ for Hispanics, $P=0.30$ for non-Hispanic whites; Fig. 1). No significant univariate association was found between genotype and glucose in patients with no diabetes or HOMA IR within any ethnicity using any of 5 genetic models. After adjustment for multiple testing, $-344C/T$ was not significant in multivariable analysis of the association between genotype or alleles and glucose in patients with no diabetes or ln-transformed HOMA IR (adjusted for ethnicity, age, sex, and percent body fat) or in ethnicity-stratified multivariable analyses.

In univariate testing, there was no significant association within any ethnicity between $-344C/T$ genotype and ln-transformed LV mass by MRI (indexed to height) within any ethnicity ($P=0.90$ for non-Hispanic blacks, $P=0.42$ for Hispanics, and $P=0.63$ for non-Hispanic whites). Genotype was marginally significant prior to, but not after, correction for multiple testing in a regression model adjusted for ethnicity, age, sex, and mean SBP (uncorrected $P=0.03$). Genotype was not significant within any ethnicity in a linear regression model adjusted for age, sex, and mean SBP ($P=0.90$ for non-Hispanic blacks, $P=0.42$ for Hispanics, and $P=0.63$ for non-Hispanic whites).

Discussion

In a large, multiethnic population-based study, we found no association between $-344C/T$ genotype or allele and PAC, SBP, DBP, glucose in patients with no diabetes, HOMA IR, or LV mass index to height in each of 3 ethnicities. The frequency of the C allele was lower among African Americans (22%), compared with European (46%) and Hispanic Americans (41%). Indeed, the genotypes in African Americans departed from the ratio predicted by the HWE principle, although only marginally.

Our finding of no association between –344C/T genotype and BP is in keeping with a meta-analysis performed by Connell et al.²⁵ They found that addition of several thousand white patients from BRIGHT (British Genetics of HyperTension Study) and a Swedish cohort to a large, previously published meta-analysis²⁶ changed the findings. An association between –344C/T T allele and hypertension was no longer seen after the addition of these patients. The authors attributed this change in the results of the meta-analysis to the strict minimization of population stratification in the BRIGHT and Swedish study patients. We agree that population stratification may have contributed to the positive findings of some prior investigations. However, a large meta-analysis in a Japanese population found an association between –344C/T and hypertension. As our study did not include Japanese patients, our data neither refute nor confirm this finding.

Barbato et al.¹ found an association of –344C/T genotype with aldosterone in a multiethnic cohort. In that study, the relationship between genotype and aldosterone was examined in the entire population, disregarding ethnicity in the analysis. In contrast, we assessed for associations after adjusting for ethnicity or after stratifying by ethnicity, more common approaches that account for potential population stratification. In addition, Barbato et al. found an association between –344C/T TT genotype and higher SBP and DBP after adjusting for age, sex, and ethnicity. Because we used consistent methods to study 3 ethnicities, our study presented the opportunity to assess whether genotype-phenotype associations were specific to 1 or more ethnicities. The lack of such associations was consistent across the 3 ethnic groups we studied.

Our study has several limitations. –344C/T genotypes for non-Hispanic blacks were found to deviate from HWE. Such departures can be caused by genotyping error. However, using an α of 0.05 to reject the null hypothesis, 1 in 20 population samples is expected to have genotype frequencies that fall outside HWE by chance. It is reasonable to correct for multiple testing because we tested HWE in 3 ethnic populations, and a common correction (Bonferroni) yields a nonsignificant *P* value. In addition, ethnicity was self-assigned, rather than assessed by ancestry-informative markers. Although our data suggest a lack of association between –344C/T genotype and PAC, a limitation in the aldosterone data must be considered. Many of the patients in our cohort had a PAC below the limit of detection. Irrespective of the manner of handling such data (several methods have been proposed in the literature), the study's power to find associations with PAC is limited by the lack of quantifiable PAC in these individuals.

In conclusion, previously reported associations between –344C/T and PAC, SBP, DBP, glucose, HOMA IR, and LV mass indexed to height were not seen in a large, multiethnic population-based study. These findings were consistent in each ethnicity, diminishing the likelihood that particular genetic admixtures interact with –344C/T to produce cardiovascular phenotypes. Confounding by population stratification likely has contributed to some of the previously reported associations between variation at this locus and phenotypes. Future studies that include genetic markers of ancestry may help further clarify whether population stratification figures in the lack of consistency between studies of –344C/T.

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Figure 1.

Log-transformed plasma aldosterone (Ln PAC), mean SBP, log-transformed HOMA IR (Ln HOMA IR), and log-transformed LV mass indexed to height (Ln LV mass) according to aldosterone synthase promoter polymorphism genotype within each of the 3 ethnic populations. The horizontal black line within each box indicates the median, and each box spans the first and third quartiles. The whiskers extend to 1.5 times the interquartile range. Extreme observations outside 1.5 times the interquartile range are indicated by black circles.

Table 1
Characteristics of Study Participants Genotyped for CYP11B2 Polymorphism

	Non-Hispanic black		Hispanic		Non-Hispanic white		<i>P</i>
	Mean	SD	Mean	SD	Mean	SD	
	(n = 1813)		(n = 599)		(n = 1040)		
Age, y	44.6	10.2	40.0	9.2	44.7	10.0	<0.001
Sex (% male)	42.1		41.9		47.8		0.008
SBP,* mm Hg	131.1	18.1	120.3	14.9	122.8	13.8	<0.001
DBP,* mm Hg	80.8	9.5	75.3	8.0	77.1	7.9	<0.001
BMI, kg/m ²	30.5	7.6	29.5	6.0	28.4	6.5	<0.001
Body fat by DXA, %	31.9	10.7	33.4	9.0	32.1	9.3	<0.018
Na, serum, mmol/L	137.3	2.5	137.7	2.3	138.0	2.4	<0.001
K, serum, mmol/L	4.2	1.6	4.4	1.8	4.3	2.0	0.35
Cr, serum, mg/dL	1.0	0.6	0.8	0.3	0.9	0.2	<0.001
Aldosterone, plasma, ng/dL	5.9	8.3	7.2	9.5	7.9	10.6	<0.001
Hypertension, %	44.7		17.3		25.9		<0.001
Diabetes mellitus, %	14.2		12.0		6.6		<0.001
Total cholesterol, mg/dL	177.7	40.1	182.2	40.1	183.6	38.3	<0.001
Cr, urine, mg/dL	155.2	89.5	142.0	75.5	127.1	70.1	<0.001
Na, urine, mEq/L	125.8	58.6	126.8	55.8	109.9	53.0	<0.001
LV mass, g	175.9	51.1	147.6	36.2	157.0	41.9	<0.001
LVEF by MRI, %	71.5	8.6	73.8	7.2	71.4	7.3	<0.001

* Mean of nonmissing BP values from all 3 study visits. For some characteristics, data for a subset of the n were available. BMI indicates body mass index; Cr, creatinine; K, potassium; Na, sodium.

Table 2
CYP11B2 –344C/T Genotype and Allele Frequencies by Ethnicity

	Non-Hispanic Black	Hispanic	Non-Hispanic White
	n = 1813	n = 599	n = 1040
Genotype, n (%)			
TT	1083 (59.7)	205 (34.2)	314 (30.2)
CT	657 (36.2)	302 (50.4)	496 (47.7)
CC	73 (4.0)	92 (15.4)	230 (22.1)
Allele			
T	0.78	0.59	0.54
C	0.22	0.41	0.46