Association of African Ancestry With Electrocardiographic Voltage and Concentric Left Ventricular Hypertrophy
The Dallas Heart Study

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IMPORTANCE Compared with white individuals, black individuals have increased electrocardiographic voltage and an increased prevalence of concentric left ventricular (LV) hypertrophy. Whether environmental or genetic factors lead to these racial differences is unknown.

OBJECTIVE To determine whether proportion of genetically determined African ancestry among self-reported black individuals is associated with increased electrocardiographic voltage and concentric LV hypertrophy (LVH).

DESIGN, SETTING, AND PARTICIPANTS The Dallas Heart Study is a probability-based cohort study of English- or Spanish-speaking Dallas County, Texas, residents, with deliberate oversampling of black individuals. Participants underwent extensive phenotyping, which included electrocardiography (ECG), cardiac magnetic resonance imaging (CMR), and dual-energy radiography absorptiometry (DEXA) at a single center. Participants aged 18 to 65 years who enrolled in the Dallas Heart Study between July 2000 and December 2002, self-identified as black (n = 1251) or white (n = 826), and had ECG, CMR, and DEXA data were included in this analysis. Data were analyzed from June 2017 to September 2018.

EXPOSURES Proportion of African ancestry.

MAIN OUTCOMES AND MEASURES Electrocardiographic voltage (12-lead and 9-lead) and markers of concentric LVH as assessed by CMR (LV concentricity0.67 [LV mass/end-diastolic volume0.67], LV wall thickness [LVWT], and prevalent LVH [defined by LV mass/height2.7]).

RESULTS Of the 2077 participants included in the study, 1138 (54.8%) were women, and the mean (SD) age was 45.2 (9.9) years. Black race and African ancestry were individually associated with increased ECG voltage, LV concentricity0.67, LVWT, and prevalent LVH in multivariable analyses adjusting for age, sex, systolic blood pressure, antihypertensive medication use, and body composition. When African ancestry and black race were entered together into multivariable models, African ancestry but not black race remained associated with ECG voltage, LVWT, LV concentricity0.67, and prevalent LVH. Among black participants, African ancestry remained associated with these 4 phenotypes (12-lead voltage: β, 0.05; P = .04; LVWT: β , 0.05; P = .02; LV concentricity0.67: β, 0.05; P = .045; prevalent LVH: odds ratio, 1.2; 95% CI, 1.03-1.4; P = .02).

CONCLUSIONS AND RELEVANCE Genetically determined African ancestry was associated with electrocardiographic voltage, measures of concentric LV remodeling, and prevalent LVH. These data support a genetic basis related to African ancestry for the increased prevalence of these cardiovascular traits in black individuals.

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Compared with white individuals, black individuals are at an increased risk of a number of adverse cardiovascular events, including incident heart failure.\textsuperscript{1,2} Subclinical cardiovascular phenotypes, including increased electrocardiographic voltage\textsuperscript{3,4} and prevalent concentric left ventricular hypertrophy (LVH),\textsuperscript{5} are also more common in black individuals. The basis of these racial differences remains uncertain, including the relative contributions of genetic or environmental factors.\textsuperscript{6}

Geographical ancestry is known to correlate with self-identified race, is a key determinant of genomic variation, and holds the potential to replace race as a construct when making therapeutic decisions.\textsuperscript{7} Self-identified black individuals in the United States are a genetically admixed population, comprising both African ancestry and European ancestry. Here, we tested whether proportion of African ancestry as assessed by genetic markers was associated with increased electrocardiographic voltage and concentric LV remodeling among self-reported black individuals, hypothesizing that such associations would provide evidence for a genetic contribution to the racial differences in these traits.

**Methods**

**Dallas Heart Study**

The design and methods of the Dallas Heart Study have been described previously.\textsuperscript{8} In short, the Dallas Heart Study is a probability-based cohort study of noninstitutionalized English- or Spanish-speaking Dallas County, Texas, residents aged 18 to 65 years. Black individuals were oversampled to ensure they comprised 50% of the final study population. Enrollment of eligible participants occurred from July 2000 to December 2002. Participants were invited to participate in 3 stages, consisting of 2 home visits, during which a survey was administered and blood and urine specimens were obtained, and a visit to the University of Texas Southwestern Medical Center, during which electrocardiography (ECG) and imaging studies were obtained. The present study population was restricted to participants who had cardiac magnetic resonance imaging (CMR), dual-energy radiography absorptiometry (DEXA), and ECG data, reported whether they used antihypertensive medications, and self-identified as black (n = 1251) or white (n = 826). Written informed consent was obtained from all participants. The institutional review board of the University of Texas Southwestern approved the study protocol.

**Cardiac Magnetic Resonance Imaging**

We used short-axis, breath-hold, ECG-gated cine CMR images obtained from 2 comparable 1.5-T magnetic resonance imaging systems (Intera and Intera Achieva; Philips Medical Systems).\textsuperscript{5,6,9} We manually traced endocardial and epicardial borders of slices from the apex to the base of the left ventricle at end diastole using QMass (Medis Medical Imaging Systems). The difference between the end-diastolic epicardial and endocardial contours was multiplied by 1.05 g/mL (specific gravity of myocardium) to allow calculation of LV mass. The papillary muscles were identified independently of the LV wall and included in the myocardial mass (ie, excluded from the LV volume).\textsuperscript{9} Average LV wall thickness (LVWT) was measured via the short-axis images, excluding the most apical and basal slices, as described previously.\textsuperscript{9} Interobserver and intraobserver differences and interscan variability have been reported.\textsuperscript{9}

**Definition of Variables**

Sex, race, age, and use of antihypertensive medications were self-reported. Systolic blood pressure (SBP) was defined as the average SBP in measures 3 through 5 at the third visit, during which 5 blood pressure measurements were obtained using an automatic oscillometric device validated against catheter measurement of arterial pressure.\textsuperscript{10} Lean and fat mass were calculated based on DEXA scans using a dual-beam absorption energy unit (Delphi W unit; Hologic Inc) bone densitometer in array mode. Body composition was quantified using Oasis software (Hologic Inc). Left ventricular concentricity\textsuperscript{0.67} was defined as LV mass/LV end-diastolic volume\textsuperscript{0.67}, which has been shown to be more highly correlated with both LVWT and SBP compared with LV mass/LV end-diastolic volume.\textsuperscript{31} Left ventricular hypertrophy was defined as 38.1 g/m\textsuperscript{2.7} or greater for men and 34.1 g/m\textsuperscript{2.7} or greater for women. Increased LV concentricity\textsuperscript{0.67} was defined as 7.2 g/mL\textsuperscript{0.67} or greater for men and 5.8 g/mL\textsuperscript{0.67} or greater for women.\textsuperscript{9}

**ECG Criteria**

Twelve-lead ECG was performed at the third visit and measured using a Marquette Medical System (General Electric) with MAC 5000 hardware and software configuration, which measured rate, rhythm, intervals (PR, QRS, and QT), and voltages. Twelve-lead QRS voltage criteria was calculated by summing the QRS amplitudes from each lead, according to the method of Siegel and Roberts\textsuperscript{52} in which QRS amplitude was measured from the peak of the R wave to the bottom of the Q or S wave, whichever was deeper. Left ventricular hypertrophy criteria for 12-lead QRS voltage was defined as greater than 123 millimeters. Studies have shown improved sensitivity and specificity by subtracting aVR, aVL, and aVF voltage from the

**Key Points**

**Question** Is there a genetic contribution to the increased electrocardiographic voltage and higher prevalence of concentric left ventricular (LV) hypertrophy in black vs white individuals?

**Findings** In this cohort study including 2077 patients, genetically inferred proportion of African ancestry was associated with increased electrocardiographic voltage and measures of concentric LV hypertrophy as assessed by cardiac magnetic resonance imaging in multivariable models adjusting for age, sex, blood pressure, antihypertensive medication use, and body composition. These associations persisted in analyses restricted to black individuals only.

**Meaning** These data support the possibility that genetic factors mediate, in part, the higher electrocardiographic voltage and predisposition to concentric LV remodeling and LV hypertrophy in black individuals compared with white individuals.
12-lead QRS voltage because of the redundancy of limb leads to yield 9-lead QRS voltage. Left ventricular hypertrophy criteria for 9-lead QRS voltage was defined as greater than 110 millimeters.

Ancestry
To estimate the ancestral admixture of Dallas Heart Study participants, we used genotyping data from the Infinium Human Exome BeadChip version 12.1 (Illumina). A total of 4591 Dallas Heart Study participants, including 2369 self-reported non-Hispanic black participants, 1355 non-Hispanic white participants, 746 Hispanic participants, and 121 participants of other ethnicities, were previously genotyped using the Illumina array. We excluded variants with a genotype call rate less than 99% or a deviation from Hardy-Weinberg equilibrium among African American individuals with a P value less than .0001. We further excluded variants with a minor allele frequency less than 1% and those in high linkage disequilibrium (r² > 0.1). This process left a total of 25 707 autosomal variants for ancestry estimation. Global admixture proportions were estimated using ADMIXTURE version 1.3.0 software (University of California, Los Angeles), assuming 3 ancestral populations. 

Perceived Discrimination
During the first visit of the Dallas Heart Study, participants underwent a computer-assisted structured interview, including questions about race and health beliefs. They were asked, “In general, have you ever been discriminated against because of your race or ethnicity?” Responses were categorized as yes or no. Participants who responded that they didn't know were excluded from the analysis, corresponding to 1.1% of the population.

Statistical Analysis
Continuous variables are expressed as means and SDs, and categorical variables are expressed as numbers and percentages within the group. We first tested whether genetically inferred African ancestry and self-reported black race were associated with ECG and CMR parameters in multivariable linear regression and logistic regression models. Additional covariates in the multivariable models included age, sex, SBP, use of antihypertensive medications, lean mass, and fat mass. Next, we entered both African ancestry and black race into the same multivariable models. In multivariable analyses restricted to black participants, we then tested the association of genetically inferred African ancestry with these phenotypes followed by sex-stratified analyses. Categorical variables were compared between black and white individuals by the χ² test and continuous variables by unpaired t tests. In black participants, the percentage of genetically inferred African ancestry was compared between those who did or did not report perceived discrimination by the Wilcoxon rank sum test. P values were 2-tailed, and the level of significance was set at a P value less than .05. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results
Compared with the white subgroup, the black subgroup had more women and higher SBP, BMI, lean mass, fat mass, LV mass, 12-lead QRS voltage, 9-lead QRS voltage, LV concentricity, and LVWT (Table 1). The average age and LV ejection fraction was comparable between the 2 groups.

We compared the distribution of genetically inferred African ancestry among self-reported black participants and white participants (Figure). Black participants were estimated to have a mean (SD) of 86.3% (9.1) African and 12.6% (8.7) European ancestry, similar to estimates reported for other African American cohorts. Among self-reported white participants, most
African ancestry; the mean (SD) proportion of African ancestry was 0.4% (2.6), and the highest African ancestry was 48.8%.

In the entire study cohort, when black race and African ancestry were entered separately into multivariable models, each was associated with increased ECG 12-lead QRS voltage and 9-lead QRS voltage as well as the dichotomized voltage criteria for LVH (Table 2). Next, we entered both black race and African ancestry in the same multivariable model (Table 2). African ancestry but not black race remained significantly associated with 12-lead QRS voltage, 9-lead QRS voltage, and 9-lead LVH criteria. In this analysis, neither African ancestry nor black race were associated with 12-lead LVH criteria (Table 2). To evaluate whether the proportion of African ancestry among black participants was associated with ECG voltage, we examined the association of African ancestry with these variables in analyses restricted to self-reported black participants. In these multivariable models, African ancestry was associated with 12-lead QRS voltage and 9-lead LVH criteria but not with 9-lead voltage or 12-lead LVH criteria (Table 2).

We next assessed the association of black race and African ancestry with measures of LV remodeling (Table 3). As previously reported, black race was significantly associated with LV mass and LVH as defined by LV mass/height$^2.7$ criteria. The association of black race with LV mass occurred because of increased LVWT rather than LV dilation; thus, black race was also associated with increased LV concentricity$^{0.67}$ (continuous or dichotomous). A similar pattern of associations with African ancestry and parameters of increased concentric LV remodeling were noted (Table 3). When both African ancestry and black race were entered together into the same models, African ancestry but not black race remained associated with increased LVWT, LV concentricity$^{0.67}$ (continuous or dichotomous), and prevalent LVH. To evaluate whether the proportion of African ancestry among black participants would be associated with concentric LV remodeling, we next examined the association of African ancestry with CMR parameters in analyses restricted to self-reported black participants. In these multivariable models, African ancestry was associated with increased LVWT, LV concentricity$^{0.67}$ (continuous or dichoto-

### Table 2. Association of Black Race and Genetically Inferred African Ancestry With Electrocardiographic Voltage*

<table>
<thead>
<tr>
<th>Cohort</th>
<th>12-Lead Voltage</th>
<th>9-Lead Voltage</th>
<th>LVH Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
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<td>0.02</td>
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<tr>
<td>African ancestry</td>
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</table>

Abbreviations: LVH, left ventricular hypertrophy; OR, odds ratio. * Models adjusted for age, sex, systolic blood pressure, antihypertensive medication use, lean mass, and fat mass. ** Odds ratios are presented per 10% increase in African ancestry or for self-reported black vs white race. *** Both African ancestry and black race entered into the same model.

(80%) had 0% African ancestry; the mean (SD) proportion of African ancestry was 0.4% (2.6), and the highest African ancestry was 48.8%.

In the entire study cohort, when black race and African ancestry were entered separately into multivariable models, each was associated with increased ECG 12-lead QRS voltage and 9-lead QRS voltage as well as the dichotomized voltage criteria for LVH (Table 2). Next, we entered both black race and African ancestry in the same multivariable model (Table 2). African ancestry but not black race remained significantly associated with 12-lead QRS voltage, 9-lead QRS voltage, and 9-lead LVH criteria. In this analysis, neither African ancestry nor black race were associated with 12-lead LVH criteria (Table 2). To evaluate whether the proportion of African ancestry among black participants was associated with ECG voltage, we examined the association of African ancestry with these variables in analyses restricted to self-reported black participants. In these multivariable models, African ancestry was associated with 12-lead QRS voltage and 9-lead LVH criteria but not with 9-lead voltage or 12-lead LVH criteria (Table 2).
Table 3. Association of Genetically Inferred African Ancestry With Cardiac Magnetic Resonance Imaging Parameters of Left Ventricular (LV) Remodeling

<table>
<thead>
<tr>
<th>Cohort</th>
<th>LV Mass</th>
<th>EDV</th>
<th>Wall Thickness</th>
<th>Concentricity</th>
<th>LV Hypertrophy</th>
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<td>β</td>
<td>P Value</td>
<td>β</td>
<td>P Value</td>
<td>β</td>
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<td>Black and white</td>
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<td>participants</td>
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<td>African ancestry</td>
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<td>.33</td>
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<td>0.05</td>
</tr>
<tr>
<td>Abbreviations: EDV, end-diastolic volume; OR, odds ratio.</td>
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</tr>
<tr>
<td>* Models adjusted for age, sex, systolic blood pressure, antihypertensive medication use, lean mass, and fat mass.</td>
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</table>

Discussion

Using a large, well-phenotyped, biracial cohort, we demonstrated that markers of African ancestry were more strongly associated with ECG voltage and CMR assessment of concentric LV remodeling and prevalent LVH than self-identified black race. Furthermore, African ancestry remained associated with these cardiac phenotypes in analyses restricted to black participants. These associations were independent of other potential risk factors, including age, sex, SBP, use of antihypertensive medications, and measures of body composition. The association of African ancestry with increased LVWT was independent of perceived discrimination. These data support the possibility that genetic factors mediate, in part, the higher ECG voltage and predisposition to concentric LV remodeling and LVH in black individuals compared with white individuals.

Electrocardiographic voltage in black individuals is increased compared with that in white individuals. As such, the specificity of traditional ECG criteria for LVH is reduced in black vs white individuals. Indeed, some have suggested that race-specific electrocardiographic criteria for LVH are needed. The basis of these racial differences remains uncertain. Electrocardiographic voltage can be related to sex, age, hematocrit level, LVWT, thoracic diameter, obesity, pericardial fluid, and lung disease, among other parameters. In the current study, African ancestry remained associated with ECG voltage independent of age, sex, and measures of body composition, including body fat. We recognize that the association of African ancestry with ECG voltage may be mediated via the former's association with concentric LV remodeling. Nevertheless, the association of African ancestry with subclinical phenotype measured via an entirely distinct modality (ie, ECG) provides additive information to the associations of African ancestry with concentric LV remodeling as measured by CMR.

Left ventricular hypertrophy is more prevalent in black individuals vs white individuals. In particular, black individuals are at risk of increased LVWT (ie, concentric remodeling) rather than LV dilation. It is unclear why some patients with hypertension develop increased LVWT and other LV di-
lotion. Undoubtedly, some of the variability in LV remodeling will be caused by unappreciated differences in blood pressure (eg, duration, magnitude, or rate of onset), but the possibility of genetic predisposition to patterns of hypertrophic response is high.\textsuperscript{10} We previously demonstrated that 2 highly linked nonsynonymous polymorphisms in \textit{Corin} were present more commonly in black individuals than white individuals and were associated with an increased hypertrophic response to hypertension.\textsuperscript{2-0} The current data extend that observation and provide further support of the possibility of a genetic contribution to ethnic differences in the LV hypertrophic response. Of note, genetically inferred African ancestry was not associated with LV end-diastolic volume but rather with phenotypes that are measures of a concentric hypertrophic response (increased LVWT and LV concentricity\textsuperscript{6,0,7}), consistent with what we have termed \textit{thick hypertrophy} as opposed to dilated hypertrophy.\textsuperscript{11}

Prior studies have demonstrated that African ancestry is associated with pulmonary and cardiovascular traits. In the Coronary Artery Risk Development in Young Adults study,\textsuperscript{21} African ancestry was inversely associated with the forced expiratory lung volume in 1 second. The Multi-Ethnic Study of Atherosclerosis investigators demonstrated that African ancestry was inversely associated with N-terminal pro–B-type natriuretic peptide levels.\textsuperscript{12} Our data are consistent with and substantially extend these previous studies by linking African ancestry with LVH, an important intermediate phenotype on the pathway to heart failure.

Limitations

There are several limitations to our study. First, the observed associations may be a result of residual confounding from variables other than those adjusted for in multivariable models. However, because of the detailed phenotyping performed in the Dallas Heart Study, we were able to adjust for carefully measured blood pressure, body composition, and self-reported discrimination. Second, the association of ancestry with concentric LV remodeling was not replicated in an independent cohort. However, we were able to demonstrate an association of African ancestry with 2 conditions (increased ECG voltage and concentric LVH) measured by independent modalities, namely the ECG and CMR.

Conclusions

In conclusion, the degree of African ancestry was associated with increased ECG voltage, markers of concentric LV remodeling measured by CMR, and prevalent LVH. These data support the hypothesis that genetic differences between black and white individuals contribute to the higher prevalence of these traits in black individuals.

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