Study Design for Genetic Analysis in the Jackson Heart Study

Objective: This paper describes the preparation of genetic materials and the recruitment and initial characterization of a nested Family Study within the Jackson Heart Study (JHS) cohort.

Methods: Genomic DNA was prepared from all consenting JHS participants. In addition, family members of a subset of JHS participants were recruited to the JHS Family Study to allow heritability and linkage analyses and family-based association studies. Family Study participants completed the same questionnaires, measures, and procedures as all other JHS participants and provided blood samples for lymphocyte cryopreservation and transformation.

Results: DNA samples were obtained from 4726 JHS participants, including 1499 members of 291 families. In the family cohort, estimated heritabilities of body mass index, selected lipid levels, and blood pressure are highly significant, supporting the validity of the sample.

Discussion: The JHS data and genetic materials (DNA and cryopreserved cells) offer valuable opportunities to identify susceptibility alleles for common complex diseases by positional and candidate gene approaches.

Key Words: African Americans, Cardiovascular Disease, Family Study, Genetics, Jackson Heart Study, Longitudinal Study

INTRODUCTION

Genetic studies of several large observational cohorts are in progress and have suggested the location of risk alleles for a number of common complex disorders, including hypertension\(^1\)–\(^6\) and dyslipidemia,\(^7\)–\(^14\) among others. Technical advances in genotyping and the existence of rich databases of common polymorphisms\(^15\)–\(^18\) increase the likelihood that the relevant genes within some of these loci will soon be found. Although genetic studies in African-American populations have been limited in the past, several such studies are now in progress. Examples are: 1) the Howard University Family Study (HUFS),\(^19\) a random sample of multigenerational pedigrees from the Washington, DC metropolitan area; 2) the African-American Hereditary Prostate Cancer (AAHPC) study,\(^20,21\) with sites in Detroit, Mich, Atlanta, Ga, Columbia, SC, Washington, DC, Houston, Tex, Chicago, Ill, and New York, NY; 3) the Dallas Heart Study\(^22\); and 4) the HERITAGE family study,\(^23\) which includes both African-American and European-American families. In addition, two of the networks of the Family Blood Pressure Program\(^24\) have enrolled African-American siblings: GenNet in the Chicago, IL area and GENOA in the Jackson, Miss area.

African Americans in Mississippi have rates of diabetes, cardiovascular disease (CVD), and stroke far exceeding those of other populations in the United States.\(^25,26\) The Jackson Heart Study (JHS) is a long-term observational study to identify environmental and genetic factors that contribute to these and related disorders in African Americans in and around Jackson, Miss. An extensive body of historical, physical, and biochemical data has been collected from a cohort of 5302 participants. Nested within this cohort, the JHS Family Study includes 1499 members of 291 families that were identified through index family members who had been recruited into the overall study population (Fig. 1). Genomic DNA was prepared from all consenting JHS participants, and cryopreserved lymphocytes (for transformation) were prepared from consenting Family Study participants. The current paper describes methods and initial results of pedigree development and verification, family recruitment, and preparation of genetic materials, and discusses our approaches to ethical issues that are related to genetic studies in this vulnerable population.

FAMILY SELECTION AND RECRUITMENT

The JHS has recruited men and women 35–84 years old who live in Hinds, Madison, or Rankin County, Mississippi. These counties contain the city of Jackson, its suburbs, and a few rural communities and have populations of approximately the following size and composition: Hinds County, pop. 250,000 (61.5% African American); Madison County, pop. 77,000 (37.3% African American); and Rankin County, pop. 119,000 (17.3% African American).\(^27\) A goal of the JHS has been to include participants from across the socioeconomic spectrum.\(^28\) Thus the JHS Family Study has recruited...
the relatives of index participants from the overall JHS cohort, so that the family cohort will also, as nearly as possible, be representative of the local African-American population. The demographic, historical, physical, and biochemical data collected from Family Study participants were identical to those collected from all other JHS participants.

Home Induction Interview

Initial contact with JHS participants occurred in the home. Potential index participants for the Family Study were identified from information in the eligibility form, which recorded the number of parents, grandparents, siblings, children, grandchildren, aunts, uncles, nieces, and nephews of appropriate age who lived in the tri-county area. Relatives of the index participant who were ≥21 years old could participate in the Family Study and were included on the eligibility form. The participant’s permission to contact listed relatives was also solicited and recorded. Persons with at least two full siblings and four other first-degree relatives, all of whom met age and residence requirements and could be contacted, were eligible to become Family Study index participants. Eligibility criteria were established based on an average African-American sibship size of three in the Jackson area. Recruiters were trained to determine Family Study eligibility immediately and, while still in the home, to discuss the Family Study and to provide a “family address book,” with a request that the participant record contact information for other family members and bring the address book to their clinic appointment. The recruiter then marked the participant’s profile sheet as “Family Study eligible” to alert the clinic staff to collect additional information and blood samples (see below) during the participant’s clinic visit.

The Clinic Visit

All eligible participants were introduced to the JHS social worker when they entered the clinic. The beginning of the clinic visit was devoted to discussion and completion of the informed consent document, including responses to questions related to the Family Study and the use of genetic materials (see below, under Ethical, Legal, and Social Implications). The social worker had received additional genetics training and was able to address genetics-related questions during the consent process. Blood samples were collected from each consenting JHS participant for the preparation of genomic DNA (all JHS participants) and cryopreserved cells (for eventual transformation; Family Study only).

The clinic visit lasted approximately four hours, and included morphometrics, phlebotomy, echocardiography, carotid ultrasound, electrocardiograph, and pulmonary function tests; participants also completed questionnaires about diet, physical activity, personal and family medical history, and social and psychological issues. Constructing graphic pedigrees during the clinic visit was difficult and ultimately unsuccessful. Instead, we found that a satisfactory initial pedigree could be generated from data in the family address book, with progressive refinement of the pedigree during family recruitment. Information in the family address book included the name, address, age, birth date, telephone numbers, and any email addresses of participants’ spouses, children, parents, paternal and maternal grandparents, whole- and half-siblings, grandchildren, nieces, nephews, and spouses’ parents, grandparents, and siblings. Participant burden in the clinic was minimized by having the social worker join the participant during intervals between tests to assist in the fullest possible completion of the address book, using local telephone directories and other resources as needed. Further, all Family Study participants completed a parental identification form during the clinic visit, recording the full names (including maiden name) and birthdays of the participant’s biological parents and identifying any relatives who may have already participated in JHS or in the Atherosclerosis Risk in Communities (ARIC) study. Accurate identification of the parents of each person in a family allows the construction of an unambiguous pedigree. Thus information from the parental identification form was used to establish the definitive historical pedigree for each family before verification by molecular markers.

Preparation of the Working Pedigree and Release for Recruitment

Completed family address books were reviewed by the Family Study research associate to construct an initial “working” pedigree using Progeny2000® software (Progeny Software, LLC, South Bend, Ind). This pedigree and available contact information were provided to the Family Study patient representative, who worked by telephone during afternoon and evening hours to contact the index participant and (with verbal consent) additional family members, progressively completing family contact information through a series of calls and correcting and extending each pedigree based on the data obtained. When reasonable efforts
to complete contact information for each family had been exhausted, information that had been obtained was reported back to the Family Study research associate, who updated Progeny2000 and forwarded the data to the JHS Coordinating Center. The forwarded data were entered into the Data Management System and the identified family members were added to the recruitment sample and released to the director of recruitment. The family recruitment list was accompanied by all contact information, a copy of the working pedigree, and the identity of the index participant. Letters were mailed to the potential participants, describing the JHS Family Study and telling them that they had been identified through the index participant and would be contacted for possible recruitment to the study. Each family was then assigned to a family study recruiter.

Family Study participants are distinguished from other JHS participants by the association of their JHS participant ID number with a family ID number. Linkage between participant ID and family ID is established by the family linking form, which records the participant’s last name, initials, participant ID, and a code to distinguish the index participant from other family members. Both the participant ID and family ID were assigned when the home induction interview was completed.

Family Recruitment and Pedigree Extension in the Field

As noted, each family was assigned to a single Family Study recruiter, which allowed the recruiter to develop a rapport with family members and to identify those who might be particularly helpful. In most cases initial contact (after letters had been sent) was by telephone. During the home induction interview, attempts were made to extend each participant’s pedigree and to gather additional contact information. Tables or diagrams of family information obtained from one family member were not shown to other family members. Instead, the recruiter recorded the names of each participant’s parents, grandparents, siblings, children, and grandchildren who met age and residence requirements, plus any new contact information, and asked the informant’s permission to contact additional family members. New pedigree information was submitted to the Family Study research associate, who updated the working pedigree and added eligible family members to the recruitment sample.

When recruiters identified additional qualifying family members during a home visit who were either represented in the working pedigree or were first-degree relatives of those represented, they were instructed to recruit them immediately. When such individuals were not first-degree relatives of pedigree members, their names, relationship, age, residence status, and contact information were recorded and discussed with members of the genetics committee. Spouses who shared biologic children with living or deceased pedigree members were recruited to the Family Study; spouses not sharing biologic children with pedigree members were not eligible for the Family Study but could participate in the overall observational study. Recruiters discussed their progress and any difficulties during weekly meetings with the chairman of the genetics committee and were encouraged to contact him by cell phone as needed.

**ETHICAL, LEGAL, AND SOCIAL ISSUES**

The example of the US Public Health Syphilis Study shows the physical, social, and psychological injury that can be caused by unethical medical research. Study participants and populations can also be harmed, however, by selective or inappropriate interpretation of data, either by investigators or other commentators who extrapolate from their findings. African Americans in particular have been harmed by such studies and in many cases have a general and understandable mistrust of medical research and medical investigators. However, it is also recognized that African Americans have been underrepresented in prior clinical and observational studies and that health factors that are especially important to them may thus be poorly understood. These problems have been the subject of an open and ongoing discussion among JHS investigators, ethicists, and members of the community. Community representatives have been involved extensively in study design and oversight.

Participants in genetic studies could be harmed through any of several mechanisms, including breach of privacy within a family; inappropriate disclosure of information to employers, insurance companies, or others; or disclosure to participants of data that are experimental, incompletely understood, and potentially disturbing. Nonparticipants of the same social or ethnic group being studied could also be harmed, for example, through inappropriate generalizations about intellect, alcoholism, drug use, sexual behavior, or medical conditions that affect insurance status or fitness for employment. These considerations, most of which also apply to nongenetic data, have led the JHS to develop careful review processes regulating data disclosure, analysis, and publication.

Informed consent for genetic studies requires that participants have some understanding of genetics and genetic testing. Thus the JHS has conducted a series of lectures, first to recruiters, clinic staff, and other JHS employees and then to prospective participants in the community. These lectures have been supplemented in the clinic by
selected educational materials and in the community by distributing pamphlets specifically describing JHS genetic studies. Investigators, in turn, are educated about the concerns of the community by discussions that occur during lectures and by the input of community advisory groups that meet regularly at the JHS and have voting representatives on JHS committees.

Participant IDs allow the storage and retrieval of data without personal identifiers. Laboratory specimens are labeled with barcodes only. Procedures to protect the privacy and integrity of computerized data are described elsewhere. A certificate of confidentiality from the Department of Health and Human Services protects records from review by government agencies. Privacy is protected within families by policies that prohibit showing data obtained from one family member to another family member. This commitment to privacy precludes showing a pedigree developed from one family member’s responses to another family member and has resulted in development of the procedures described above for pedigree checking and extension in the field.

If, during the course of the JHS, a genetic polymorphism is discovered that has clear clinical relevance, a description of the polymorphism and its health implications will appear in a newsletter that is sent to JHS participants. This description will be accompanied by a telephone number that can be called for more information and referral for genetic testing, if available. The JHS results that are considered to be of research value only will not routinely be reported to participants, though they may be released on an ad hoc basis in response to a written request from the participant, at the discretion of the principal investigator. Under no circumstances will genetic information bearing on paternity issues be released to any participant or other individual. To decrease the likelihood of harm to African Americans through inappropriate interpretation of JHS results, the JHS publications committee will review manuscripts before they are submitted to assure that data are presented in an accurate and responsible manner.

The JHS uses a layered consent document to give participants clear choices regarding the use of their genetic materials. This layering allows participants, if they wish, to withhold permission for family studies, production of genomic DNA, or cryopreservation of mononuclear cells. They also may limit the use of their genetic materials to the study of diseases that are the principal focus of the Jackson Heart Study, versus “any major diseases or health conditions,” and must specify whether studies may be done by JHS investigators only, other qualifying investigators, or private companies.

PREPARATION AND STORAGE OF GENETIC MATERIALS

Genomic DNA was prepared from all consenting JHS participants. Mononuclear leukocytes were isolated from consenting Family Study participants and were cryopreserved. Venous blood was collected in two 10-mL EDTA tubes and two BD Vacutainer® CPT tubes (containing density gradient solution, anticoagulant, and gel barrier), respectively, for the isolation of genomic DNA and for cryopreservation of lymphocytes. Tubes were bar coded and shipped at ambient temperature by overnight carrier to the JHS sample repository at the University of Minnesota (Michael Steffes, MD, PhD, principal investigator).

The DNA was extracted by a method based on sodium dodecylsulfate cell lysis and ammonium acetate precipitation of proteins (Puregene®, Gentra System, Inc., Minneapolis, Minn). For each participant, each 10-mL EDTA tube was processed separately, and the isolated DNA was stored at −80°C in separate aliquots located in different buildings. DNA samples were obtained from 4726 participants, with an average yield from each participant of $434 \pm 229 \mu g/20 \mu L$; low yields of 40–100 $\mu g/20 \mu L$ were obtained from 157 participants. $A_{260}/A_{280}$ ratio was routinely 1.7–1.9, which indicated high-quality DNA.

For lymphocyte cryopreservation, peripheral blood mononuclear cells (PBMCs) isolated from each of the CPT tubes were washed in Hanks Balanced Salt Solution (HBSS), counted, and resuspended in RPMI-1640 media containing 20% fetal calf serum and Hepes buffer. The suspended cells were diluted 1:1 with cryopreservation solution containing 20% dimethylsulfoxide and were frozen in the vapor phase of liquid nitrogen. As in the case of genomic DNA, separate aliquots from each donor were stored in different buildings. For lymphocyte transformation, cryopreserved cells are quick-thawed under running warm water until a single small ice crystal remains and are washed in HBSS. B lymphocytes are infected by Epstein-Barr Virus (EBV) contained in supernates of saturated cultures of B95-8 cells, in the presence of cyclosporin A. Fresh medium is added twice weekly. Successful transformation is observed at four to five days, and proliferation is seen at two to three weeks. Transformation is usually complete after 21 days, at which time aliquots of the transformed cells are cryopreserved and stored in the vapor phase of liquid nitrogen, as described above. Typically four vials of $8 \times 10^6$ cells/vial are produced, and two vials are placed in each of two liquid nitrogen systems located at different sites. Transformation is successful for >99% of samples, whether mononuclear cells were cryopreserved after one night at ambient temperature, or in the case of blood collected on Saturdays, two nights. Except for test samples, cryopre-
served cells from the JHS will not be transformed until funding is awarded to support this.

**DATA MANAGEMENT**

Data management procedures for the overall JHS are described elsewhere. Pedigree data are stored as a free-standing dataset that uses Progeny2000 software, which provides graphic representation of pedigrees that can be generated automatically from tabular data or custom drawn by point-and-click methods. The Progeny2000 master file for each family contains all the information necessary to generate an unambiguous pedigree, including participant ID, family ID, participant age and sex, each parent’s name (first, last, middle, and maiden) and age, father ID, and mother ID. “Dummy parent” IDs are generated for parents who link participating siblings but are themselves either deceased or unavailable. Pedigree symbols are color-coded and otherwise annotated to indicate eligibility status, availability of contact information, completed home induction interview, completed clinic visit, or refusal to participate. Progeny2000 allows multiple independent data files bearing the same participant ID to be merged as needed with the master file and supports export and import of ASCII files to and from other database systems.

For each Family Study participant, the overall data set in the DMS is linked to pedigree information in Progeny2000 through a single relational table based on data from the family linking form. This table has three data fields, including the participant ID, the family ID, and a code indicating whether the participant is the index family member (code=1) or a secondary family member (code=2). When more than one member of a family is recruited into the JHS by chance rather than through a family contact, a family linking form is completed for each such participant, assigning a single family ID. The person through whom the family was first identified as meeting eligibility criteria for recruitment is considered the index participant; all others in the family are considered secondary family members.

**Pedigree Data Checking**

Automated family structure analysis by Progeny2000, S.A.G.E., and Pedsys® software is used for error checking of the pedigree data structure. Examples of errors that may be detected include married persons with the same sex code, a participant who is his or her own ancestor, or more than one person with the same participant ID. Certain types of consanguineous matings and pedigree loops may also be identified. Genotype data will be assessed for marker-typing inconsistencies between parents and offspring, presence of more than four alleles in a sibship, presence of more than three alleles in a sibship that includes a homozygous individual, or males homozygous for an x-linked allele. Mendelian consistency will be verified for all pedigrees. The genotype of some individuals may be set to missing in some cases to save a family.

**INITIAL RECRUITMENT RESULTS**

The JHS Family Cohort includes 1499 members of 291 families (≈5.2 members/family), all of whom have provided DNA samples and consent for DNA analysis. Table 1 presents the numbers of relative pairs of different types in the family cohort, illustrating a rich family structure. The distribution of family sizes is shown in the left panel of Figure 2. Sixteen families had ≥12 participating members, and nine families had ≥18. Ninety and 36 families, respectively, were represented by only two or three members. The number of small families was increased somewhat because participants in the overall cohort were recruited from eligible households; whenever two or more participants came from one household, efforts were made to clarify family relationships, thus identifying many smaller family units. The right panel of Figure 2 shows the distribution of Family Study participants by family size. Approximately half of participants are from families with at least seven participating members, and >80% are from families with four or more JHS participants. The cohort is 66.6% female and has a median age of 50 years (mean ± SD, 50.3 ± 14.5) (Figure 3), somewhat younger than the overall JHS cohort (64% female, median age 55 years, mean 54.9 ± 12.9 years).

Table 2 presents maximum likelihood heritability estimates for selected phenotypes, calculated by a variance components method as implemented in

<table>
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<th>Degree of Relationship</th>
<th>Relative Type</th>
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<td>1st</td>
<td>Parent-offspring</td>
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<tr>
<td></td>
<td>Siblings</td>
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<td></td>
<td>Grandparent-grandchild</td>
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<td>Avuncular</td>
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<td>Half-siblings</td>
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<td>3rd or more distant</td>
<td>Great grandparent-grandchild</td>
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<td></td>
<td>Grand avuncular</td>
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<td></td>
<td>Half avuncular</td>
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<td></td>
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<tr>
<td></td>
<td>Half first cousins</td>
<td>12</td>
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<td></td>
<td>Second cousins</td>
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Estimated heritabilities for height, BMI, and selected serum lipid levels were highly significant. Relatively low heritabilities of systolic and diastolic blood pressure presumably reflect confounding by medication; 663 of the 1499 family cohort members are on antihypertensive therapy. Hypertension status was defined as systolic blood pressure $\geq 120$ and/or diastolic blood pressure $\geq 80$, or on antihypertensive medication, which pooled participants with pre-hypertension or hypertension (JNC-7 criteria) to reduce confounding by medications. The heritability of hypertension status was quite significant.

**SUMMARY**

African Americans are an understudied population with a striking burden of illness from the common complex diseases: diabetes, hypertension, renal disease, cardiovascular disease, and stroke. This circumstance offers both moral challenges and opportunities to analyze the gene-environment interactions that produce these diseases. The JHS was initiated to address these challenges and opportunities.

Much of human history passed before the first, prehistoric migration(s) out of Africa, and the small groups of people who then left Africa carried with them only a limited sample of the human genetic diversity that existed at the time. Thus modern Africans and people of recent African ancestry (eg, African Americans) may have physiologically important genetic polymorphisms that are not present in other populations. They also exhibit extended haplotypes (groups of tightly linked markers) that are uniquely African, some of which are the products of recombination between more ancient haplotypes. Because of such recombination, the “haplotype blocks” observed in African Americans are, on average, only approximately half the size of those found in Europeans and Asians. Selective pressures that may have been imposed by events of the African Diaspora, and the subsequent admixture of Africans with Europeans and Native Americans, have produced a genetic heritage that is uniquely African American. Thus, finding alleles that are associated with disease phenotypes in African Americans may be expected to complement findings made in predominantly White populations. Finally, African Americans, particularly those in Mississippi, live in an environment that appears to promote cardiovascular disease and related disorders. All of these considerations make it likely that the JHS, rather than recapitulating the results of other powerful genetic studies, will produce novel findings that are of particular importance to the health of African Americans.

The extended pedigrees in the JHS family cohort will allow traditional sib-pair and parent-offspring analyses, including transmission disequilibrium tests as well as variance components methods. The latter methods use the relatedness among all relative pairs and the genotypic information at a specific locus to decompose the phenotypic variance into that attributable to the specific locus, residual polygenic heritability, and an environmental component. The method allows for simultaneous covariate adjustment to the mean and variance component estimation. By
analyzing all relationships in a pedigree as a matrix rather than pairwise, greater statistical power to detect specific loci can be achieved.

The pedigrees in the JHS Family Study will also allow family-based association studies with the FBAT software package. The default null hypothesis tested by FBAT is \( H_0 \): no linkage and no association between the marker and any gene influencing the trait. \( H_0 \) is calculated by using the distribution of offspring genotype, conditional on the trait and on the parental genotype to avoid biases due to population stratification, misspecification of the trait distribution, and/or selection based on the phenotype. If either or both parental genotypes are unknown, FBAT uses the distribution of offspring genotype conditional on the trait and on the sufficient statistics for the unobserved parental genotype.

Genomic DNA has been prepared from all consenting JHS participants (not just those in the Family Study), to allow both genome-wide association studies and candidate gene analysis. For association studies, genome-wide genotyping of approximately one marker per five to six kilobases is now technically feasible and is becoming more affordable, though still expensive. In addition, the JHS cohort is particularly well suited to an alternative approach, “admixture mapping,” which may achieve much of the power of genome-wide association studies but requires genotyping 200- to 500-fold fewer markers. Admixture mapping is only possible in populations that are the product of relatively recent admixture between distinct ancestral populations.

<table>
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<th>Phenytype</th>
<th>h²</th>
<th>SE(h²)</th>
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<tbody>
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<td>Height</td>
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<td>.049</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
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<tr>
<td>HDL-C</td>
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<tr>
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<tr>
<td>Lipoprotein (a)</td>
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<td>.060</td>
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</table>

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

* Dichotomous variable comparing hypertensive vs. normotensive individuals (all others).

ACKNOWLEDGMENTS
The authors thank the staff and participants in the Jackson Heart Study for their long-term commitment to the study. This research was supported by NIH contracts N01-HC-95170, N01-HC-95171, and N01-HC-95172 that were provided by the National Heart, Lung, and Blood Institute and the National Center on Minority Health and Health Disparities.

REFERENCES
4. Rao DC, Province MA, Leppert MF, et al. A genome-wide affected sib pair linkage analysis frequency differs significantly between the two ancestral populations. In such cases, the chromosomal region surrounding the relevant gene in affected individuals should have an increased proportion of markers derived from the population in which the risk allele was more common. Suitable marker sets and statistical methods for admixture mapping have recently become available, and the technique has already been used to identify loci that may be relevant to hypertension and multiple sclerosis.

The JHS cohort has high prevalence of common complex diseases including obesity, diabetes, hypertension, stroke, ischemic heart disease, and renal disease, among others, and all JHS participants have been phenotyped uniformly and extensively. The JHS data and genetic materials thus offer valuable opportunities, through both positional and candidate gene approaches, to find risk alleles for diseases that are important to African Americans. These studies may identify new targets for diagnostic or therapeutic approaches to common complex diseases.