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ORIGINAL ARTICLE

Genetic markers for ancestry are correlated with body composition traits in older African Americans

J. R. Shaffer · C. M. Kammerer · D. Reich · G. McDonald · N. Patterson · B. Goodpaster · D. C. Bauer · J. Li · A. B. Newman · J. A. Cauley · T. B. Harris · F. Tylavsky · R. E Ferrell · J. M. Zmuda · for the Health ABC study

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Abstract
Summary Individual-specific percent European ancestry was assessed in 1,277 African Americans. We found significant correlations between proportion of European ancestry and several musculoskeletal traits, indicating that admixture mapping may be a useful strategy for locating genes affecting these traits.
Introduction Genotype data for admixed populations can be used to detect chromosomal regions influencing disease risk if allele frequencies at disease-related loci differ between parental populations. We assessed evidence for differentially distributed alleles affecting bone and body composition traits in African Americans.
Methods Bone mineral density (BMD) and body composition data were collected for 1,277 African and 1,790 European Americans (aged 70–79). Maximum likelihood methods were used to estimate individual-specific percent European ancestry for African Americans genotyped at 37 ancestry-informative genetic markers. Partial correlations between body composition traits and percent European ancestry were calculated while simultaneously adjusting for the effects of covariates.
Results Percent European ancestry (median=18.7%) in African Americans was correlated with femoral neck BMD in women ($r=-0.18$, $p<10^{-5}$) and trabecular spine BMD in both sexes ($r=-0.18$, $p<10^{-5}$) independently of body size, fat, lean mass, and other covariates. Significant associations of European ancestry with appendicular lean mass ($r=-0.19$, $p<10^{-10}$), total lean mass ($r=-0.12$, $p<10^{-4}$), and total body fat ($r=0.09$, $p<0.002$) were also observed for both sexes.
Conclusions These results indicate that some population differences in body composition may be due to population-specific allele frequencies, suggesting the utility of admixture mapping for identifying susceptibility genes for osteoporosis, sarcopenia, and obesity.

Keywords Admixture mapping · Body composition · Genetic ancestry · Linkage analysis · Osteoporosis · Single nucleotide polymorphisms (SNPs)

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J. R. Shaffer (✉) · C. M. Kammerer · A. B. Newman · J. A. Cauley · R. E. Ferrell · J. M. Zmuda
Graduate School of Public Health, University of Pittsburgh,
130 DeSoto Street,
Pittsburgh, PA 15261, USA
e-mail: john.shaffer@hgen.pitt.edu

D. Reich · G. McDonald
Department of Genetics, Harvard Medical School,
Boston, MA, USA

D. Reich · G. McDonald · N. Patterson
Broad Institute of Harvard and MIT,
Cambridge, MA, USA

B. Goodpaster
Department of Endocrinology, University of Pittsburgh,
Pittsburgh, PA, USA

D. C. Bauer · J. Li
University of California San Francisco,
San Francisco, CA, USA

T. B. Harris
National Institute of Aging,
Bethesda, MD, USA

F. Tylavsky
University of Tennessee Health Science Center,
Memphis, TN, USA

Introduction

Linkage disequilibrium occurs when individuals from genetically separate parental populations mate to produce a new population deriving its ancestry from both sources. This process results in members of the admixed population inheriting stretches of chromosome from each parental population, which can be utilized by linkage disequilibrium analysis to detect chromosomal regions associated with phenotypes distributed differentially between parental populations. In practice, the specific ancestry of each genetic locus can be determined and then tested for association with a particular disease or other phenotype that differs between populations. This approach, called admixture mapping, offers us a new tool in the search for genes that influence disease susceptibility and could be especially useful given that identification of genes influencing complex traits, such as body composition, has proven difficult. Admixture mapping also has several theoretical advantages over family-linkage methods, including the recruitment of unrelated individuals, and the need for fewer markers and a smaller sample size to achieve comparable power [1–5]. However, admixture mapping will not detect all of the alleles that influence a trait, only those that are differentially distributed between ancestral populations.

To date, there have been very few attempts to use admixture mapping to search for loci implicated in disease, partly because this approach requires a high-density map of markers known to differ substantially in allele frequency among parental populations, and partly because the suitability of phenotypes for this type of analysis are still being addressed. Recent work has suggested, however, that mapping by admixture linkage disequilibrium has potential for identifying disease related loci. One recent study has successfully used admixture mapping to identify a candidate locus on chromosome 1 associated with multiple sclerosis susceptibility [6]. Another study has demonstrated excess African ancestry for loci on chromosomes 6q and 21q in hypertensive African Americans, but not in normotensive individuals [7]. In the hypertension study, microsatellite markers, which are weakly informative for ancestral origin, were used to determine locus-specific ancestry. Others have recently validated a genome-wide suite of ancestry informative single nucleotide polymorphisms (SNPs), to facilitate admixture mapping [8]. Additional work, including the study presented herein, have focused on finding phenotypes appropriate for admixture mapping. Blood glucose level, for example, has been shown to be correlated with ancestry in African Americans, and may be a good candidate for admixture mapping [9].

Body composition related phenotypes may be appropriate traits for admixture mapping [5] because differences in body composition between African and European Americans, after adjusting for known environmental predictors, are well established [10–12]. For example, peak bone mineral density (BMD) and bone size differ between populations of African and European Americans [10, 12, 13]. Similarly, measures of areal and volumetric BMD of the hip, and volumetric BMD of the spine are greater in black women compared to white women from South Africa [14]. Other studies have shown differences in lean muscle mass [11, 15, 16]. Moreover, body composition traits have been shown to be highly heritable [17–19], and genetic effects are thought to be largely responsible for residual population differences [20].

The goal of the present study was to determine whether genetic ancestry is correlated with bone mineral density, lean body mass, and fat mass within a population of African Americans. Significant correlations would represent the population-specific differences in the effects of genes on traits of interest (rather than the total genetic effect). The presence of differentially distributed alleles affecting body composition would suggest that these phenotypes are good targets for future admixture mapping studies.

Methods

Population recruitment and data collection

The Health, Aging and Body Compostion Study is an observational cohort study designed to define the relationship of body composition to weight related health conditions and functional limitations in 3,075 men and women (41.8% African American and 51.5% female, aged 70–79) [21]. Partipants were recruited from a random sample of Medicare enrollees from the Pittsburgh, PA and Memphis, TN areas. Race or ethnicity was assessed via self-report as one of the following options: Asian/Pacific Islander, Black/African American, White/Caucasian, Latino/Hispanic, Don't Know, Other, or Refused to disclose. To be eligible for the study, participants were required to experience no difficulty walking 400 m or climbing 10 steps, no difficulty with activities of daily living, no history of cancer treatment in the preceding 3 years, and no plans to move outside the area within the following 3 years. All participants provided written informed consent for examination, and all protocols were approved by the Institutional Review Boards at the University of Pittsburgh and University of Tennessee Health Science Center.

Lifestyle, anthropometric, and medical characteristics were ascertained via an initial interview and subsequent clinical evaluation. Smoking history and alcohol consumption were assessed by self-report, and physical activity level

(kcal/kg/wk) was estimated based on response to a questionnaire administered by an interviewer [22]. Medical conditions were determined jointly by self-report and history of medication use. Nontraumatic bone fracture was determined by self-report and verified by radiology-report [23]. Anthropometrics were assessed during a clinical exam as follows: standing and sitting height (cm) were measured without shoes with a stadiometer (Harpenend, Wales, UK); weight (kg) was measured in a light gown, without shoes on a calbrated balance beam scale; BMI was calculated as weight (kg) divided by height (m) squared; trunk length was calculated as the difference between sitting height and 30 cm seat; leg length was calculated as the difference between height and trunk length (cm).

Body composition assessment

Areal bone mineral density (g/cm^2) at the proximal femur and its sub-regions (femoral neck, intertrochanter, trochanter), and whole body was measured by dual energy x-ray absorbtiometry (DXA) as previously described (Hologic 4500A, software version 9.03; Hologic, Bedford, MA, USA) [24]. Whole body DXA was also used to assess soft tissue lean body mass, and total and percentage fat mass. DXA scan data were available for 98.9% of study participants. Volumetric BMD and bone size were quantified by computed tomography scan (GE CT-9800 Advantage; General Electric, Milwaukee, WI, USA) [25]. CT scan data were available for 97.6% of participants recruited at the Pittsburgh center (51.0% of total sample).

Genetic ancestry assessment

African Americans were genotyped for 37 ancestry-informative genetic markers, which are known to differ in allele frequency by 0.6 or more (mean difference=0.79) between European and African populations. These markers occur at spacing of at least 20 centimorgans across chromosomes 1 to 22, and are not in linkage disequilibrium in either parent population (see Electronic Supplementary Material S1 for marker information). Using these genotype data we estimated the proportion of European ancestry for each self-reported African American by employing a maximum likelihood estimation procedure, which has been shown to give estimates of European ancestry that correspond with high fidelity to values obtained from a Markov Chain Monte Carlo approach [2, 26]. In brief, to estimate the maximum likelihood proportion of European ancestry for an individual, we explored a range of proportions from 0–100%, and found the most probable value based on the observed genotypes. (The 95% credible interval for the ancestry proportion is determined by likelihood ratio test as the range in which the likelihood is within a factor of 6.8 of the maximum). Specifically, to calculate the probability of the genotype at SNP i with frequency f_{EA} in European Americans and f_{WA} in West Africans, we estimated its frequency as $F_i = pf_{EA} + (1-p)f_{WA}$, and then calculated the probability of the observed data as $(1-F_i)\times(1-F_i)$ for a homozygous reference genotype, $2\times F_i\times(1-F_i)$ for a heterozygous genotype, and $F_i\times F_i$ for a homozygous variant genotype. To estimate the overall likelihood of the data for an individual under the hypothesis of a given proportion of European ancestry p, we then multiplied these probabilities across all the SNPs for which genotypes were available. We note that European Americans used in this study may have a small proportion of African ancestry; however, this would not affect results of our analyses within-African Americans, and would cause the African American-European American comparisons to be conservative.

Statistical analyses

Distributions of all variables were assessed separately in both European Americans and African Americans, and variance-stabilizing transformations were applied to variables found to deviate from normality, including natural logarithm transformations for measurements of volumetric BMD, total spine volume, and lean body mass, and square root transformations for physical activity level, trabecular spine volume, trunk fat, and total body fat. Then, population-specific outlying points that were greater than ± 4.5 SD from the mean for each variable were omitted from further analyses (up to 7 points removed per trait). Significant mean differences by sex between African and European Americans for demographic and anthropometric traits were assessed via Student's T-test, and then raw (zero-order) correlations between estimated European ancestry and these traits were calculated in African American females and males separately and together. For body composition traits, T-tests were also used to determine significant mean differences between European and African Americans, after controlling for the effects of significant covariates. Because our sample size is large (nearly 1,300 individuals) we were able to incorporate a number of covariates into our analyses. The suite of possible covariates considered in analyses included recruitment site, age, sex, diabetes, physical activity level, alcohol consumption, smoking, height, total body fat, and total lean mass. Of this suite of potential covariates, only those with significant effects as determined by multiple-regression were included in the analyses for any given body composition trait, with the following exceptions: (1) height was forced into the model for lean traits, (2) total body fat mass was excluded as a possible covariate for fat traits, and (3) total lean mass was excluded as a possible covariate for lean mass traits. Partial correlations between European ancestry and body

composition traits, while simultaneously controlling for the indicated covariates, were calculated for African American females and males together and separately. For those body composition phenotypes showing marked sex differences, sex × genetic ancestry interaction terms were tested using multiple-regression. Because osteoarthritis may affect measures of BMD, partial correlations with ancestry were re-estimated for a subset of participants (n=1147) after removing 130 individuals with symptomatic or asymptomatic osteoarthritis. All descriptive statistics were computed using the R statistical environment (R Foundation for Statistical Computing, Vienna, Austria).

Results

Genotype information from 37 ancestry-informative markers was utilized to individually estimate the degree of European ancestry for the 1,277 African Americans enrolled in the study. Figure 1 depicts the distribution of European ancestry in the African American study population, which varied from 0.1% to 89.9%, with median 18.7%. Individual ancestry estimates have standard errors of ±5.42%, obtained as one-fourth of the 95% credible intervals, as described in the methods section. Mean European ancestry did not differ between men and women, but did differ significantly between the Pittsburgh and Memphis sites (mean±SD=24.5±16.2% and 18.5±12.5%, respectively; p-value<0.05).

Significant differences between African Americans and European Americans were present for many anthropometric and body composition traits including measures of trunk and leg length, femoral neck cross-sectional area, bone volume, areal BMD, and volumetric BMD, as well as lean body mass and body fat. Table 1 displays the unadjusted mean population characteristics by sex and population. While total height did not differ between populations, leg length was significantly longer, and trunk length was significantly shorter in African Americans as compared to European Americans ($p<10^{-5}$ for both). To determine whether variation in trunk and leg length is related to the proportion of European ancestry *within* African Americans, we calculated the correlation between European ancestry and these traits. Table 2 shows the correlations between European ancestry and body composition after adjusting for significant covariates (see Table 3 for specific covariates). Consistent with the mean differences between African Americans and European Americans, greater European ancestry was significantly correlated with shorter leg length (r=−0.16, p<0.0001) and longer trunk length (r=0.12, p=0.0001) in both sexes.

DXA measures of whole body BMD also differed between African Americans and European Americans in both sexes. However, only in women was whole body BMD significantly negatively correlated with proportion of European ancestry (r=−0.11, p=0.005). Decreased areal BMD was also significantly correlated with European ancestry in African American women for femoral neck, trochanter, intertrochanter, and total hip measurements ($p\leq 0.001$ for all). This result is consistent with the significant differences in areal BMD between European American and African American women at these skeletal sites. In men, however, mean hip BMD did not differ between European and African Americans, and there was no correlation with ancestry. These sex differences motivated the test for a sex × genetic ancestry interaction term, which was significant for femoral neck (p=0.03) and trochanter (p=0.02) bone sites.

As with areal BMD of the hip, measurements of volumetric BMD of the lumbar spine were also negatively correlated with European ancestry for total BMD (r=−0.19, p<0.001) and trabecular BMD (r=−0.20, p<0.001) in women, and trabecular BMD (r=−0.13, p=0.04) in men. Total spine bone volume did not differ between ancestral

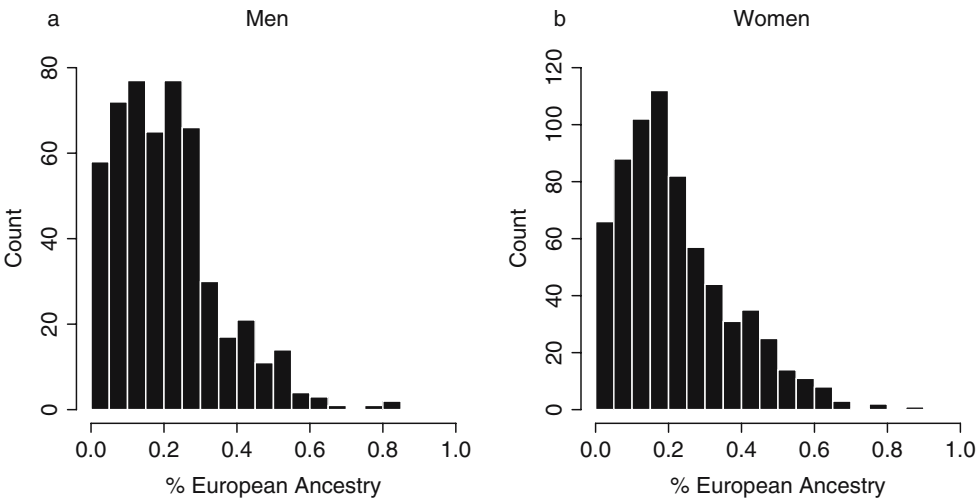

Fig. 1 Histograms of estimated degree of European ancestry in African American (**a**) men and (**b**) women. Maximum likelihood estimates of European ancestry were calculated for each African American from 37 unlinked single nucleotide polymorphisms with mean inter-marker distance of 20 cM

Table 1 Mean (±SD) population characteristics by sex and race

	Women		Men	
	African American	European American	African American	European American
Demographic				
Sample, n	726	853	551	937
Age, years[b]	73.4 (3.0)	73.6 (2.8)	73.5 (2.8)	73.9 (2.9)
European ancestry	0.22 (0.15)		0.21 (0.14)	
Recruitment site, %[a]	53.6	46.2	50.1	49.3
Anthropometric				
BMI, kg/m^2[a]	29.5 (5.7)	26.0 (4.5)	27.2 (4.3)	27.0 (3.7)
Height, cm	159.6 (6.3)	159.5 (6.0)	173.0 (7.)	173.5 (6.4)
Weight, kg[a]	75.6 (15.8)	66.2 (12.2)	81.4 (14.5)	81.4 (12.4)
Trunk length, cm[a, b]	80.5 (4.0)	82.1 (3.7)	86.6 (4.2)	89.0 (3.8)
Leg length, cm[a, b]	79.1 (5.3)	77.4 (4.8)	86.4 (6.)	84.5 (5.1)
Lifestyle				
Lifetime smoking history, %	44.3	41.1	69.3	71.1
Lifetime history of alcohol use, %	56.8	64.7	81.0	84.8
Physical activity, kcal/kg/wk	79.9 (73.6)	85.5 (62.5)	81.3 (78.5)	83.8 (66.0)
Prevalent disease				
Diabetes, %	21.3	7.5	21.9	13.9
Osteoarthritis, knee, %	11.3	13.1	4.4	6.2
Osteoarthritis, hip, %	4.1	7.5	2.0	3.4
Whole body				
Areal BMD, g/cm^2[a, b]	1.04 (0.11)	0.98 (0.10)	1.21 (0.13)	1.15 (0.11)
Proximal femur BMD, g/cm^2				
Femoral neck[a]	0.75 (0.13)	0.65 (0.11)	0.85 (0.14)	0.76 (0.13)
Trochanter[a]	0.65 (0.13)	0.58 (0.11)	0.79 (0.14)	0.74 (0.13)
Intertrochanter[a]	1.01 (0.18)	0.91 (0.16)	1.19 (0.18)	1.11 (0.17)
Total hip[a]	0.86 (0.15)	0.77 (0.13)	1.02 (0.16)	0.94 (0.14)
Lumbar spine				
Trabecular volumetric BMD, g/cm^3[a, b]	116.8 (42.9)	93.5 (33.0)	142.7 (42.2)	112.6 (38.0)
Total volumetric BMD, g/cm^3[a]	254.5 (51.9)	221.6 (44.1)	282.8 (56.5)	247.1 (49.4)
Bone volume, cm^3[a]	17.61 (2.62)	17.19 (2.32)	21.82 (3.47)	21.75 (3.07)
Lean body mass, kg				
Appendicular[a, b]	18.53 (3.28)	15.53 (2.43)	25.45 (4.03)	23.62 (3.24)
Total body[a, b]	42.56 (6.31)	38.11 (5.11)	56.14 (7.9)	54.96 (6.75)
Body fat				
Percent body fat[a, b]	39.96 (6.14)	39.03 (5.59)	26.81 (5.37)	28.74 (4.76)
Total body fat mass, kg[a, b]	30.88 (10.0)	26.41 (7.91)	22.28 (7.5)	23.76 (6.85)

[a] significant differences between populations in women ($p \leq 0.05$);
[b] significant differences between populations in men ($p \leq 0.05$)

groups of either sex, and was not correlated with European ancestry. We also repeated our analyses in the subset of African Americans after removing individuals with symptomatic and asymptomatic osteoarthritis (130 individuals removed) and, with one exception, obtained similar results (data not shown). In contrast to the full sample, total spine volumetric BMD in the non-osteoarthritic subset was significantly correlated with European ancestry in African American men ($r=-0.15$, $p=0.029$), which was not surprising given the high prevalence of spinal degenderative disease in men [27].

Overall, the direction and significance of correlations between European ancestry and various bone measurements in African Americans were consistent with the mean differences observed between African Americans and European Americans, although these mean differences may partly be due to effects of unmeasured cultural and environmental factors. Nevertheless, taken together, these results support our conclusion that European ancestry is associated with body composition.

The predicted difference in femoral neck BMD between African Americans having 0% versus 100% European ancestry was 0.094 g/cm^2 or 0.70 standard deviations, which is similar to the observed mean BMD difference between African and European populations [10, 28]. Likewise, mean percent European ancestry differed

Table 2 Estimated Pearson correlation coefficients between European ancestry and demographic, anthropometric, and body composition traits

	Total (n≈1200) cor. (p-value)	Women (n≈680) cor. (p-value)	Men (n≈520) cor. (p-value)
Demographic[a]			
Site	**0.20 (1×10^{-12})**	**0.26 (2×10^{-12})**	0.12 (.007)
Age	0.04 (.207)	0.05 (.190)	0.02 (.656)
Anthropometric[a]			
BMI	−0.02 (.533)	−0.05 (.218)	0.00 (.920)
Height	−0.05 (.102)	−0.01 (.765)	−0.04 (.423)
Weight	−0.04 (.121)	−0.05 (.154)	−0.01 (.805)
Trunk length	**0.12 (4×10^{-5})**	**0.21 (2×10^{-8})**	0.13 (.003)
Leg length	**−0.16 (2×10^{-8})**	**−0.19 (6×10^{-7})**	−0.14 (.002)
Whole body[b, c]			
Areal BMD	−0.05 (.103)	−0.11 (.005)	0.02 (.583)
Proximal femur areal BMD[b, c]			
Femoral neck	**−0.12 (8×10^{-5})**	**−0.18 (4×10^{-6})**	−0.03 (.480)
Trochanter	−0.07 (.019)	−0.13 (.001)	0.02 (.689)
Intertrochanter	−0.08 (.006)	**−0.13 (6×10^{-4})**	−0.01 (.840)
Total hip	−0.09 (.002)	**−0.16 (7×10^{-5})**	−0.01 (.852)
Lumbar spine[b, c, d]			
Trabecular volumetric BMD	**−0.18 (1×10^{-5})**	**−0.20 (2×10^{-4})**	−0.13 (.041)
Total volumetric BMD	−0.14 (.001)	**−0.19 (4×10^{-4})**	−0.10 (.121)
Bone volume	0.03 (.506)	0.02 (.665)	0.03 (.668)
Lean body mass[b]			
Appendicular	**−0.19 (9×10^{-11})**	**−0.20 (2×10^{-7})**	**−0.18 (7×10^{-5})**
Total body	**−0.12 (3×10^{-5})**	**−0.14 (5×10^{-4})**	−0.09 (.038)
Body fat[b]			
Total body fat	0.09 (.002)	0.09 (.020)	0.09 (.050)
Percent fat	0.10 (.001)	0.10 (.010)	0.09 (.035)

[a] Correlations for demographic and anthropometric traits are not adjusted for covariates;
[b] Adjusted for recruitment site, age, (sex), diabetes history, physical activity level, drinking history, smoking history, and height, where significant;
[c] Adjusted for total body fat and total lean mass, where significant;
[d] CT scan data were available for PA recruitment site only, total n ≈600, women n ≈340, men n ≈250;
Bold indicates Bonferroni adjusted pvalue < 0.05 (note, this adjustment for multiple testing is overly conservative due to the high correlation among body composition traits of interest); cor. = Pearson correlation.

between African American women who experienced non-traumatic bone fracture versus those who did not (one-sided empirical p=0.069), which is consistent with the role of greater European ancestry as a risk factor for osteoporosis. Based on the results of the regression analyses, the odds-ratio for fracture in women with 100% versus 0% European ancestry was projected to be 1.137 (p=0.071).

Similar to the bone traits, measurements of soft tissue lean body mass differed significantly between populations and were negatively correlated with European ancestry for appendicular lean body mass and total lean body mass in both sexes ($r=-0.19$, $p<10^{-10}$; $r=-0.12$, $p<10^{-4}$). Furthermore, mean percent fat and total body fat differed between African American and European American men and women, and were positively correlated with percent European ancestry ($p<0.002$ for both traits) in both sexes.

The results presented above show significant correlations between body composition phenotypes and ancestry while adjusting for demographic, lifestyle, and medical covariates shown to have statistically significant effects on the relationship (Table 3). These adjusted correlations closely follow unadjusted zero-order correlations (results not shown). In addition, because other researchers have reported that socioeconomic status explained the relationship between phenotype and genetic ancestry [9], we also looked at the effects of socioeconomic status on the relationship between genetic ancestry and body composition. We found that adjusting for socioeconomic status, as estimated by education and family income, did not affect the correlation with ancestry (results not shown).

Discussion

In this study we examined whether residual variation in body composition traits, shown to differ between African Americans and European Americans, were correlated with genetic ancestry in older individuals from an admixed U.S. population. Our estimates of European ancestry in African Americans in the Health ABC study, approximately 20%

Table 3 Significant covariates for which analyses are adjusted

	Significant covariates		
	Total sample	Women	Men
Whole body			
Areal BMD	ST,AG,SX,DB,PH,SM,FT,LN	ST,AG,DB,DR,SM,HT,FT,LN	ST,DB,PH,SM,FT,LN
Proximal femur BMD			
Femoral neck	SX,DB,PH,HT,FT,LN	ST,AG,DB,DR,FT,LN	FT,LN
Trochanter	ST,SX,PH,SM,HT,FT,LN	AG,DB,PH,DR,FT,LN	ST,SM,HT,LN
Intertrochanter	ST,AG,SX,DB,PH,HT,FT,LN	ST,AG,DB,PH,DR,HT,FT,LN	ST,PH,HT,LN
Total hip	ST,AG,SX,DB,PH,HT,FT,LN	ST,AG,DB,PH,DR,HT,FT,LN	ST,PH,HT,LN
Lumbar spine			
Trabecular volumetric BMD	AG,SX,PH,SM,HT,LN	AG,PH,DR	HT,LN
Total volumetric BMD	AG,SX,PH,SM,HT,LN	AG,PH,DR,FT	HT,LN
Bone volume	AG,SX,HT,FT,LN	AG,DR,HT,FT,LN	AG,HT,FT,LN
Lean body mass			
Appendicular	AG,ST,SX,PH,DR,HT,FT	DB,SM,HT,FT	AG,ST,DB,PH,DR,HT,FT
Total body	ST,SX,DB,PH,HT,FT	ST,DB,PH,HT,FT	ST,PH,HT,FT
Body fat			
Total body fat	ST,SX,DB,PH,HT,LN	ST,DB,PH,HT,LN	ST,AG,PH,DR,SM,HT,LN
Percent fat	ST,SX,DB,PH,HT,LN	ST,DB,PH,SM,HT,LN	ST,AG,PH,SM,HT,LN

ST = site; AG = age; SX = sex; DB = diabetes status; PH = physical activity; DR =drinking history; SM = smoking history; HT = height; FT = total fat mass; LN = total lean mass.

for most individuals, were consistent with previous reports of admixture in the U.S. population [8, 9, 29]. After adjusting for known covariates, we detected significant associations between the proportion of European ancestry and measures of bone length, lean soft tissue mass, and body fat in both men and women. Likewise in women, we detected significant associations with European ancestry for areal and volumetric density at the hip and spine, respectively. In all cases, the direction of the correlation with ancestry was consistent with the differences in trait means between African Americans and European Americans.

Consistent with previous results, we have observed greater leg length and shorter trunk length among African Americans [13, 30], and we have shown that residual axial and appendicular skeleton lengths are strongly related to genetic ancestry in both African American women and men. We also found significant associations with ancestry for trabecular BMD of the spine in both sexes; however, the rest of the bone-related phenotypes were associated with ancestry only in women. This result is consistent with our observation that the means of the bone-related traits were significantly different between African American and European American women only. That the relationship between areal hip BMD and ancestry is entirely absent in men raises the possibility of a gene × gender interaction, which is consistent with previous genetic analyses in humans [19, 31, 32] as well as recent results in inbred strains of mice [33].

The associations reported herein may be conservative due to possible over-adjusting for covariates that could mediate the relationships between body composition traits and European ancestry. For example, the mean proportion of European ancestry differed markedly between African Americans from the two recruitment sites (Memphis, TN and Pittsburgh, PA). By incorporating recruitment site into our analytical models, and thereby accounting for differences in body composition that may be due to the effects of unknown environmental factors at the two study locations, we also were removing part of the relationship between body composition and genetic ancestry. Although unadjusted correlations revealed a relationship between measurements of body composition and European ancestry, we incorporated several covariates (including recruitment site, age, sex, diabetes status, physical activity, drinking history, smoking history, height, body fat, and lean mass) into our analyses to reduce the probability that unknown confounders, rather than ancestry, are responsible for the observed relationships. We also analyzed the subset of African Americans after removing individuals with definite or possible osteoarthritis, which could affect results for bone-related traits, and again, obtained similar results.

Because the percentage of European ancestry for individual African Americans was estimated based on genotype data, and we did not model non-African, non-European ancestry (e.g., Native American), a degree of uncertainty is present in these estimates. This uncertainty would bias our correlations with ancestry toward the null hypothesis of no observed relationship. Accordingly, we may have failed to detect a real (but weak) correlation between a phenotype and European ancestry because the relationship was masked by the imprecision in our estimate

of genetic ancestry. The Bonferroni correction used for multiple testing is overly conservative due to the high correlations between the traits of interest. However, despite the potential issues of over-adjusting and bias, we found highly significant correlations between genetic ancestry and bone and muscle related traits, which suggests that there may be allelic variation between African and European populations at genes that influence variation in body composition. We must note, however, that the magnitude of the correlations between ancestry and traits of interest do not represent a global view of the importance of genetic effects; rather, the correlations reported herein are only reflective of the portion of the genes' effects that are acting in a population-specific way. And as is true with all other gene detection methods, our ability to use admixture mapping to identify loci affecting disease is largely dependent on both the number of risk genes, and their respective effect sizes. Successful detection of risk genes would be more likely in the case of a single locus responsible for the entire ancestry effect, rather than many individual loci each contributing weaker effects. Nonetheless, those traits presenting larger and highly significant correlations with European ancestry may be the best candidate phenotypes for future admixture mapping to detect chromosomal regions that affect body composition.

Although traits that differ between population groups are the most obvious phenotypes on which to perform admixture mapping, traits that do not differ between African and European Americans may still be worthwhile traits to study. For example, total height did not differ between the European Americans and African Americans; however, population-specific allelic effects (as estimated by ancestry) were observed for trunk length and leg length, both of which are components of total height. In this example, allelic effects acting in opposite directions on trunk length and leg length result in a minimal net effect on overall height. Therefore, specific chromosomal regions, which differ in allele frequency between parental groups and which influence total height (some positively, some negatively), could be detected by admixture mapping. A similar situation is possible for other phenotypes if two or more differentially distributed genetic effects are acting in opposite directions [3]. In summary, we report a novel association between genetic ancestry and body composition, suggesting the presence of differentially distributed alleles affecting these traits, and providing impetus for further analysis via genome-wide admixture mapping.

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