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Genetic and environmental influences on skeletal muscle phenotypes as a function of age and sex in large, multigenerational families of African heritage

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Abstract

The aim of this study was to estimate the heritability of and environmental contributions to skeletal muscle phenotypes (appendicular lean mass and calf muscle cross-sectional area) in subjects of African descent and to determine whether heritability estimates are impacted by sex or age. Body composition was measured by dual-energy X-ray absorptiometry and computed tomography in 444 men and women aged 18 yr and older (mean: 43 yr) from eight large, multigenerational Afro-Caribbean families (family size range: 21–112). Using quantitative genetic methods, we estimated heritability and the association of anthropometric, lifestyle, and medical variables with skeletal muscle phenotypes. In the overall group, we estimated the heritability of lean mass and calf muscle cross-sectional area ($h^2 = 0.18–0.23$, $P < 0.01$) and contribution of environmental factors to these phenotypes ($r^2 = 0.27–0.55$, $P < 0.05$). In our age-specific analysis, the heritability of leg lean mass was lower in older vs. younger individuals ($h^2 = 0.05$ vs. 0.23 , respectively, $P = 0.1$). Sex was a significant covariate in our models ($P < 0.001$), although sex-specific differences in heritability varied depending on the lean mass phenotype analyzed. High genetic correlations ($\rho_G = 0.69–0.81$; $P < 0.01$) between different lean mass measures suggest these traits share a large proportion of genetic components. Our results demonstrate the heritability of skeletal muscle traits in individuals of African heritage and that heritability may differ as a function of sex and age. As the loss of skeletal muscle mass is related to metabolic abnormalities, disability, and mortality in older individuals, further research is warranted to identify specific genetic loci that contribute to these traits in general and in a sex- and age-specific manner.

Keywords

heritability; lean mass; race; aging

Skeletal muscle mass and strength decline as much as 12–14% per decade after the fourth decade of life (for review, see Ref. 40). This decline in muscle mass (sarcopenia) is associated with several adverse health consequences, including reductions in bone density, aerobic capacity, and resting metabolic rate, the latter of which may contribute to obesity and the prevalence of insulin resistance, Type 2 diabetes, dyslipidemia, and hypertension (for review, see Refs. 15 and 24). Furthermore, sarcopenia is related to a reduction in the performance of activities of daily living (33), which may lead to further declines in muscle mass and strength and greater reductions in the performance of those activities. The net effect of this cycle can result in marked disablement, predisposing older individuals to falls, injuries, and disability (39).

Differences in skeletal muscle traits between individuals may be due to environmental factors, genetic factors, or the interaction of both. While the effects of nongenetic factors such as physical activity have been broadly investigated, only recently have studies begun to address the genetic influences on skeletal muscle traits in subjects of European descent. Studies using dizygotic (DZ) and monozygotic (MZ) twins have estimated that heritability of lean body mass (6,17,42) and limb circumference (11,22,26) ranges from 30–50% and 80–93%, respectively. Twin studies have also revealed that the heritability of muscle strength phenotypes ranges from 30 to 83%, depending on the conditions of the strength measure (e.g., contraction angle, velocity, and type) (46,47).

Although these studies have estimated the heritability of skeletal muscle phenotypes in populations of European ancestry, considerably less is known about the heritability of such traits in non-white populations. Moreover, most previous investigations have studied homogeneous samples without examining age or sex differences. Such differences are possible, as significant differences in skeletal muscle phenotypes exist between individuals of European and African descent, men and women, and younger and older individuals. For example, muscle mass (2,19,23,51) and strength (30) are greater in subjects of African descent than in subjects of European descent. Likewise, men and women exhibit differences in muscle mass and strength (25,28), and muscle mass and strength decline with aging (40). We are unaware of previous investigations of sex differences in the heritability of skeletal muscle phenotypes; however, sex differences (14,31,43,44) and sex-specific genetic loci have been reported for fat-free mass (41,53) and related traits such as muscle strength (12,13) and body height and bone mineral density (35).

In this report, we estimate the heritability of and environmental contributions to arm, leg, and appendicular lean tissue mass and calf muscle cross-sectional area in large, extended multigenerational families of African descent. Because skeletal muscle phenotypes differ as a function of age and sex, we hypothesized that heritability and the environmental contributions to these phenotypes would be different in young vs. older individuals and in men vs. women.

METHODS

Subjects

As part of a large, population-based study of all age-eligible men on the Caribbean island of Tobago (7), we recorded the number of living siblings for each participant, as well as the vital status and residence of their parents. All of the men in our study served as potential probands for the family study and were selected without regard to medical history or other physical characteristics. These potential probands were sorted by family size; individuals with the largest family sizes were recruited first. To be eligible, a proband had to be Afro-Caribbean, have had a spouse who was willing to participate in the study, and have at least six living offspring and/or siblings aged 18+ yr and residing in Tobago. Ethnicity was self-reported, and participants were defined as Afro-Caribbean if they reported that all four of their grandparents

are Afro-Caribbean. All probands for the Tobago Family Health Study were between 52 and 103 yr of age. In addition, all first-, second- and third-degree relatives of these probands and their spouses were invited to participate regardless of their medical history or other physical characteristics.

To date, we have recruited 471 individuals age 18 and older in eight multigenerational families of the following sizes: 102, 26, 49, 28, 113, 21, 38, and 94, with a mean family size of >50 individuals. These 283 women and 188 men ranged in age from 18 to 103 yr (mean age, 43 yr). Among these 471 individuals in eight pedigrees, we have the following relationships: 361 parent-offspring, 495 full siblings, 101 grandparent-grandchildren, 1,137 avuncular, 61 half siblings, and 1,380 cousins. Written informed consent was obtained from every participant using forms and procedures approved by the Tobago Ministry of Health and Social Services and University of Pittsburgh Institutional Review Boards.

Lean soft tissue mass

Whole body dual-energy X-ray absorptiometry (DXA) measurements of appendicular lean soft tissue mass were obtained from 444 of the family members using a Hologic QDR 4500W densitometer (Hologic, Bedford MA). Standardized procedures for participant positioning and scan analysis were followed according to the manufacturer's recommended protocol. Scans were analyzed with QDR software version 8.26a. Densitometry staff were trained and certified by Hologic. The DXA technician completed a weekly quality control whole body air scan before completing any scans. Densitometry quality assurance (QA) and quality control (QC) were completed by SYNARC (Maynard, MA). Longitudinal machine stability was assessed from plots of daily spine phantom scans and reviewed monthly. A weekly printout of QC plots was generated to detect short-term inconsistencies and long-term drift.

Measures of appendicular lean mass by DXA have been validated against criterion methods including potassium counting (18), nitrogen analysis (21), and computed tomography (CT) (21,52). The calculation of appendicular lean mass by DXA has been described in detail (21). In brief, specific anatomic landmarks are used to isolate the arms and legs on the skeletal X-ray planogram (anterior view). The arm encompasses all soft tissue extending from the center of the arm socket to the phalange tips. Contact with the ribs, pelvis, or greater trochanter is avoided. The leg consists of all soft tissue extending from an angled line drawn through the femoral neck to the phalange tips. The DXA system software provides the total mass and bone mineral content for the isolated regions. Total arm lean mass is calculated as: arm lean mass = total arm mass - (arm fat mass + arm bone mineral content). Similar calculations were made for leg lean mass. Leg and arm lean mass represent the sum of both the right and left extremities. Total appendicular lean mass was taken as the combined sum of leg and arm skeletal muscle mass.

Calf muscle cross-sectional area

Measurements of calf muscle cross-sectional area were made in 418 of the family members. Single axial tomographic slices of the left tibia were scanned using a Stratec XCT 2000 scanner (Stratec Medizintechnik, Pforzheim, Germany) according to standardized measurement and analysis procedures. The coefficient of variation (CV) for this measurement is 1.8%, and the test-retest coefficient is 0.958. Each scan was acquired with a 0.5-mm voxel size, slice thickness of 2.5 mm, and at a speed of 20 mm/s. To acquire this scan, we first measured tibia length from the medial malleolus to the medial condyle of the tibia. We then marked the leg at 66% of the total length using a ruler and manually placed the gantry and positioning laser over the marked site. In adults, the proximal two-thirds site is associated with the largest muscle belly. In the pQCT images, a region of interest (ROI) was defined around the whole leg cross section. Within this ROI, the different soft tissues and bone were separated according to different density

thresholds applied in two segmentation steps. First, the total area of the muscle and bone was determined with a threshold set at 40 mg/cm³ for peel mode 2 (and -100 mg/cm³ for contour mode 1). The threshold used for contour mode 1 distinguished the leg from the background, and the threshold selected for peel mode 2 distinguished muscle and bone areas from fat. Next, the total areas of the fibula and the tibia were determined using cortmode 1 with the threshold set at 710 mg/cm³. The bone areas determined in this second step were subtracted from the total muscle area and bone area found by step 1 and thus yielded muscle cross-sectional area.

Covariates and other measurements

Body weight was measured to the nearest 0.1 kg with participants wearing indoor clothing but without shoes using a balance beam scale. Standing height was measured to the nearest 0.1 cm without participants wearing shoes using a wall-mounted stadiometer. The average of two measurements was used. Body mass index (BMI) was calculated by dividing body weight (kg) by height (m²).

Information on demographic characteristics, medical history, reproductive characteristics, and lifestyle habits was obtained by standardized questionnaires administered by trained and certified clinical interviewers. Determination of race was based on self-declaration, and participants provided detailed information on the origin of their parents and grandparents. The Tobago population is predominantly of West African origin [92% of the island according to the most recent census data (48)] with low non-African admixture. Previous studies using ancestry-informative genetic markers have confirmed low admixture (6% non-African) in this population (27) compared with 12–23% non-African admixture in African-Americans (34).

We assessed a number of potential covariates for each participant, including current smoking status (Yes/No; participants who had smoked fewer than 100 cigarettes in their lifetime were considered nonsmokers), alcohol consumption >2 drinks/wk (Yes/No), caffeine consumption (mg/day), physical activity (min/wk), time spent watching television (min/wk), medication use, medical history, oral contraceptive use (Yes/No), postmenopausal status, and history of pregnancy (Yes/No and number of pregnancies). Participants were asked to bring prescription and nonprescription medications to the clinic for verification. Current use was defined as use within the preceding 30 days. A study-specific medication dictionary was used to categorize the type of medication from product brand and generic names obtained from the medication containers. Dose or duration of use or specific indication was not queried. Subjects were asked whether a doctor or health care provider had ever told them they had certain medical conditions including arthritis, cancer, or cardiovascular disease. Hypertension was defined as a diastolic blood pressure exceeding 90 mmHg, systolic blood pressure exceeding 140 mmHg, or currently taking blood pressure medication. Diabetes was defined as fasting glucose level exceeding 126 mg/dl or currently taking diabetes medication. Because walking is the predominant form of physical activity on the island, we recorded minutes walked per week as a measure of physical activity. Women were defined as postmenopausal if they declared that they no longer had menses and were greater than 40 yr old or they had experienced a hysterectomy or ovariectomy. Because only 5 of 283 (1.8%) women reported ever using postmenopausal hormone therapy, we did not consider this variable as a potential correlate of skeletal muscle phenotypes in subsequent analyses.

Statistical analysis

Before performing statistical analyses, we assessed the distributions of all muscle-related traits for nonnormality and outliers. We removed all outliers greater than 3.5 SDs from the mean, resulting in the removal of four values. All analyses were conducted using only those subjects for whom data on all covariates was available. To determine the extent to which genetic and environmental factors affect muscle traits, we initially assessed potential covariates (age, sex,

weight, height, waist circumference, time spent walking per week, current smoking, alcohol use, use of oral contraceptives, and history of pregnancy) by combined forward and backward stepwise regression using the statistical package R (R, version 2.1.0) (4) using a threshold of $P < 0.10$. Using the program SOLAR (1), these potential covariates were next formally evaluated by maximum likelihood methods within a variance components framework; the significance level for the inclusion of covariates was set at $P < 0.05$ for these analyses. To indicate the effects of covariates on skeletal muscle phenotypes, we report the strength of association between covariates and the phenotypes as a percent difference in the phenotype per unit of the covariate, instead of the beta coefficients. Percent differences were calculated as $(\text{beta coefficient} \times \text{unit range})/(\text{phenotype mean})$. The unit range was 5 yr for age and 8.5 cm (1 SD) for height. The unit range for dichotomous covariates equaled 1 (9).

Within the variance components framework, we simultaneously estimated fixed covariate effects, additive polygenic genetic effects, and residual error. Heritability (h^2), defined as the additive genetic (or polygenic) component of variance, was estimated from the covariance among relatives. The significance of each covariate was estimated using the likelihood ratio (LR) test in which a complete model (containing the variable of interest) was compared with a nested model in which the factor was removed (or in the case of heritability, set equal to zero). The LR statistic asymptotically follows a χ^2 distribution, with the degrees of freedom equal to the number of constrained parameters. The total phenotypic variation of each trait was decomposed into three parts: additive genetic (estimated by heritability), measured covariates (estimated by r^2), and residuals. These analyses were also performed for subsets of the sample: men and women, as well as young (≤ 45 yr) and older (> 45 yr) subjects.

Bivariate maximum likelihood methods in SOLAR were used to assess the possible genetic and environmental correlation between traits (56). These methods decompose the total phenotypic correlations (ρ_P) between two traits into the portions due to a common set of genes and environmental factors. To estimate the genetic correlations (ρ_G) and environmental correlations (ρ_E) for pairs of traits, the matrix of kinship coefficients is generated conditioning on all the related individuals within each pedigree. Using the standard quantitative genetic theory, the phenotypic variance-covariance matrix and its genetic and environmental components are then obtained. LR statistics were used to test the significance of ρ_G between any pair of traits.

RESULTS

The physical characteristics, lean mass, and muscle cross-sectional area for the men and women are reported in Table 1. Participants ranged in age from 18 to 103 yr. In general, men exhibited greater height, lean mass, and calf muscle area than women ($P < 0.01$); women exhibited greater BMI and body fat percentage than men ($P < 0.01$).

In all participants, 13% reported regular consumption of alcohol (> 2 drinks/wk), 5% reported being current smokers, 28% had hypertension, and 15% had Type 2 diabetes. Participants reported viewing an average of 15.9 h (SD = 8.0 h) of television per week and 47.9 min (SD = 96.7 min) of walking per week. In women, 32% were postmenopausal, 33% reported current use of oral contraceptives, and 77% reported a history of pregnancy. Significant covariates for each skeletal muscle phenotype measure are shown in Table 2. In this analysis, age was associated with calf muscle cross-sectional area ($P < 0.05$), and sex was associated with all lean mass measures and calf muscle cross-sectional area ($P < 0.001$). There was no significant age $\times$ sex interaction for any muscle trait. Current smoking, history of pregnancy, and oral contraceptive use were significant environmental contributors to measured skeletal muscle phenotypes in stepwise regression analyses (Table 2, $P < 0.05$ for all). Together, these

covariates explained a significant proportion ($r^2 = 0.27–0.55$) of the variance in lean mass and calf muscle area.

Upon determination of significant environmental and additional contributors to skeletal muscle phenotypes, we estimated the heritability (h^2) of these phenotypes (Table 3). After accounting for all significant covariates, there was significant heritability of lean mass and calf muscle cross-sectional area ($P < 0.01$ for all). To further understand heritability as a function of age and sex, we estimated heritability values in younger (age ≤ 45 yr) and older (age > 45 yr) participants (Table 4, *top*) and in men and women (Table 4, *bottom*). The age of 45 yr was established as the point for age stratification because the age-lean mass relationship changes dramatically between 40 and 50 yr of age within this group of subjects (data not shown). In younger subjects, we found significant heritability of arm, leg, and appendicular lean mass ($P < 0.01$ for all) and calf muscle cross-sectional area ($P < 0.05$). Heritability estimates were lower for leg lean mass and calf muscle cross-sectional area in older participants, and the only statistically significant heritability values were those for arm lean mass ($P < 0.01$) and appendicular lean mass ($P < 0.05$). In men, we found significant heritability of arm, leg, and appendicular lean mass ($P < 0.01$ for all), as well as calf muscle cross-sectional area ($P < 0.05$). The heritability estimates for appendicular lean mass and calf muscle cross-sectional area were similar in women compared with men, but the heritability estimate for leg lean mass was lower in women, whereas heritability estimates for arm lean mass were higher.

Finally, we determined the proportion of the heritability of skeletal mass phenotypes that is determined by shared genetic factors by examining genetic correlations (ρ_G). We found that ~66% of the joint variation in arm lean mass and leg lean mass is due to shared genetic factors ($\rho_G = 0.81 \pm 0.08$, $P < 0.001$). Likewise, ~48% of the joint variation in arm lean mass and calf cross-sectional area appears to be due to shared genetic factors ($\rho_G = 0.69 \pm 0.12$, $P = 0.001$). We also found that ~55% of the joint variation in leg lean mass and calf cross-sectional area may be explained by shared genetic factors ($\rho_G = 0.74 \pm 0.12$, $P = 0.003$).

DISCUSSION

The present report is the first comprehensive analysis, to our knowledge, to dissect the genetic and environmental factors influencing skeletal muscle traits in large extended multigenerational families of African ancestry, and it is the largest family study of these traits to date. It is also one of only a few reports to assess the relationship of age and sex to the heritability of skeletal muscle phenotypes and the contribution of shared genetic components to these traits. The major findings are: 1) a modest but statistically significant heritability of lean soft tissue mass and muscle cross-sectional area in the overall group; 2) estimates of heritability appear to differ between men and women, as well as between young and older subjects; and 3) a significant proportion (48–66%) of the joint variation in arm lean mass, leg lean mass, and calf muscle cross-sectional area is determined by shared genes, but there appear to be unique, muscle compartment-specific genetic factors as well.

When we estimated the heritability of skeletal muscle phenotypes in young and older subjects separately, we found the heritability values of leg lean mass and calf muscle cross-sectional area to be lower in older individuals compared with younger individuals, but the heritability estimates of arm lean mass and appendicular lean mass were similar in these groups. To our knowledge this is the first report of age-related differences in the heritability of lean mass; however, there is previous evidence from a longitudinal study suggesting that the heritability of hand grip strength decreases with aging (8). We speculate that aging contributes additional environmental factors (illness, lifestyle changes, etc.) that reduce the relative genetic contribution to muscle phenotypes, without reducing the total number of contributing genetic factors.

We also observed a lower heritability estimate of leg lean mass in women compared with men, while the heritability of arm lean mass was higher in women than in men. One previous study has addressed age and sex differences in the heritability of limb circumference measures in adolescent twins (10–14 yr of age), finding that the additive genetic contribution to limb circumference was 0.87–0.95, but that different genetic models were required to explain the genetic contribution to limb circumference between younger boys and girls and between younger and older adolescents, implying age- and sex-specific genetic factors (26). We are unaware of any previous reports of sex-related differences in the genetic contribution to lean mass in adults with which to compare our results; however, sex differences in the heritability of femoral bone mineral density (31) and body height (43,44) have been reported.

Interestingly, heritability estimates were not uniformly different for limb-specific lean mass measures as a function of sex or age. We determined what proportion of the phenotypic correlation between lean mass measures in different limbs is attributable to genes, in which a perfect genetic correlation (i.e., $\rho_G = 1.0$) indicates that all of the phenotypic correlation between lean mass measures in different limbs is due to the same set of genes. Our analyses suggest that 66% of the total phenotypic correlation between arm lean mass and leg lean mass is due to the same set of genes but that genetic loci specific to the upper or lower limb may also contribute. Potential sex or age interactions with these limb-specific genetic loci may explain our observation that the heritability of certain lean mass measures is lower in older individuals or women (i.e., leg lean mass), while it is higher or remains similar for other measures (i.e., arm lean mass). Sex-specific quantitative trait loci that contribute to the differences in bone mineral density between men and women have previously been identified (35); the differences we observed in the heritability of lean mass in individuals of African descent indicate that similar sex- or age-specific genetic loci may also influence lean mass in this population.

To date, relatively few specific genes have been shown to be associated with skeletal muscle-related phenotypes (for review, see Ref. 38), and some have been shown to have sex- or age-specific associations (12,41,49,50,53). Given the significant interindividual variability in muscle mass, the loss of muscle mass with aging, and the heritability of skeletal muscle phenotypes, these and other unidentified loci are likely to contribute to that proportion of the variance in skeletal muscle traits that is not due to environmental factors. Further investigation is warranted to uncover additional genetic contributors and to determine their effects in a sex-, age-, and limb-specific manner.

In addition to estimating the heritability of lean mass and calf muscle cross-sectional area, we also identified specific environmental factors that contribute to the variance in skeletal muscle phenotypes. While our measures of environmental factors were somewhat limited and some confounding by factors such as physical activity may remain, ours is one of the first heritability studies to take into account this breadth of environmental factors. We found that smoking, which has recently been associated with reduced muscle protein fractional synthetic rate (36), is negatively associated with lean mass in the overall group. We also found that oral contraceptive use or a history of pregnancy may favorably impact skeletal muscle phenotypes in women. To our knowledge, this is the first report of positive associations between oral contraceptive use and calf muscle cross-sectional area, in contrast with one previous report showing similar forearm muscle cross-sectional area in oral contraceptive users and nonusers (45). Likewise, we know of no previous report of association between childbearing and arm lean mass, but there may be an influence of caring for infants on upper body muscle mass in younger women.

Generally, the heritability estimates for lean mass or skeletal muscle mass in the present study are lower than those previously reported for lean mass or skeletal muscle mass (0.30–0.80) in

twin studies using subjects of European descent and a variety of measurement techniques (DXA, hydrodensitometry, and ^{40}K counting) (5,17,42). The heritability estimates derived from twin studies may be higher, in part, because unmeasured environmental factors are incorporated into the estimate of heritability. In the present report, we account for several environmental factors as covariates. The use of covariates in our models not only adjusted for confounding factors but also for factors that may contribute to the heritability estimates, thus reducing our heritability estimates. Our statistical models included covariates with a genetic component (e.g., sex and height), and it is likely that some of the genes affecting these covariates have pleiotropic effects on muscle traits (e.g., genes with effects on body size and muscle mass). By removing these and the additional environmental covariates, the contribution of genes affecting those covariates is also removed from the analysis of muscle traits. Compared with a model with no covariance (data not shown), the inclusion of covariates reduced our heritability estimates by ~ 0.10 on average. Therefore, we did expect somewhat lower estimates of heritability in our study, but our estimates in the overall group were still lower than the range noted above and may still be somewhat inflated because not all shared environmental factors were adjusted for in the analyses.

It is possible that differences in lifestyle and health characteristics between our Afro-Caribbean subjects and subjects of European descent could contribute to differences in heritability estimates. While the prevalence of diabetes (3) and hypertension (16) in our subjects were similar to those in the United States and other Caribbean countries, we did observe differences in other lifestyle variables. The prevalence of both regular alcohol consumption (29) and smoking (10) in Americans is higher than was found in our subjects. Additionally, our subjects reported substantially less time spent watching television and walking than what has been reported for adults in the United States (32,54). It is possible that this is due to the subjective nature of our questionnaire, coupled with underestimation of either variable by subjects. Last, compared with men, the women in our study had a higher prevalence of obesity (as defined by BMI), a trend that is not observed in Caucasians (20), although our findings are similar to other data reported for African subjects (37). Given that the majority of these variables were not statistically significant covariates in our models, it is difficult to ascertain whether systematic differences in these lifestyle measures explain the lower heritability estimates observed in our data compared with other studies.

Although previous studies have established a genetic influence on skeletal muscle-related traits, there is still considerable uncertainty about the potential magnitude of heritability. Even within studies, SEs and 95% confidence intervals for heritability estimates are often quite large, which may in part be due to studies that are underpowered. Heritability estimates for skeletal muscle phenotypes have largely been derived from correlations or variance components analysis in twin studies, not with more precise and powerful approaches such as variance-components analysis in large, extended pedigrees as we have performed (55). Variance components analysis also allows the simultaneous estimation of heredity and environmental influences (55). Although many studies have attempted to distinguish between environmental and genetic influences on skeletal muscle-related traits, none have considered the wide range of environmental covariates that we have assessed. While it is likely that we have not accounted for all components of the shared environmental influence on skeletal muscle traits, our analysis had greater power to distinguish between influences attributable to genes and those due to environmental factors than previous studies based on only relative pairs and may provide a more reliable estimate of heritability.

Summary

We have identified modest but statistically significant heritability of lean soft tissue mass and muscle cross-sectional area in individuals of African heritage, and have identified smoking,

oral contraceptive use, and a history of pregnancy as environmental factors impacting these skeletal muscle phenotypes. Our results also indicate that a large proportion of the joint variation in different lean mass measures is determined by genetic factors these traits may have in common (i.e., the same genes or genetic variants) but that other genes may act in an age-, sex-, or limb-specific manner. These findings provide a basis for further investigation of these and other genetic and environmental factors affecting skeletal muscle phenotypes. A better understanding of these factors may ultimately lead to new ways to improve skeletal muscle phenotypes and sarcopenia-related comorbidities such as obesity, metabolic abnormalities, and disability.

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Table 1

Characteristics of Afro-Caribbean men and women

	Men (<i>n</i> = 172)		Women (<i>n</i> = 267)	
	Mean	SD	Mean	SD
Age, yr	43.0	16.8	43.0	16.4
Height, cm	177.1	7.4	166.5*	6.5
Weight, kg	82.4	15.6	79.9	17.9
BMI, kg/m ²	26.4	4.5	29.4*	6.7
Body fat, %	18.7	6.6	35.3*	7.8
Arm lean mass, kg	8.8	1.6	6.1*	1.4
Leg lean mass, kg	22.6	3.5	17.4*	3.0
Appendicular lean mass, kg	31.3	5.0	23.5*	4.2
Calf muscle cross-sectional area, cm ²	73.7	11.4	61.5*	10.2

For calf muscle cross-sectional area, *n* = 169 men and *n* = 247 women. BMI, body mass index.

* Significant difference between sex groups (*P* < 0.01).

Table 2

Contributors to skeletal muscle phenotypes

	Age	Sex	Height	Oral Contraceptive Use	Smoking	Pregnancy History	Model r^2
Arm lean mass		++++ [‡]	++++ [‡]		— [‡]	+++ [‡]	0.52
Leg lean mass		++++ [‡]	++++ [‡]		— [‡]		0.53
Appendicular lean mass		++++ [‡]	++++ [‡]		— [‡]		0.55
Calf muscle cross-sectional area	++*	++++ [‡]	++ [‡]	++ [‡]			0.27

Symbols indicate positive (+) and negative (–) correlations between various covariates and the dependent variables of interest. The strength of each correlation is approximately indicated by the number of symbols: 1 symbol indicates less than a 1% difference in the trait per unit of the covariate; 2 symbols indicates a 1%–5% difference; 3 symbols indicates a 5%–10% difference; and 4 symbols indicates a 10% or greater difference. All reported covariates are statistically significant

* $P < 0.05$,
[‡] $P < 0.01$,
^{‡‡} $P < 0.001$.

Table 3
Proportion of total phenotypic variation attributable to genetic and measured environmental factors considering all significant covariates

Genetic Component				
	h^2	SE*	Measured Covariates r^2	Covariates
Arm lean mass	0.23 [†]	0.11	0.52	Sex, height, smoking, pregnancy
Leg lean mass	0.18 [†]	0.12	0.53	Sex, height, smoking
Appendicular lean mass	0.18 [†]	0.12	0.55	Sex, height, smoking
Calf muscle area	0.23 [†]	0.12	0.27	Age, sex, height, oral contraceptive use
Remainder				

h^2 , heritability.

* SEs are based on h^2 estimates.

[†] Significant genetic component ($P < 0.01$). Remainder is attributed to nonmeasured environmental factors and residual error.

Proportion of total phenotypic variation attributable to genetic factors in younger vs. older subjects, and in men vs. women

Table 4

	Younger Subjects (Age ≤ 45 yr) (n = 255)		Older Subjects (Age > 45 yr) (n = 185)		Covariates
	h ²	SE*	h ²	SE*	
Arm lean mass	0.25 [‡]	0.18	0.31 [‡]	0.23	Sex, height
Leg lean mass	0.23 [‡]	0.19	0.05	0.20	Sex, height
Appendicular lean mass	0.23 [‡]	0.20	0.20 [‡]	0.23	Sex, height
Calf muscle cross-sectional area	0.20 [‡]	0.16	0.08	0.22	Sex, height

	Men (n = 172)		Women (n = 267)		Covariates
	h ²	SE*	h ²	SE*	
Arm lean mass	0.29 [‡]	0.24	0.55 [‡]	0.16	Height, smoking, pregnancy [§]
Leg lean mass	0.47 [‡]	0.20	0.24 [‡]	0.16	Height, smoking
Appendicular lean mass	0.28 [‡]	0.22	0.32 [‡]	0.16	Height, smoking
Calf muscle cross-sectional area	0.31 [‡]	0.20	0.36 [‡]	0.16	Age, height

For calf muscle cross-sectional area in younger and older subjects (*top*), n = 238 younger and n = 176 older subjects. For calf muscle cross-sectional area in men and women (*bottom*), n = 169 men and n = 247 women.

* SEs are based on h² r estimates.

[‡] Significant genetic component: P < 0.05.

[‡] P < 0.01.

[§] Covariate used in analysis of women only.