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## Myostatin and Follistatin Polymorphisms Interact with Muscle Phenotypes and Ethnicity

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### Abstract

**Purpose**—We examined associations among myostatin (MSTN) 2379 A > G and 163 G > A and follistatin (FST) –5003 A > T and –833 G > T single nucleotide polymorphisms (SNP) on the muscle size and the strength response to resistance training (RT).

**Methods**—Subjects ( $n = 645$ , age =  $24.1 \pm 0.2$  yr, body mass index [BMI] =  $24.2 \pm 0.2$  kg·m<sup>-2</sup>) self-disclosed themselves as Caucasian (78.9%), African American (3.6%), Asian (8.4%), Hispanic (5.0%), or Other (4.2%). They were genotyped for MSTN 2379 A > G ( $n = 645$ ), MSTN 163 G > A ( $n = 639$ ), FST –5003 A > T ( $n = 580$ ), and FST –833 G > T ( $n = 603$ ). We assessed dynamic (one repetition maximum [1RM]) and isometric (maximum voluntary contraction [MVC]) muscle strength and size (cross-sectional area [CSA]) of the elbow flexors before and after 12 wk of unilateral upper-arm RT. Repeated-measures ANCOVA tested associations among genetic variants and muscle phenotypes with age and BMI as covariates.

**Results**—Baseline MVC was greater among African Americans who were carriers of the MSTN G<sup>2379</sup> allele (AG/GG,  $n = 15$ ) than the A2379A homozygotes ( $n = 8$ ;  $64.2 \pm 6.8$  vs  $49.8 \pm 8.7$  kg). African Americans who were carriers of the FST T<sup>-5003</sup> allele ( $n = 12$ ) had greater baseline 1RM ( $11.9 \pm 0.7$  vs  $8.8 \pm 0.5$  kg) and CSA ( $24.4 \pm 1.3$  vs  $19.1 \pm 1.2$  cm<sup>2</sup>) than African Americans with the A-5003A genotype ( $n = 14$ ;  $P < 0.05$ ). No MSTN or FST genotype and muscle phenotype associations were found among the other ethnic groups ( $P = 0.05$ ).

**Conclusion**—MSTN 2379 A > G and FST -5003 A > T were associated with baseline muscle strength and size among African Americans only. These ethnic-specific associations are hypothesis generating and should be confirmed in a larger sample of African Americans.

### Keywords

EXERCISE; GENOMICS; MRI; RACE; STRENGTH TRAINING

Although muscle strength is a highly heritable trait (3,39), research identifying specific genes that account for the individual variability in the response to resistance training (RT) is limited (35). Myostatin (MSTN), or growth and differentiation factor 8, is a member of the transforming growth factor  $\beta$  family of cytokines and a powerful regulator of muscle mass (10,21,22,30). MSTN expression has been shown to be responsive to muscle loading in animal models (18,43) and in young and older men and women (14,27).

The MSTN gene is located on chromosome 2q32.2. Its function is highly conserved across species (22), and it is an important marker for muscle strength phenotypes (15). MSTN 2379 A > G (rs1805086, Arg153Lys) is a non-synonymous single nucleotide polymorphism (SNP) located in exon 2, and MSTN 163 G > A (rs1805065, Ala55Thr) is a nonsynonymous SNP located in exon 1 of the MSTN gene. The minor allele of both MSTN SNP occurs more frequently in African Americans (11–31%) than in Caucasians (<5%) (7,29), with African Americans who carry either of the minor MSTN alleles more likely to inherit favorable muscle phenotypes (29). The locations of these MSTN SNP suggest that they influence protein function. Along similar lines, muscle phenotypes also differ by ethnicity with greater inherent muscle density (31), strength (24), muscle mass (1,5,8), and percentage of type II muscle fibers (36) found in African Americans compared with Caucasians.

Attempts to study associations among MSTN SNP and muscle strength and size phenotypes in humans have generated mixed results. Seibert et al. (32) reported that African American women with the MSTN A2379A genotype ( $n = 39$ ) had higher combined isometric hip, thigh, and grip scores ( $72.50 \pm 13.9$  kg) than African American women with MSTN A2379G ( $n = 13$ ;  $67.14 \pm 11.4$  kg) and G2379G genotypes ( $n = 3$ ;  $63.1 \pm 11.3$  kg). Corsi et al. (6) reported that older Italian men and women carrying the MSTN G<sup>2379</sup> allele ( $n = 6$ ) had lower hand grip strength compared with those with the MSTN A2379A genotype ( $n = 444$ ); when adjusted for age, this association was eliminated (6).

Studies examining the influence of MSTN genetic variants on the muscle size and the strength response to RT in humans are limited. Ferrell et al. (7) found that muscle mass was not different among Caucasian ( $n = 96$ ) and African American ( $n = 93$ ) men and women according to MSTN 2379 A > G and 163 G > A genotype after 6 months of vigorous RT (7).

Similarly, Ivey et al. (16) found that the MSTN 2379 A > G genotype did not explain the hypertrophic response to a 9-wk RT program among 23 younger men and women or 24 older adult men and women (16). Although some studies report lower strength in those who carry the MSTN G<sup>2379</sup> allele (6,32), others report no difference in the muscle strength (16) or mass response to RT (7) and MSTN 2379 A > G. Small numbers of subjects with the MSTN G<sup>2379</sup> allele preclude definitive conclusions regarding the influence of MSTN 2379 A > G on the muscle size and the strength response to RT (7,16,38) and associations among MSTN 2379 G > A and baseline muscle strength (6,32).

Evidence examining the influence of MSTN 163 G > A on the muscle size and the strength response to RT is limited. The location and the biology of this SNP suggest an influence on skeletal muscle phenotypes in humans (29). MSTN enters circulation bound to its propeptide. In this form, MSTN is latent and is thus prevented from influencing muscle growth. MSTN 163 G > A results in an amino acid transition in the N-terminus (propeptide) region of the MSTN protein (17). By influencing the stability of the MSTN propeptide, MSTN 163 G > A may also influence muscle mass. Additionally, because MSTN expression has been affected by muscle loading (14,27), we speculate an influence of MSTN 163 G > A on muscle mass may also be modulated by RT. To the best of our knowledge, only Ferrell et al. (7) has examined the influence of MSTN 163 G > A on the muscle mass response to RT (7).

Follistatin (FST) is a secreted glycoprotein that inhibits MSTN activity (2,11,20). The FST gene is located on chromosome 5q11.2. FST -5003 A > T (rs722910) is located in the 3'UTR of the FST gene and is highly conserved in mammalian species. FST -833 G > T (rs1423560) is located in 5'UTR of the FST gene near several transcription binding sites. The conservation and the position of these SNP suggest that they influence gene transcription (23). To date, the influence of these FST SNP on muscle strength and size has not been studied.

Thus, the purpose of our study was to examine associations among MSTN 2379 A > G and 163 G > A and FST -5003 A > T and -833 G > T and the muscle size and the strength response to a 12-wk, unilateral, upper-body RT program in a large sample of healthy adults. We hypothesized that the MSTN 2379 A > G and 163 G > A and the FST -5003 A > T and -833 G > T would associate with the exercise-induced changes in muscle size and strength.

## METHODS

This study was part of a larger multicenter study titled, Functional Single Nucleotide Polymorphisms Associated with Human Muscle Size and Strength (FAMuSS). FAMuSS was conducted by the Exercise and Genetics Collaborative Research Group consisting of researchers from the University of Connecticut, the Dublin City University, the University of Massachusetts, the Central Michigan University, the University of Central Florida, the Florida Atlantic University, the West Virginia University, the Yale University, the Hartford Hospital, and the Children's National Medical Center. The experimental design of FAMuSS has been described (13,40). The institutional review boards from the 10 institutions involved with FAMuSS approved the study protocol.

Potential study volunteers were recruited from the eight RT sites via strategic flyer placement and in-house listserv and radio announcements. All study participants gave written informed consent before participation in a 12-wk standardized, progressive RT intervention consisting of elbow flexor and extensor training of the nondominant arm (i.e., the hand with which the subject did not write). Pre- and post-RT measurements included dynamic (one repetition maximum [1RM]) and isometric (maximum voluntary contraction [MVC]) strength and cross-sectional area (CSA) of the nondominant arm by magnetic resonance imaging (MRI) and body mass index (BMI;  $\text{kg}\cdot\text{m}^{-2}$ ).

**Subjects**—Subjects from the FAMuSS cohort who were genotyped for the MSTN 2379 A > G, MSTN 163 G > A, FST -5003 A > T, and/or FST -833 G > T SNP were selected for the current study.

Potential volunteers were excluded from study participation if they

1. used medications known to affect skeletal muscle such as corticosteroids, antihypertensive, antilipemics, anabolic steroids, diuretics, arthritis medications (Vioxx and Celebrex), Depo-Provera contraceptive injection, Clenbuterol, Rhinocort nasal inhaler, lithium, and chronic use of nonsteroidal anti-inflammatory drugs;
2. had chronic medical conditions such as diabetes mellitus;
3. had metal implants in arms, eyes, head, brain, neck, or heart;
4. had performed any regular activity that required repetitive use of the arms, including RT within the prior year;
5. consumed, on average, more than two alcoholic drinks daily;
6. used dietary supplements reported to build muscle size/strength or to cause weight gain such as protein supplements, creatine, or androgenic precursors; and
7. gained or lost more than 2.2 kg within 3 months of study participation.

**Anthropometric measurements**—Pre- and post-RT assessments included weight (pounds, using a standard balance beam scale) and height (inches) that were used to calculate BMI. Subjects were instructed to follow their usual diet throughout the study. To ensure weight stability defined as  $\pm 2.2$  kg of pre-RT weight, body weight was also measured every 3 wk of study participation.

**Isometric strength testing (MVC)**—MVC of the elbow flexor muscles was assessed using a custom made preacher curl bench and strain gauge (model 32628CTL; Lafayette Instrument Company, Lafayette, IN). Baseline MVC was assessed on three separate days 24–48 h apart, and post-RT measurements were assessed on two separate days 24–48 h apart and within 48 h of the final RT session. Baseline values were recorded as the average of the second and the third pre-RT testing days with the first day serving as a familiarization session. Each MVC attempt began with a verbal cue from the tester with subjects gradually increasing to a maximal effort, which was sustained for 3 s with 1 min allowed between contractions. Before each test, the tester calibrated the strain gauge and positioned the

subject's arm to be tested at 90°. The subject's other arm rested on their lap with the hand supine (to minimize compensatory movement). The tester who administered a pre-RT MVC test for a subject also administered the post-RT MVC test. The testing session ended once three measurements were within 2.2 ft·kg<sup>-1</sup> of each other or a maximum of six attempts had been made. The closest three measurements were averaged and recorded in kilograms. The intersite within-subject coefficient of variation based upon baseline measurements made on days 2 and 3 was 7.4%, indicating adequate reliability among sites.

**One repetition maximum strength testing (1RM)**—The dynamic strength of the elbow flexor muscles was assessed by 1RM on a standard preacher curl bench (Yukon International Inc., Cleveland, OH) using Powerblocks (Powerblocks; Intellbell, Inc., Owatonna, MN), which are hand-held weights resembling dumbbells adjustable in increments of 1.1 and 2.2 kg. If needed, additional weight could also be added in 0.6-kg increments using Platemates® (Benoit Built Inc., Boothbay Harbor, ME). Each subject performed two warm-up sets with increasing weight. The arm not being tested rested on the lap with the hand in a pronated position. Study investigators then verbally instructed subjects to perform one full range of motion repetition, extending the elbow to 180° and curling the weight back up to the shoulder with the weight at 100% of estimated maximum. If the lift was unsuccessful, a 3-min rest was taken and the weight decreased slightly. If the lift was successful, a 3-min rest was taken and the weight increased. The procedure was repeated until subjects failed to complete a full range of motion lift. Weights were chosen so that the 1RM could be determined in three to five attempts. Maximum weight lifted was recorded in kilograms as the greatest amount of weight successfully lifted one time. Study investigators gave verbal encouragement to each subject during each 1RM attempt. The tester who administered a pre-RT 1RM test for a subject also administered the post-RT 1RM test.

**Magnetic resonance imaging**—CSA of the biceps brachii was measured using MRI before the first RT session and within 48 to 96 h after the final RT session. Before entering the magnetic resonance (MR) magnet, a radiographic bead (Beekley Spots; Beekley Corp., Bristol, CT) was placed at the maximum circumference or the point of measure of the nondominant upper arm of each subject. The point of measure was determined with subject's arm abducted 90° at the shoulder, flexed 90° at the elbow, hand open, and the biceps maximally contracted. The same investigator visually located the point of measure on the subject's arm pre- and post-RT.

The subject being scanned laid supine on the scanning bed in an anatomical position, with the arm aligned to the isocenter of the magnet. The hand was supinated and taped in place on the scanner bed, and the point of measure was centered to the alignment light of the MRI. Coronal and sagittal scout images were produced to locate the long axis of the humerus and to align the eighth to ninth axial slices with the point of measure, respectively. Fifteen spoiled gradient images (time to echo = 1.9 ms, time to repeat = 200 ms, flow artifact suppression, 30° flip angle) were generated with point of measure as the center point. Axial imaging began at the superior portion of the upper arm and proceeded distally toward the elbow joint. Each individual image slice was 16 mm thick with a 0-mm interslice gap, a 256

× 192 matrix resolution, and a 22 × 22-cm field of view and with six number of experiments. All MRI operated at 1.5 T.

**Muscle CSA measurements**—MR images from each investigative site were saved via magnetic optical disk or CD-ROM in a DICOM format and sent to the central imaging facility for analysis. The same investigator analyzed MR images using a custom designed program created to function within Matlab (The Math Works, Inc., Natick, MA). This software enables the user to assign regions of interest in an image set by tracing region borders with a mouse. Because muscle is easily identifiable on MR images, CSA was measured using this computerized planimetry technique. Once the region of interest was defined, the program reported the number of pixels contained in the selected region of interest. CSA was then determined by multiplying the number of pixels within the defined area by a preset CSA value of 0.01 cm<sup>2</sup> determined from the MRI matrix and field of view. MRI standardization between sites was accomplished by comparing the radiographic bead's measured CSA with the MRI determined CSA.

To assign the slice to be assessed for this study, the analyst identified the slice immediately after the axilla and then counted down slice by slice to the slice showing the point of measure. In the minor instance that the number of slices between the axilla and point of measure differed pre-and post-RT, readily apparent discernable irregularities in the contour of the muscle and the shape of the arm pre-RT were compared with slices adjacent to the post-RT point of measure until an identical anatomical match was found. The ninth axial slice was measured for maximum biceps CSA for most subjects. The pre-CSA was subtracted from the post-CSA yielding the RT response. Interobserver reliability was +3.5%, and the intraobserver reliability for the entire process of image acquisition and analysis was 99.0%.

**Resistance training program**—The study design used a unilateral, upper-arm RT program to minimize the confounding influence of activities of daily living on the muscle size and the strength response (40). Subjects underwent 12 wk of gradually progressive, supervised RT of their nondominant arm twice per week separated by a minimum of 48 h. The exercises consisted of the biceps preacher curl, biceps concentration curl, standing biceps curl, overhead triceps extension, and triceps kickback. The primary purpose was to train the elbow flexors, but the elbow extensors were also trained to balance muscle strength across the elbow. Each RT session began with a warm-up consisting of two sets of 12 repetitions of the biceps preacher curl and the overhead triceps extension. A 3-min rest followed each warm-up set. After the warm-up series, subjects performed three sets of 12 repetitions at 65–75% of their baseline 1RM for each of the five above mentioned exercises. The speed of each repetition was 4 s, 2 s for the concentric and 2 s for the eccentric phase. A 2-min rest followed each set. At week 5, the number of repetitions was decreased to eight and then to six at week 10. Thus, the exercise intensity at weeks 5 and 10 increased to 75–82% 1RM and 83–90% 1RM, respectively. Each workout session was supervised, and priority was placed on achieving maximal strength and size gains. In the case where a subject's strength increased where the weight being lifted was greater than 75–82% of the initial 1RM at week 6, the subject continued with the greater weight. All exercises were

performed with Power-blocks, and some exercises used the preacher curl bench. All training sessions lasted approximately 45 to 60 min.

**Genotyping methods**—Blood samples were obtained from all subjects in ethylenediaminetetraacetic acid containing vacutainer tubes and sent to the coordinating site in Washington, DC, for DNA isolation using Puregene kits (Gentra Systems, Inc., MN). Genotyping was done using novel TaqMan allele discrimination assays that use the 5' nuclease activity of Taq polymerase to detect a fluorescent reporter signal generated during polymerase chain reactions (PCR). Both alleles for each SNP were detected simultaneously using allele-specific oligonucleotides labeled with different fluorophores and genotypes determined by the ratio of the two fluorophores used. Allele-specific PCR for each SNP included 20 ng genomic DNA, 900 nM forward and reverse PCR primers, 200 nM fluorescent allele discrimination probes (major allele FAM labeled; minor allele VIC labeled), and TaqMan® Universal PCR Master Mix, No AmpErase® UNG (Applied Biosystems, Foster City, CA) in a final volume of 25 µL. Table 1 shows the primer sets used for each SNP. The PCR and the fluorescent ratio profile was done using 10 min at 95°C (denaturation) and 44 cycles of 15 s at 92°C and 1 min at an annealing temperature of 60°C. Reactions were setup using an MWG robot, and fluorescence ratios and allele calling were done using an ABI 7900.

**Data administration**—Data from all investigative sites were compiled in a master database maintained by a statistical consultant at the coordinating site in Washington, DC. Each investigative site was able to access the database and manually enter data via a secure intranet using a confidential username and password.

**Quality control**—To ensure standardization among sites, the following procedures were followed at each site: biannual tester training, protocol, and methodology reviews; annual site visits to ensure protocol adherence; use of major standard operating procedure manual; frequent contact among the investigators through regular conference calls; and use of identical testing and workout equipment among sites.

**Statistical analysis**—All analyses included only subjects who finished the study. The sample consisted of mostly Caucasians (82%) with 9% who self-disclosed themselves as Asian, 5% Hispanic, 4% African American, and 4% other. Previous literature reports higher frequencies of MSTN 2379 A > G and MSTN 163 G > A (7,29) as well as greater strength (24) and muscle density (1,5,8,31) among African Americans compared with Caucasians. Thus, we categorized our sample as predominantly Caucasian (All Others, 96%) and African Americans (4%). MSTN 2379 A > G allelic frequencies among African Americans ( $n = 23$ ; A = 65.2%, G = 34.8%) and Caucasians ( $n = 509$ ; A = 99.1%, G = 0.9%) and those for MSTN 163 G > A in African Americans ( $n = 23$ ; G = 89.1%, A = 10.9%) and Caucasians ( $n = 504$ ; G = 98.3%, A = 1.7%) were in accordance with those previously reported (7,29). Multivariate ANOVA, with gender as a fixed factor, determined that African Americans had greater MVC ( $61.7 \pm 4.1$  vs  $47.9 \pm 0.7$  kg) and CSA ( $21.0 \pm 1.0$  vs  $16.6 \pm 0.2$  cm<sup>2</sup>) ( $P < 0.05$ ), although similar 1RM ( $9.9 \pm 0.6$  vs  $9.0 \pm 0.1$  kg) ( $P > 0.05$ ) compared with All Others. The greater muscle strength and size in African Americans in our sample are in

accordance with previous literature (1,5,8,24,31). Chi-square determined if SNP genotype distributions were in the Hardy–Weinberg equilibrium. Pairwise tests using Lewontin's  $D'$  and  $R^2$  for each pairwise combination tested for linkage disequilibrium. Because the SNPs were not in linkage disequilibrium, data for each SNP were analyzed and presented as a separate cohort.

Descriptive statistics and frequencies were calculated for study variables in each SNP cohort. We opted to classify the SNP genotype groups using the dominant model because the minor allele frequencies were low (<3%) in the MSTN 2379 A > G and 163 G > A cohorts. Thus, there were two genotype groups for each SNP cohort, one consisting of those homozygous for the common allele (MSTN A2379A and G163G; FST A-5003A and G-833G) and the other consisting of those who were carriers of the minor allele (MSTN G<sup>2379</sup> and A<sup>163</sup>; FST T<sup>-5003</sup> and T<sup>-833</sup>). Repeated-measures ANCOVA tested if muscle size and strength varied by group at baseline (pre-RT), after the intervention (post-RT), and by change over time (pre- to post-RT). For all analyses, independent variables included genotype group, gender, and ethnic affiliation (African American and All Others) with age and BMI as covariates. Dependent variables included pre-, post-, and pre- to post-RT 1RM, MVC, and CSA, which were represented in absolute (no corrections) and relative percentage (post-RT – pre-RT / pre-RT × 100) terms. Muscle strength (1RM and MVC) measurements were also allometrically scaled (strength (kg) × body weight (kg)<sup>-0.67</sup>) (42). Multiple variable regression tested if relative percentage change from baseline differed pre- to post-RT among the total sample and the genotype groups. No significant associations were detected for 1RM, MVC, or CSA among MSTN 163 G > A or FST –833 G > T genotype groups; thus, data from these SNPs are not shown.

The resulting  $P$  values from these linear tests were adjusted for multiple comparisons using the Bonferroni *post hoc* multiple comparison test. Statistical significance was set at  $P < 0.05$  with all data reported as mean ± SEM. All analyses were done using SPSS 14.0 for Windows.

## RESULTS

### Subject Characteristics

The total sample ( $n = 645$ ) consisted of men and women who were  $24.1 \pm 0.2$  yr and of normal weight ( $24.2 \pm 0.2$  kg·m<sup>-2</sup>). Age and BMI did not differ among the SNP cohorts or by ethnic affiliation or by SNP cohort within ethnic affiliation ( $P = 0.05$ ). Subject characteristics by SNP cohort within ethnic affiliation appear in Table 2. The MSTN 2379 A > G ( $n = 645$ ;  $\chi^2 = 0.61$ ) and the FST –5003 A > T ( $n = 580$ ;  $\chi^2 = 3.37$ ) cohorts were in the Hardy–Weinberg equilibrium for predominantly Caucasian populations ( $P > 0.05$ ), with major and minor allelic distributions of 97.3% and 2.7% for MSTN 2379 A > G and 59.5% and 40.5% for the FST –5003 A > T cohorts, respectively.

### One Repetition Maximum (1RM)

Absolute, relative, and allometric 1RM increased in the MSTN 2379 A > G ( $3.7 \pm 0.3$  kg,  $50.1\% \pm 5.0\%$ ,  $0.08 \pm 0.01$  kg·kg<sup>-0.67</sup>) and the FST –5003 A > T cohorts ( $3.7 \pm 0.2$  kg,



47.7% ± 3.9%, 0.08 ± 0.01 kg·kg<sup>-0.67</sup>), respectively ( $p < 0.05$ ). There were no associations among the MSTN 2379 A > G or FST -5003 A > T and the exercise-induced 1RM changes in All Others or African Americans (Tables 3 and 4). Pre- and post-RT 1RM did not differ by MSTN 2379 A > G or FST -5003 A > T among All Others (Table 3;  $P = 0.05$ ). Pre- and post-RT 1RM did not differ by MSTN 2379 A > G among African Americans (Table 4;  $P = 0.05$ ). However, pre- and post-RT 1RM was greater in African Americans who were carriers of the FST T<sup>-5003</sup> allele compared with African American with the FST A-5003A genotype (Table 4;  $P < 0.05$ ).

**Isometric strength (MVC)**—Absolute, relative, and allometric MVC increased in the MSTN 2379 A > G (5.5 ± 1.2 kg, 17.0% ± 3.4%, 0.14 ± 0.03 kg·kg<sup>-0.67</sup>) and the FST -5003 A > T (6.9 ± 1.1 kg, 17.7% ± 2.9%, 0.09 ± 0.00 kg·kg<sup>-0.67</sup>) cohorts, respectively ( $P < 0.05$ ). There were no associations among the MSTN 2379 A > G and the exercise-induced MVC increases (Table 5;  $P = 0.05$ ). Pre- and post-RT MVC did not differ by MSTN 2379 A > G among All Others (Table 5;  $P = 0.05$ ). Pre- and post-RT MVC were greater in African Americans who were carriers of the MSTN G<sup>2379</sup> allele compared with African Americans with the MSTN A2379A genotype (Table 5;  $P < 0.05$ ). There was no genotype by ethnicity interactions for MVC in the FST -5003 A > T cohort; thus, MVC data are not shown for this SNP.

**Muscle cross-sectional area (CSA)**—Absolute and relative CSA increased in the MSTN 2379 A > G (3.6 ± 0.3 cm<sup>2</sup>, 19.4% ± 1.5%) and the FST -5003 A > T (3.8 ± 0.2 cm<sup>2</sup>, 20.7% ± 1.2%) cohorts ( $P < 0.05$ ), respectively. There were no associations among the FST -5003 A > T and the exercise-induced CSA increases (Table 6;  $P > 0.05$ ). Pre- and post-RT CSA did not differ by FST -5003 A > T among All Others (Table 6;  $P > 0.05$ ). However, pre- and post-RT CSA was greater in African Americans who were carriers of the FST T<sup>-5003</sup> allele compared with African American with the FST A-5003A genotype (Table 6;  $P < 0.05$ ). There was no genotype by ethnicity interactions for MVC in the MSTN 2379 A > G cohort; thus, CSA data are not shown for this SNP.

## DISCUSSION

We tested for associations among MSTN 2379 A > G (Arg153Lys) and 163 G > A (Ala55Thr) and FST -5003 A > T and G > T -833 and the muscle size and the strength response to a 12-wk unilateral progressive RT intervention in a large sample of healthy adults. Contrary to our hypothesis, we found that MSTN 2379 A > G, MSTN 163 G > A, FST -5003 A > T, and FST G > T -833 did not associate with the muscle size and the strength response to the RT intervention. Although associations among the MSTN and the FST genetic variants and baseline muscle size and strength were not found in our overall sample, we observed ethnic-specific associations with several muscle size and strength phenotypes. African Americans who carried the MSTN G<sup>2379</sup> allele had greater MVC pre- and post-RT than African Americans with the MSTN A2379A genotype. Additionally, 1RM and CSA before and after were greater in African Americans who were carriers of the FST T<sup>-5003</sup> allele than African Americans who had the FST A-5003A genotype. Although we did not find any influence of MSTN 2379 A > G, MSTN 163 G > A, FST -5003 A > T, and FST G > T -833 on the muscle size and the strength response to RT in the total sample,

these genetic variants were found to influence baseline muscle size and strength among African Americans.

Our findings regarding the influence of MSTN 2379 A > G and MSTN 163 A > G on the muscle size (CSA) response to RT among All Others coincide with previous studies (7,16). Ferrell et al. (7) found no difference in muscle mass among Caucasian ( $n = 96$ ) and African American ( $n = 93$ ) men and women according to MSTN 2379 A > G and 163 G > A genotype after 6 months of vigorous RT (7). Similarly, Ivey et al. (16) found that the MSTN 2379 A > G genotype did not explain the hypertrophic response to a 9-wk RT program among 23 younger men and women or 24 older adult men and women.

Our findings regarding the influence of MSTN 2379 A > G and MSTN 163 A > G on the muscle strength response to RT among All Others agree with Seibert et al. (32) but differ from Corsi et al. (6). Seibert et al. (32) examined the influence of MSTN 2379 A > G on isometric strength (hip, knee, and handgrip) in a sample of older adult women and found no difference in strength by genotype. However, a small sample of African American women who possessed MSTN G<sup>2379</sup> allele ( $n = 16$ ) had lower strength scores than African American women ( $n = 39$ ) with the A2379A genotype. Similarly, Corsi et al. (6) reported that older Italian men and women carrying the MSTN G<sup>2379</sup> allele ( $n = 6$ ) had lower hand grip strength compared with those with the MSTN A2379A genotype ( $n = 444$ ).

The associations we found in and among African Americans and MSTN 2379 A > G differ from those of Seibert et al. (32) and Corsi et al. (6). Reasons could be related to differences in population demographics and/or the muscle strength testing modality. Seibert et al. (32) measured hip, knee, and handgrip strength in older women, and Corsi et al. (6) examined handgrip strength in older adults. In contrast, our sample was younger ( $24.1 \pm 0.2$  yr) and we measured isometric and dynamic strength of the elbow flexors. The current study is the first to examine the influence of MSTN 2379 A > G on the dynamic strength response to RT.

Explanations for the associations we found among MSTN and FST SNP and baseline muscle strength and size phenotypes among African Americans are not apparent. MSTN enters circulation as a latent precursor protein and then undergoes a proteolytic process. Once freed from the propeptide, the mature peptide then binds extracellularly with the activin type II B receptor (ActRIIB). ActRIIB then initiates either activin receptor-like kinase 4 or activin receptor-like kinase 5 to activate transcription factors Smad2/Smad3. Smad2/Smad3 then translocate into the nucleus to effect gene transcription (20,25). Through this pathway, MSTN ultimately inhibits proliferation (37) and differentiation (19,26) of myoblasts during development and satellite cells of adult muscle. By doing so, MSTN regulates muscle mass.

MSTN 2379 A > G results in an amino acid substitution that is located in the active mature peptide of the MSTN protein (17). In theory, a mutation in the mature peptide may influence proteolytic processing with its propeptide or affinity to bind with its receptor, ActRIIB. Such an influence would alter the ability of MSTN to inhibit muscle growth and development and ultimately muscle phenotypes such as strength. Furthermore, MSTN appears to exert its effects on muscle growth and development in a fiber-type-specific manner (9,28,32,43).

Type II muscle fibers incur a greater hypertrophic response to RT than type I fibers, although both fiber types are involved in muscular contraction and contribute to muscular strength (12,33,34). The baseline isometric strength differences we report in the MSTN 2379 A > G cohort could be the result of more favorable fiber-type distribution in carriers of MSTN G<sup>2379</sup> allele. Although speculative, interactions among MSTN and muscle fiber type that differ by MSTN 2379 A > G provide an explanation for our findings.

To our knowledge, this is the first study to report an association with FST -5003 A > T and muscle strength. FST inhibits MSTN in two ways. First, by binding to the MSTN mature peptide after proteolytic cleavage from the propeptide, thereby preventing MSTN from binding to ActRIIB (2,20). Second, FST also regulates activin activity and may limit availability of ActRIIB for binding with MSTN (4,41). A mutation in the FST gene affecting gene transcription may affect the amount of FST that is available to bind and thus inhibit the negative effects of MSTN on muscle growth. These actions may explain the differences in baseline muscle size and strength that we observed among FST -5003 A > T genotype groups. FST -5003 A > T is highly conserved in mammalian species, suggesting its functional importance in mammals although its importance in humans needs to be better elucidated.

Our findings are limited by the small sample size of African Americans ( $n = 26$ ). Of these, 20 (77%) African Americans carried at least one of the two alleles that favorably associated with muscle phenotypes that included MSTN A<sup>2379</sup> (greater baseline MVC) and FST A<sup>-5003</sup> (greater baseline 1RM and CSA); six (30%) of those 20 African American volunteers possessed both of these alleles. MSTN 2379 A > G and FST -5003 A > T were not in linkage disequilibrium. These genotype and muscle phenotype associations among SNP that are not in linkage disequilibrium suggest that the three SNP do not share a common marker and affect baseline muscle size and strength by different processes within the MSTN and the FST pathways.

In summary, MSTN 2379 A > G and 163 G > A and FST -5003 A > T and -833 G > T did not associate with the muscle strength or size response to RT in a large sample of healthy adult men and women. However, MSTN 2379 A > G and FST -5003 A > T did associate with baseline 1RM, MVC, and CSA among African Americans. These findings suggest that MSTN 2379 A > G and FST -5003 A > T may have a role in the modulation of inherent muscle strength among African Americans. These findings, however, should be viewed as preliminary and confirmed in a prospective RT study involving a larger sample of African Americans.

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TABLE 1

TaqMan primer sets for MSTN 2379 A > G, MSTN 163 G > A, FST -5003 A > T, and FST -833 G > T single nucleotide polymorphisms (SNP).

SNP	Forward Primer	Reverse Primer	WT Allele Probe (5' VIC)	MT Allele Probe (5' FAM)
2379 A > G	ATGGAAACCCAAAATGTTGCTTCTTAA	TCTCGACGGGTCTCAAATATATCCA	ATAAAGTAGTAAAGGGCCC	ATAAAGTAGTAAAGGGCCC
163 G > A	TGCATGTACTTGGAGACAAAACACT	GCTGTTCCAGACGGAAGTTTACTGA	CAAGAATAGAAGCCATTAAAG	TCAAGAATAGAAGCCATTAAAG
-5003 A > T	TGGCACTCTGCTGTTATGCAATAAGT	TGAGCCATTGATTTCTTCAGAACTTTCT	ATTATGCTTTAAAAAATTTTT	ATGCTTTAAAAAATTTTT
-833 G > T	CTGCCAGGTTGGAAGGT	GGTCTGTGAGTGCCTGACTTTG	CAGCCACCCCCAGCC	CAGCCACCCCCAGCC

Mean  $\pm$  SEM age and body mass index (BMI) of the total sample by MSTN 2379 A > G and follistatin (FST) –5003 A > T genotype within ethnic group.

**TABLE 2**

	All Others MSTN 2379 A > G		African American MSTN 2379 A > G		All Others FST –5003 A > T		African American FST –5003 A > T	
	A2379A	G <sup>2379</sup>	A2379A	G <sup>2379</sup>	A-5003A	T <sup>-5003</sup>	A-5003A	T <sup>-5003</sup>
<i>n</i>	603	19	8	15	196	350	14	12
Age (yr)	24.0 $\pm$ 0.2	26.1 $\pm$ 1.2	24.8 $\pm$ 2.2	25.3 $\pm$ 1.7	23.9 $\pm$ 0.4	24.5 $\pm$ 0.3	27.1 $\pm$ 1.8	24.4 $\pm$ 2.1
BMI (kg·m <sup>-2</sup> )	24.2 $\pm$ 0.2	24.0 $\pm$ 0.8	24.0 $\pm$ 2.3	25.2 $\pm$ 1.5	24.0 $\pm$ 0.3	24.5 $\pm$ 0.2	25.6 $\pm$ 1.8	25.2 $\pm$ 1.7

**TABLE 3**

Mean  $\pm$  SEM one repetition maximum (1RM) pre-, post-, and pre- to post-RT of All Others by myostatin (MSTN) 2379 A > G and follistatin (FST) –5003 A > T genotype group.

Phenotype	MSTN 2379 A > G		FST –5003 A > T	
	A2379A	G <sup>2379</sup>	A-5003A	T <sup>-5003</sup>
<i>n</i>	603	19	196	350
Pre-RT (kg)	9.0 $\pm$ 0.1	8.2 $\pm$ 0.5	8.9 $\pm$ 0.2	9.0 $\pm$ 0.1
Post-RT (kg)	13.1 $\pm$ 0.1	12.2 $\pm$ 0.6	13.1 $\pm$ 0.2	12.9 $\pm$ 0.1
Absolute (kg) <sup>a</sup>	4.1 $\pm$ 0.1	4.0 $\pm$ 0.4	4.2 $\pm$ 0.1	3.9 $\pm$ 0.1
Relative (%) <sup>a</sup>	52.0 $\pm$ 1.2	55.5 $\pm$ 7.2	54.9 $\pm$ 2.1	49.7 $\pm$ 1.5
Allometric (kg·kg <sup>-0.67</sup> ) <sup>a</sup>	0.09 $\pm$ 0.00	0.09 $\pm$ 0.01	0.09 $\pm$ 0.0	0.08 $\pm$ 0.0

1RM increased from baseline in all instances,  $P < 0.05$ .

1RM values displayed have been adjusted for age, BMI, and gender.

<sup>a</sup>Change.



**TABLE 4**

Mean  $\pm$  SEM one repetition maximum (1RM) pre-, post-, and pre- to post-RT of African Americans by myostatin (MSTN) 2379 A > G and follistatin (FST) –5003 A > T genotype group.

Phenotype	MSTN 2379 A > G		FST –5003 A > T	
	A2379A	G <sup>2379</sup>	A-5003A	T <sup>-5003</sup>
<i>n</i>	8	15	14	12
Pre-RT (kg)	9.4 $\pm$ 1.1	9.9 $\pm$ 0.6	8.9 $\pm$ 0.5	12.0 $\pm$ 0.8*
Post-RT (kg)	12.6 $\pm$ 1.4	13.5 $\pm$ 0.8	12.1 $\pm$ 0.8	16.3 $\pm$ 0.9*
Absolute (kg) <sup>a</sup>	3.2 $\pm$ 1.0 <sup>b</sup>	3.6 $\pm$ 0.5	3.2 $\pm$ 0.6	4.3 $\pm$ 0.6
Relative (%) <sup>a</sup>	47.8 $\pm$ 16.2	45.1 $\pm$ 8.8	44.3 $\pm$ 11.2	47.1 $\pm$ 9.4
Allometric (kg·kg <sup>-0.67</sup> ) <sup>b</sup>	0.08 $\pm$ 0.02 <sup>b</sup>	0.08 $\pm$ 0.01	0.07 $\pm$ 0.0	0.09 $\pm$ 0.0

1RM values displayed have been adjusted for age, BMI, and gender.

\* Significant difference between FST genotype groups (A-5003A vs T<sup>-5003</sup>),  $P < 0.05$ .

<sup>a</sup> Change.

<sup>b</sup> 1RM increased from baseline in all instances, except here,  $P < 0.05$ .

**TABLE 5**

Mean  $\pm$  SEM maximum voluntary contraction (MVC) pre-, post-, and pre-to post-RT of All Others and African Americans by myostatin (MSTN) 2379 A > G genotype.

Phenotype	All Others		African American	
	A2379A	G <sup>2379</sup>	A2379A	G <sup>2379</sup>
<i>n</i>	603	19	8	15
Pre-RT (kg)	47.9 $\pm$ 0.6	43.0 $\pm$ 3.5	49.8 $\pm$ 8.7	64.2 $\pm$ 6.8*
Post-RT (kg)	55.8 $\pm$ 0.7	50.1 $\pm$ 3.3	50.8 $\pm$ 7.3	71.3 $\pm$ 6.6*
Absolute (kg) <sup>a</sup>	7.9 $\pm$ 0.3	7.2 $\pm$ 1.6	0.8 $\pm$ 1.8 <sup>b</sup>	7.1 $\pm$ 1.1
Relative (%) <sup>a</sup>	19.8 $\pm$ 0.8	20.5 $\pm$ 8.6	10.8 $\pm$ 9.5	15.6 $\pm$ 3.9
Allometric (kg·kg <sup>-0.67</sup> ) <sup>a</sup>	0.17 $\pm$ 0.01	0.15 $\pm$ 0.03	0.07 $\pm$ 0.05 <sup>b</sup>	0.16 $\pm$ 0.03

MVC values displayed have been adjusted for age, BMI, and gender.

\* Significant difference between African American A2379A and African American G<sup>2379</sup> groups,  $P < 0.05$ .

<sup>a</sup> Change.

<sup>b</sup> MVC increased from baseline in all instances, except here,  $P < 0.05$ .

**TABLE 6**

Mean ( $\pm$ SEM) cross-sectional area (CSA) pre-, post-, and pre- to post-RT of All Others and African Americans by follistatin (FST) –5003 A > T genotype.

Phenotype	All Others		African American	
	A-5003A	T <sup>-5003</sup>	A-5003A	T <sup>-5003</sup>
<i>n</i>	196	350	14	12
Pre-RT (cm <sup>2</sup> )	17.3 $\pm$ 0.3	17.2 $\pm$ 0.3	19.1 $\pm$ 1.2	24.4 $\pm$ 1.3*
Post-RT (cm <sup>2</sup> )	20.5 $\pm$ 0.3	20.6 $\pm$ 0.3	22.8 $\pm$ 1.5	29.8 $\pm$ 1.6*
Absolute <sup>a</sup> (cm <sup>2</sup> )	3.2 $\pm$ 0.1	3.3 $\pm$ 0.1	3.6 $\pm$ 0.6	5.1 $\pm$ 0.6
Relative <sup>a</sup> (%)	19.1 $\pm$ 0.7	19.0 $\pm$ 0.5	19.3 $\pm$ 3.0	20.9 $\pm$ 3.1

CSA values displayed have been adjusted for age, BMI, and gender.

\* Significant difference between African American A-5003A and African American T<sup>-5003</sup> groups,  $P < 0.05$ .

<sup>a</sup> Change.

<sup>b</sup> CSA increased from baseline in all instances, except here,  $P < 0.05$ .