

Alpha-Actinin-3 (ACTN3) R577X Polymorphism Influences Knee Extensor Peak Power Response to Strength Training in Older Men and Women

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Background. The alpha-actinin-3 (ACTN3) R577X polymorphism has been associated with muscle power performance in cross-sectional studies.

Methods. We examined baseline knee extensor concentric peak power (PP) and PP change with ~10 weeks of unilateral knee extensor strength training (ST) using air-powered resistance machines in 71 older men (65 [standard deviation = 8] years) and 86 older women (64 [standard deviation = 9] years).

Results. At baseline in women, the XX genotype group had an absolute (same resistance) PP that was higher than the RR ($p = .005$) and RX genotype groups ($p = .02$). The women XX group also had a relative (70% of one-repetition maximum [1-RM]) PP that was higher than that in the RR ($p = .002$) and RX groups ($p = .008$). No differences in baseline absolute or relative PP were observed between ACTN3 genotype groups in men. In men, absolute PP change with ST in the RR ($n = 16$) group approached a significantly higher value than in the XX group ($n = 9$; $p = .07$). In women, relative PP change with ST in the RR group ($n = 16$) was higher than in the XX group ($n = 17$; $p = .02$).

Conclusions. The results indicate that the ACTN3 R577X polymorphism influences the response of quadriceps muscle power to ST in older adults.

MUSCLE power has been shown to account for a greater percentage of the variance in functional abilities than does muscle strength in elderly persons (1,2), and power deteriorates at a faster rate than strength with advancing age (3–5). For these reasons, recent strength training (ST) studies in elderly persons have focused on muscle power (6–12). Although muscle power has been shown to improve with ST in elderly persons, responses vary widely, even among people of similar characteristics performing the same training program (7,13,14).

These large inter-individual differences, along with the high heritability values for skeletal muscle phenotypes (15–18), suggest that genetic factors may explain at least a portion of muscle responses to ST. However, polymorphisms within specific gene loci that could potentially explain the genetic differences between responders and nonresponders to ST have not been clearly identified.

Recent cross-sectional data suggest that an alpha-actinin-3 (ACTN3) deficiency is compatible with elite athletic performance (19). A single nucleotide polymorphism (SNP) of the ACTN3 gene may be associated with muscle power and may at least partially explain the inter-individual variability in power (20). A C-to-T transition at position 1747 in exon 16 results in a premature stop codon in place of arginine at codon 577 (R577X) (21). Homozygosity of

the X-allele results in an absence of ACTN3 expression, with no apparent association with muscle disease phenotypes (22). Approximately 19% of Caucasians are ACTN3 deficient, indicating that this SNP is a common polymorphism among this racial group, and the X-allele frequency is greater than 15% in several of the world's populations (23).

Elite power athletes appear to have a significantly lower X-allele frequency than endurance athletes or controls (20,24), suggesting an influence of the X-allele on certain types of muscle performance. Recent data with young adults showed that women who are X homozygotes have lower baseline arm strength compared to heterozygotes, but have significantly greater increases in strength with ST compared to heterozygotes (25). This finding was in contrast to what would be expected for muscle power given the known function of ACTN in aiding force transmission across the Z-line.

Thus, the primary purpose of this study was to determine the influence of the ACTN3 R577X polymorphism on peak muscle power at baseline and in response to ST in older adults. A secondary purpose was to compare the influence of this polymorphism to that reported previously for muscle strength and mass at baseline and in response to ST.

METHODS

Participants

One hundred fifty-seven relatively healthy, sedentary, Caucasian men and women aged 50–85 years served as participants in this study. They were nonsmokers and were free of significant cardiovascular, metabolic, or musculoskeletal disorders. Those who were already taking medications for >3 weeks prior to the start of the study were permitted entry into the study as long as medications and dosages were not changed. After all procedures were explained, participants read and signed a consent form, which was approved by the Institutional Review Board of the University of Maryland, College Park. All participants maintained stable body weight and were asked to maintain their regular physical activity levels and dietary habits.

Genotyping

Genomic DNA was prepared from EDTA-anticoagulated whole blood samples by standard salting-out procedures (Puregene DNA Extraction kit, Gentra Systems, Inc., Minneapolis, MN). Genotyping for the ACTN3 R577X polymorphism was carried out using standard techniques following the procedures described by Mills and colleagues (23), using the *DdeI* restriction enzyme. The accuracy of the genotyping assay was verified by direct sequencing of a random selection of 16 samples, with positive control samples used in all subsequent assays.

Body Composition Assessment

Body composition was estimated by dual-energy X-ray absorptiometry (DXA) using fan-beam technology (model QDR 4500A; Hologic, Waltham, MA) using procedures we described previously (7).

Muscular Strength

One-repetition maximum (1-RM) strength tests were assessed for the knee extensors before and after the ST program using air-powered resistance knee extension machines (Keiser Co. Inc., Fresno, CA) as we described previously using standardized procedures (7). At least two familiarization sessions were performed prior to 1-RM testing, power testing, and the ST program, in which the training program exercises were performed with little or no resistance. These low-resistance training sessions were conducted to familiarize the participants with the equipment, to help control for the large 1-RM strength gains that commonly result from skill (motor learning) acquisition during the initial stages of training, and to help prevent injuries during strength testing.

Muscle Volume

To quantify quadriceps muscle volume (MV), computed tomography (CT) imaging of the trained and untrained thighs was performed (GE Lightspeed Qxi; Milwaukee, WI) at baseline and at the end of the ST program as described previously (7). Briefly, axial sections of both thighs were obtained starting at the most distal point of the ischial tuberosity down to the most proximal part of the patella, while participants were in a supine position. The quadriceps

cross-sectional area (CSA) was manually outlined in every 10-mm image, and MV was calculated using the truncated cone formula as reported previously by Tracy and colleagues (26) and described by Ross and colleagues (27). Muscle quality was calculated by dividing muscle strength (1-RM) by MV.

Peak Muscle Power

Determination of knee extensor peak power (PP) and peak movement velocity (PV) were performed at baseline and following ST on a Keiser air-powered resistance knee extension machine designed for muscle power assessment using methods we described previously (7). Participants performed three power tests on each leg at 50%, 60%, and 70% of their 1-RM. The highest PP value of the three trials for each percentage of 1-RM and the PV attained during this same trial were selected as the PP and PV, respectively, used for analyses. Muscle power quality (MPQ) and PV quality were calculated by dividing PP or PV by MV. The entire procedure at baseline was repeated 48–72 hours later, and the peak power values at each resistance level for both baseline tests were averaged in an effort to establish a more stable baseline assessment.

Training Program

The ST program was performed on Keiser A-300 air-powered leg extension machines and consisted of unilateral (one-legged) ST of the knee extensors of the right leg, three times per week, for ~10 weeks using methods we described previously (7). Briefly, the individualized ST protocol consisted of five sets of knee extension exercise for participants <75 years old and four sets for participants ≥75 years old, specifically designed to elicit near maximal effort in an individualized manner on all repetitions following warm-up, while maintaining a high training volume. Participants who were ≥75 years old did not perform the last set because a total of 50 repetitions performed at near maximal effort were required when performing all sets, and we believed that this might have caused overtraining for this age group. Overtraining has been shown to result in a reduction in strength gains (28). The untrained control leg was kept in a relaxed position during all ST sessions.

Statistical Analyses

The ACTN3 genotype distribution was evaluated for conformity with Hardy–Weinberg equilibrium by using a chi-square test with two degrees of freedom. Differences in physical characteristics for men and women were tested by paired *t* tests. Because a previous report suggested that the influence of ACTN3 R577X genotype on muscle function may depend on what sex group is studied (25), and because there was little overlap between men and women with respect to strength and fat-free mass (FFM), separate analyses were performed for each sex group by ACTN3 genotype. Differences in means among genotype groups (using the R and X alleles) were determined using three level (RR, RX, and XX genotype groups) two-way analysis of covariance (ANCOVA), covarying for age, body mass index (BMI), % fat, FFM, baseline values, change or

Table 1. Physical Characteristics at Baseline and After Strength Training (ST) in Men and Women

Characteristic	Men (<i>N</i> = 71*)		Women (<i>N</i> = 86 [†])	
	Baseline	After ST	Baseline	After ST
Age, y	65 (8)	—	64 (9)	—
Height, cm	174.7 (6.9)	—	161.5 (6.8)	—
Weight, kg	87.0 (13.2)	86.0 (12.8)	74.0 (15.9)	72.7 (15.2)
BMI, kg/m ²	28.4 (3.9)	28.1 (3.6)	28.4 (6.0)	27.9 (5.5)
Body fat, %	28.8 (5.4)	28.2 (4.7)	39.8 (5.5)	39.0 (5.4)
FFM, kg	61.0 (8.3)	61.0 (7.6)	43.7 (7.0)	43.2 (6.7)
1-RM, N	307 (88)	388 (98) ^{‡,§}	160 (47)	205 (54) [‡]
Muscle volume, cm ³	1758 (268)	1916 (303) [‡]	1085 (208)	1180 (205) [‡]

Notes: Values are means (standard deviation). Data presented are for all participants with baseline and after ST measurements.

*There were 58 participants for weight and BMI, 56 for body fat %, 53 for FFM, 61 for 1-RM, and 54 for muscle volume (MV) who had both baseline and after ST values.

[†]There were 60 participants for weight, BMI, FFM, and body fat %, 64 for 1-RM, and 58 for MV who had both baseline and after ST values.

[‡]Significantly different than baseline, *p* < .001.

[§]Significantly greater change than women when covarying for baseline differences, age, and FFM, *p* = .006.

^{||}MV of the knee extensors.

BMI = body mass index; FFM = fat-free mass; 1-RM = knee extension one-repetition maximum; N = Newtons.

drift in the control leg, and medication use by using backward regression (*p* < .10 to remain in the model). Medication use was classified into four categories: diuretics, angiotensin-converting enzyme (ACE) inhibitors, hormone replacement therapy, and antiinflammatories/pain reducers. To reduce experiment-wise error rate, pairwise comparisons that were not preplanned (RR/RX vs XX) were reported only when a significant global *F* (*p* < .05) was found. Contrasts were used to determine if there was a dominant, recessive, or additive effect of the X-allele on PP. To estimate the proportion of the variance explained by the ACTN3 R577X polymorphism for an observed association, the *R*² of the full model with ACTN3 genotype and all covariates was compared to the *R*² of the constrained model without ACTN3 genotype in the model.

RESULTS

Participant characteristics and muscle function measures at baseline and after ST for men (*n* = 71) and women (*n* = 86) are shown in Table 1. There was a significant increase in 1-RM in both men (*n* = 61) and women (*n* = 64) with ST (both *p* < .001), but men had a significantly greater increase than did women (*p* = .006) when baseline differences, age, and FFM were covaried. MV also increased significantly in men (9.0 ± 1%) and women (8.8 ± 1%; both *p* < .001). There were no significant changes in BMI, body weight, % body fat, or total body FFM in men or women with ST.

Genotype Results

The genotype distribution of the ACTN3 R577X polymorphism for the entire cohort did not fit the expectations of Hardy-Weinberg equilibrium ($\chi^2 = 7.90$, *p* = .02), though

Table 2. Baseline Differences in Knee Extensor Strength, Muscle Volume (MV), Muscle Quality, Peak Power, Muscle Power Quality, Peak Movement Velocity, and Movement Velocity Quality by ACTN3 R577X Genotype in Women

Characteristic	ACTN3 R577X Genotype		
	RR (<i>N</i> = 29)	RX (<i>N</i> = 33)	XX (<i>N</i> = 24)
1-RM, N	174 ± 8	156 ± 7	159 ± 10
MV, cm ³ *	1158 ± 37	1059 ± 34	1108 ± 39
Muscle quality [†] (N/cm ³) × 10 ⁻¹	1.5 ± 0.05	1.4 ± 0.05	1.5 ± 0.05
Absolute peak power, W [‡]	200 ± 11	210 ± 10	242 ± 10
Relative peak power, W [§]	191 ± 10	199 ± 9	235 ± 9
Absolute muscle power quality [‡] (W/cm ³) × 10 ⁻¹	2.0 ± 0.1	1.9 ± 0.1	2.2 ± 0.1 [¶]
Relative muscle power quality [§] (W/cm ³) × 10 ⁻¹	1.9 ± 0.1	1.8 ± 0.1	2.1 ± 0.1 ^{#,**}
Absolute peak movement velocity, rad/s [‡]	4.3 ± 0.1	4.5 ± 0.2	4.8 ± 0.2 ^{††}
Relative peak movement velocity, rad/s [§]	3.8 ± 0.1	3.8 ± 0.1	4.2 ± 0.1
Absolute movement velocity quality [‡] (rad/s/cm ³) × 10 ⁻³	4.2 ± 0.2	4.1 ± 0.2	4.4 ± 0.2
Relative movement velocity quality [§] (rad/s/cm ³) × 10 ⁻³	3.8 ± 0.2	3.5 ± 0.2	3.9 ± 0.2

Notes: Values are least-square means ± standard error of the mean.

*MV of the knee extensors.

[†]1-RM/MV.

[‡]The same absolute resistance at both baseline and after strength training.

[§]70% of 1-RM at baseline.

[¶]Significantly different than the RX group when covarying for age and baseline FFM, *p* < .05.

^{||}Significantly different than the RR and RX groups when covarying for age and baseline FFM, *p* < .05.

[#]Significantly different than the RX group when covarying for age and baseline FFM, *p* < .01.

^{**}Significantly different than the RR group when covarying for age and baseline FFM, *p* < .05.

^{††}Significantly different than the RR group when covarying for age and baseline fat-free mass (FFM), *p* < .01.

ACTN3 = alpha-actinin-3; 1-RM = One-repetition maximum; W = watts; rad/s = radians/s; N = Newtons.

the frequencies were similar to those in previous studies (23) in predominantly Caucasian cohorts. Genotype distributions for the ACTN3 R577X genotype groups for the cohort were 58 (37%), 60 (38%), and 39 (25%) for the RR, RX, and XX genotype groups, respectively. There were no significant differences by ACTN3 R577X genotype in men or women at baseline for age, height, weight, BMI, % body fat, or FFM (data not shown).

Table 2 shows the differences in baseline muscle function measures by ACTN3 genotype in women. X-homozygotes had significantly higher baseline absolute (*p* = .005) and relative PP values than did the RR and RX groups (*p* = .002) when age and baseline FFM were covaried. Partial *R*² analysis indicated that the ACTN3 R577X polymorphism explained 8.2% of the variation in baseline relative PP in women. Contrasts indicate a significant additive effect of the X-allele on baseline absolute (*p* = .005) and relative PP in women (*p* = .002). Furthermore, women X-homozygotes had a significantly greater absolute MPQ than the RX group had (*p* = .02) and greater relative MPQ than both the RR (*p* = .03) and RX groups had (*p* = .005),

when age and baseline FFM were covaried. Finally, women X-homozygotes had a significantly greater absolute PV than the RX group had ($p = .04$) and a greater relative PV than the RR ($p = .02$) and RX groups had ($p = .03$). There were no differences by ACTN3 genotype in men for any of the baseline muscle function measures shown in Table 2 (Table 3).

Figure 1 shows that, in men and women grouped separately by ACTN3 genotype, the increase in absolute PP with ST in the RR group in men approached significance for being greater than the X-homozygotes ($p = .07$), when the data were adjusted for age and change in the untrained leg. The ACTN3 R577X polymorphism explained 4.7% of the variation in the change in absolute PP in men. Contrasts failed to confirm an additive or dominant effect of the X-allele on the change in absolute PP with ST in men ($p = .08$). There were significant within-group increases in absolute PP in all ACTN3 genotype groups from baseline with ST in men ($p < .05$). There were no differences in the change in absolute PP in women by ACTN3 genotype with ST, but all genotype groups significantly increased in absolute PP with ST (Figure 1).

Figure 2 shows that, in men and women separately grouped by ACTN3 genotype, there was a significantly greater increase in relative PP in women in the RR group compared to the X-homozygotes ($p = .02$) with ST, when the data were adjusted for age and changes in the untrained leg. There were significant within-group increases in relative PP with ST in the RR ($p = .007$) and RX genotype groups ($p = .03$) in women, but not in the X-homozygotes. The ACTN3 R577X polymorphism explained 14.3% of the variation in the change in relative PP in women. Contrasts indicate an additive effect of the X-allele on the change in relative PP with ST in women ($p = .02$). Although there were no differences in the change in the relative PP in men by ACTN3 genotype, only the RR group demonstrated a significant increase with ST ($p = .01$, Figure 2). There were no genotype differences in men or women for change in 1-RM, absolute PV, MPQ, or PV quality with ST.

DISCUSSION

The results of the present study demonstrate for the first time, and in support of our expectations, that increases in knee extensor peak power with ST are influenced by ACTN3 R577X genotype in both men and women, such that older adults who are R-allele homozygotes have a greater PP response to ST than X-homozygotes have. This difference was observed when PP was measured in women at the same percentage of 1-RM at baseline and after ST (i.e., relative PP), and when men were tested for PP at the same absolute load before and after ST (i.e., absolute PP). Contrary to our expectations, however, the data demonstrate that baseline PP in women is significantly greater in X-homozygotes than in R-homozygotes and RX-heterozygotes. Nevertheless, these results do provide support for our hypothesis that the ACTN3 R577X polymorphism influences baseline PP, as well as PP and PV responses to ST in older adults. Only one other report (with a small sample size) studied the influence of the ACTN3

Table 3. Baseline Differences in Knee Extensor Strength, Muscle Volume (MV), Muscle Quality, Peak Power, Muscle Power Quality, Peak Movement Velocity, and Movement Velocity Quality by ACTN3 R577X Genotype in Men

Characteristic	ACTN3 R577X Genotype		
	RR (N = 29)	RX (N = 27)	XX (N = 15)
1-RM, N	322 ± 13	317 ± 15	302 ± 19
MV, cm ³ *	1799 ± 47	1759 ± 45	1780 ± 62
Muscle quality [†] (N/cm ³) × 10 ⁻¹	1.8 ± 0.07	1.7 ± 0.07	1.7 ± 0.1
Absolute peak power, W [‡]	415 ± 20	443 ± 21	413 ± 27
Relative peak power, W [§]	390 ± 20	432 ± 21	396 ± 26
Absolute muscle power quality [†] (W/cm ³) × 10 ⁻¹	2.4 ± 0.1	2.5 ± 0.1	2.4 ± 0.1
Relative muscle power quality [§] (W/cm ³) × 10 ⁻¹	2.2 ± 0.1	2.4 ± 0.1	2.4 ± 0.1
Absolute peak movement velocity, rad/s [‡]	5.0 ± 0.2	5.3 ± 0.2	5.2 ± 0.2
Relative peak movement velocity, rad/s [§]	4.2 ± 0.2	4.5 ± 0.2	4.6 ± 0.2
Absolute movement velocity quality [†] (rad/s/cm ³) × 10 ⁻³	2.8 ± 0.2	3.1 ± 0.2	3.0 ± 0.2
Relative movement velocity quality [§] (rad/s/cm ³) × 10 ⁻³	2.4 ± 0.1	2.6 ± 0.1	2.7 ± 0.2

Notes: Values are least-square means ± standard error of the mean. There were no significant baseline differences between genotype groups in men.

*MV of the knee extensors.

[†]1-RM/MV.

[‡]The same absolute resistance at both baseline and after strength training.

[§]70% of 1-RM at baseline.

1-RM = One-repetition maximum; ACTN3 = alpha-actinin-3; W = watts; rad/s = radians/s; N = Newtons.

R577X polymorphism on muscle strength in older adults and found no relationship between ACTN3 genotype and baseline muscle strength. However, muscle power, velocity, and quality variables were not measured, nor were changes in these skeletal muscle phenotypes with ST (29).

The ACTN3 protein may allow for skeletal muscle to have a greater capacity for the conduction of force at the Z-line during a rapid contraction (30,31). Because ACTN3 expression is limited to type II fibers (those most involved in maximal force, contractile speed, and power production), the measurement of PP might be a preferred phenotype for testing the influence of the ACTN3 polymorphism over typical strength measures. Based on the apparent physiological role of ACTN3 in force transmission, we hypothesized that participants who were ACTN3 deficient (XX) would not be as strong or produce as much instantaneous power, or show similar strength and power responses to ST as would R-allele carriers. Although the strength portion of this hypothesis was not supported by Clarkson and colleagues (25), the physiological role of the ACTN3 protein provided a biologically plausible rationale for ACTN3 enhancing PP and therefore support for our finding of an advantage for R-homozygotes in PP responses to ST. However, the higher baseline PP observed in the women X-homozygotes was unexpected.

In a cross-sectional study by Yang and colleagues (20), few X-homozygotic men and no X-homozygotic women were found in a group of elite power athletes, suggesting an advantage for R-allele carriers in muscle power performance. Those individuals were highly trained young

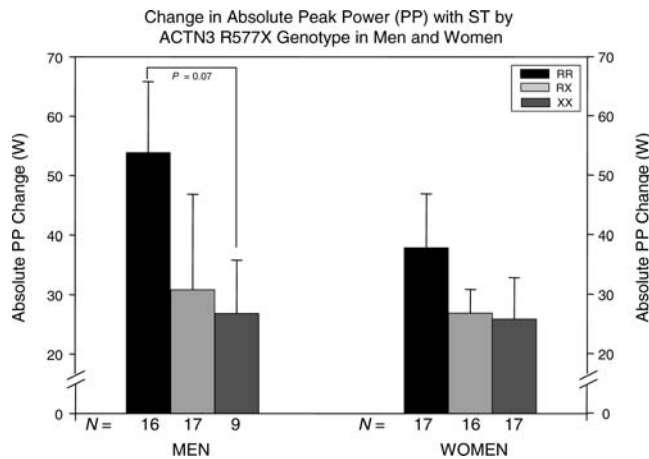


Figure 1. Changes in knee extensor absolute (same absolute resistance before and after strength training [ST]) peak power (PP) with ST by alpha-actinin-3 (ACTN3) R577X genotype in men and women. When covarying for age and changes in the untrained leg, there was a tendency toward a significantly greater increase in absolute PP in the RR group than in the XX group with ST in men ($p = .07$). There were no significant differences in absolute PP change among genotype groups in women. Values are least-square means \pm standard error of the mean.

athletes, whose muscle function values may not correspond to those observed in the older, sedentary adults who were studied in the current investigation. Nevertheless, our data showing greater improvements in RR men and women in response to ST are consistent with the findings of Yang and colleagues (20), which suggest a Gene \times Environment interaction with training necessary to elicit performance differences among ACTN3 genotype groups.

Why baseline muscle power values were higher in X-homozygotes than in the RR and RX genotype groups in women but not in men is unclear. Data from a previous investigation by Clarkson and colleagues (25) found that young (~ 25 years) women X-homozygotes had lower arm flexor isometric strength at baseline than RX-heterozygotes had, consistent with expectations for the X-allele. We did not observe baseline strength differences among genotype groups in either men or women. Contrary to their expectations, Clarkson and colleagues (25) reported that women X-homozygotes have a greater strength response than RX-heterozygotes have in response to ST. In contrast, we report here an $\sim 14\%$ training-induced increase in relative peak power in women R-homozygotes, but no significant increase in women X-homozygotes, and greater increases in absolute peak power in men R-homozygotes than in X-homozygotes. Substantial differences in age, muscle groups studied (knee extensors vs biceps), and muscle phenotypes prevent clear comparisons between the two investigations. A recent report suggests that the ACTN3 R577X polymorphism influences baseline serum creatine kinase (CK) levels, which are associated with skeletal muscle damage (32). In this regard, muscle damage is thought to be a stimulus for ST-induced muscle hypertrophy (32) and, therefore, muscle strength, based on the high correlation between strength and muscle mass. It could be argued that the force component of muscle power could then be associated with muscle damage and

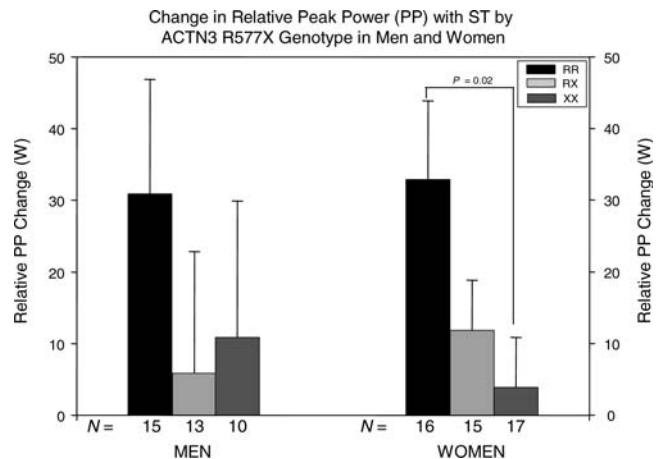


Figure 2. Changes in knee extensor relative (70% of one-repetition maximum [1-RM] to baseline and after strength training [ST]) peak power (PP) with ST by alpha-actinin-3 (ACTN3) R577X genotype in men and women. When covarying for age and changes in the untrained leg, there was a significantly greater increase in relative PP in the RR group than in the XX group with ST in men ($p = .02$). There were no significant differences in relative PP change among genotype groups in women. Values are least-square means \pm standard error of the mean.

therefore CK levels, but the association between CK and muscle power has not been established, particularly as it applies to ST effects.

Finally, it is unclear how to explain sex differences in the influence of ACTN3 on PP responses to ST observed in the present study. Clarkson and colleagues (25) suggested that sex differences in this regard may be associated with sex steroid hormone differences.

The finding of a greater increase in absolute MPQ in men R-homozygotes than in X-homozygotes with ST further demonstrates that there are factors other than muscle hypertrophy that are responsible for genotype differences in peak power. Further evidence for this comes from the finding that there were no significant differences in MV change among genotype groups. Earlier reports estimate that $\sim 60\%$ of the increase in muscular strength with ST is due to factors other than muscle hypertrophy (33). Although we are not aware of any data to support these genotype differences, there is support for the conclusion that increases in power and strength with ST in older adults can be influenced substantially by neural adaptations (33). Nevertheless, the specific mechanisms responsible for these findings will require further investigation.

Our finding of a genotype difference in absolute PP responses in men when using relatively low loads ($\sim 50\%$ of 1-RM after training vs 70% of 1-RM for relative PP) may have important consequences for functional ability performance. This conclusion is based on recent data, which suggest that certain functional performance tasks in older adults may be more dependent on movement velocity at lower external loads than at higher loads (34).

There are several limitations to the current investigation. For example, muscle power is a complex phenotype, which is likely influenced by numerous genes and polymorphisms, as well as other environmental factors that may be inter-

acting with these genes in unknown ways. The limited sample size in the current investigation, especially when stratifying by sex, does not allow for the analysis of the interaction of multiple loci. Additionally, participants in this investigation were trained using a moderate-velocity training protocol. A higher velocity training protocol would likely produce greater gains in power (10). We chose an ST protocol that is more commonly used for the improvement of strength and mass, with a track record for being safe and effective in older adults for producing substantial improvements in all the major components of sarcopenia (7,14,33,35–38). It is still not well-established whether a high-velocity training program is well tolerated by older persons (39). Another limitation was that there was a relatively wide range of ages. Age might be an effect modifier with regard to the influence of this polymorphism, as there are significant structural changes (e.g., motor unit denervation, muscle fiber loss, fiber type grouping) that occur in the skeletal muscle of older adults (40). It is conceivable that the youngest participants in the study may have slightly different training responses than the older ones, but age was included as a covariate in our analyses and there were no significant age differences between genotype groups.

Future studies will need to not only use much larger homogeneous sample sizes, but will need to carefully develop research designs to accommodate the limitations of this study and the ones highlighted by Clarkson and colleagues (25). Establishing the influence of the ACTN3 R577X SNP on functional abilities, likely an even more complex phenotype, in elderly populations is necessary to determine if this genotype is of importance for targeting individuals who may be more susceptible to the effects of sarcopenia and who may need specific interventions.

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