# ACTN3 Genotype Does not Influence Muscle Power

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# *ACTN3* Genotype Does not Influence Muscle Power

Authors **E. D. Hanson, A. T. Ludlow, A. K. Sheaff, J. Park, S. M. Roth**

Affiliation University of Maryland, Department of Kinesiology, School of Public Health, College Park, MD, United States

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- genetics
- alpha-actinin-3
- skeletal muscle

## Abstract

The R577X polymorphism within the *ACTN3* gene has been associated with elite athletic performance, strength, power, fat free mass, and adaptations to strength training, though inconsistencies exist in the literature. The specific muscle power phenotypes most influenced by the polymorphism are uncertain. The purpose of this study was to examine the association between *ACTN3* R577X genotype and muscle power phenotypes. Recreationally active young men and women (N = 57) were selected to complete 2 muscle performance assessments, an isokinetic fatigue protocol at testing speeds of 180 ° $s^{-1}$ and 250 ° $s^{-1}$ and a 30 s Wingate test. Isokinetic torque and Wingate power significantly decreased over the duration of each test, but no differences in the rate of decline were observed among *ACTN3* genotype groups. Similarly, no significant genotype differences were observed for isokinetic peak torque, Wingate absolute or relative peak power, or fatigue index. These results indicate that in recreationally active individuals the *ACTN3* R577X polymorphism is not associated with muscle performance phenotypes, supporting recent findings that R577X may only be important for predicting performance in elite athletes. Our data also indicate that using this polymorphism for genetic screening in the lay population is scientifically questionable.

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**Bibliography**
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**Correspondence**
***Stephen M. Roth***
University of Maryland
Department of Kinesiology
School of Public Health
College Park, MD 20742
United States
Tel.: +1/301/405 2504
Fax: +1/301/405 5578
sroth1@umd.edu

## Introduction

The α-actinins are members of a family of highly conserved actin-binding proteins known as spectrins [1]. There are 4 isoforms in humans with only 2, α-actinin two (ACTN2) and α-actinin three (ACTN3), being expressed in skeletal muscle. ACTN2 and ACTN3 are structural proteins of the Z-line and it is hypothesized that these proteins anchor the actin-containing thin filaments to stabilize the muscle contractile apparatus [16]. Both proteins appear structurally and functionally similar [20], however, ACTN2 is expressed in all types of skeletal muscle fibers while ACTN3 is expressed in fast twitch fibers [21,28].

A single nucleotide polymorphism in the *ACTN3* gene results in the conversion of an arginine (R) to a premature stop codon (X) at residue 577 and the creation of a non-functional protein [20]. No known disease phenotypes result from the X/X genotype [16,20], suggesting an adequate compensatory role for ACTN2. Moreover, in the *Actn3* -/- mouse model, there is significant upregulation of ACTN2 in skeletal muscle [12]. In the context of human athletic performance, investigations have demonstrated differing *ACTN3* allele frequencies between elite sprint and power athletes and controls [5,8,18,22,23,25,30] as well as interactions with *ACTN3* and other performance-related polymorphisms [6,7,24]. Studies in the general population have yielded mixed results, with *ACTN3* genotype-related differences being observed in a variety of speed and power traits [17,28,29] whereas others have failed to identify such differences [13,14,19,26]. While the equivocal findings between studies may be the result of differences in phenotype measurement or study design, the findings do raise concerns about the importance of this genetic variant in non-elite populations. Despite these mixed findings, the *ACTN3* R577X polymorphism has widespread attention as a possible "predictor" variant for identifying individuals with potential for future elite level performance. Direct-to-consumer genetic tests for this variant are currently readily available to the general public.

While there is evidence of an association between the X/X genotype and reduced sprint and power

performance, the exact phenotype(s) responsible for these differences are not well characterized. The significant associations in the literature predominantly carry the common theme of high velocity, powerful contractions [5–8,17,18,22,24,25,30], but the case-control studies comparing elite athletes vs. sedentary controls do not quantify athletic performance. In the present study, we hypothesized that in recreationally active individuals, *ACTN3* R577 allele carriers would exhibit superior peak torques and muscle power compared to X/X carriers and would better sustain these phenotypes throughout short-term fatigability tests compared to X/X carriers.

## Materials and Methods

The study was performed over 2 non-consecutive days (3–7 days apart) with the first day providing a familiarization session while the second day served as a data acquisition session during which subjects completed 2 specific power-oriented performance tasks in which peak torque, peak power, and short-term fatigability were determined. Subjects arrived at the laboratory rested, hydrated, and having eaten in the few hours preceding the session. Subjects completed a 5 min warm up on a cycle ergometer prior to each session.

### Subjects

Ethical approval for this study was provided by the University of Maryland Institutional Review Board and subjects provided written consent prior to participation. Research was performed to meet the ethical standards described previously [10]. Subjects were considered to be recreationally active but untrained, defined as participating in structured aerobic exercise training for ≤20 min per session on ≤2 days per week and no lower body strength training for at least the preceding 6 months. Most subjects engaged in recreational sporting activities approximately 1–2 times per week but were not currently training with a team or group beyond the allowances afforded in the inclusion criteria. Subjects were free from any cardiovascular, metabolic, or neurological disorders, and any lower extremity injuries that may have hindered performance. Because the X/X genotype occurs in only ~16% of the population [20], subject recruitment was tailored to enrich the X/X genotype group such that R577X genotype distributions were approximately balanced. Subjects with the R/R and R/X genotypes were randomly accepted for participation while all X/X subjects were enrolled in the study. Of the 133 potential subjects who met all inclusion criteria and provided DNA samples, 57 subjects (21 men and 36 women), aged 18–31 years, completed all aspects of the study.

### Genotyping

Genomic DNA was extracted from buccal cells using standard salting-out procedures (Puregene DNA Extraction kit, Gentra Systems, Inc., Minneapolis, MN, USA). Genotyping for the *ACTN3* R577X polymorphism was performed based on methods described by Mills et al. [16] Briefly, DNA was amplified using PCR and digested with the DdeI restriction enzyme (New England Biolabs, Ipswich, MA). The primer set was: forward 5'-CTGTTGCCTGTGGTAAGTGGG-3' and reverse 5'-TGGTCACAGTATGCAGGAGGG-3'. R-allele carriers produced PCR products of 250 and 85 base pairs lacking the DdeI cut site, whereas X-allele carriers had a DdeI cut site and produced PCR products of 108, 97, and 86 base pairs. Sequence-verified controls were included in all genotyping assays. Genotyping was performed in a blind fashion such that investigators involved in the muscle performance testing were unaware of any participant's genotype.

### Anthropometric data

Height and mass were measured with subjects wearing workout clothing (Detecto Scales, Webb City, MO, USA). Percent body fat was estimated using skinfold calipers (Lange, Cambridge, MD, USA) and the 3 site skinfold method.

### Isokinetic testing

Consecutive repetitions of knee extension and knee flexion were performed on a Kin Com isokinetic dynamometer (Kin Com, Harrison, TN, USA). Subjects were seated with the lower leg being secured to the dynamometer slightly superior to the medial malleolus. The range of motion for each repetition began with the knee joint in 80° of knee flexion and terminated at 15° of flexion. Gravity compensation was employed to account for the weight of the lower extremity.

For familiarization, subjects completed 3 sets of 3 repetitions at 135° $s^{-1}$. They then completed an additional 3 sets of 10 repetitions at the respective testing speed at efforts ranging from 50% up to 100% of maximum. Testing was completed at 2 different speeds, 180° $s^{-1}$ and 250° $s^{-1}$, with 1 speed per leg. The testing order and speed of each leg were chosen randomly and kept constant throughout all isokinetic testing. The procedure was then repeated on the opposite leg using the other testing speed.

The experimental session differed such that it consisted of 2 warm up sets of 5 repetitions followed by the testing set of 30 consecutive repetitions. The first warm up set was performed at 135° $s^{-1}$ and the second warm up set and the data acquisition set were completed at the respective testing speed (either 180° or 250° $s^{-1}$). 2 min of rest separated all efforts. All Kin Com data files were smoothed using a 4$^{th}$ order Butterworth low-pass filter and the local maximum and minimum torque values for each repetition were determined using MatLab software (MathWorks, Natick, MA, USA). The repetition x torque relationship was examined by averaging the 3 consecutive values at 5 repetition intervals, for a total of 6 time points. Isokinetic torque fatigue indices were calculated as the difference between peak and minimum torque as a percentage of peak torque.

### Wingate anaerobic cycling test

Seated recovery (20 min) separated isokinetic testing from the Wingate Anaerobic Cycling Test (WAnT). The WAnT was performed on a Monark 824E ergometer (Monark, Varberg, Sweden) using a resistance equal to 7.5% of body weight. Subjects warmed up briefly before completing 2 practice starts. Subjects rested for 2 min before performing a maximal effort WAnT. Pedal revolutions were counted using a custom built electronic counter. Absolute power outputs were determined for each 5 s interval and were then related to body mass and estimated fat free mass. WAnT fatigue index was calculated as the difference between peak and minimum power as a percentage of peak power. A 15-s WAnT was used for familiarization, whereas a 30-s WAnT was used for data acquisition. Warm-up procedures were the same for both sessions.

### Statistical analyses

1-way ANOVA was performed with *ACTN3* genotype as the independent variable with 3 genotype groups, though dominant model analyses were also performed (X/X vs. R/X + R/R). Depend-

**Table 1** Subject characteristics across all genotypes and using the dominant allele model.

| | R/R (N = 19) | R/X (N = 24) | X/X (N = 14) | *P* | R/R + R/X (N = 43) | *P*‡ |
|---|---|---|---|---|---|---|
| age (y) | 21 ± 1 | 24 ± 1* | 21 ± 1 | *0.002* | 22 ± 1† | *0.050* |
| height (cm) | 166.4 ± 2.8 | 166.4 ± 2.0 | 167.8 ± 2.4 | 0.905 | 166.4 ± 1.7 | 0.654 |
| body mass (kg) | 64.8 ± 3.4 | 66.4 ± 3.3 | 75.8 ± 4.6 | 0.128 | 65.7 ± 2.4† | *0.044* |
| fat (%) | 19.3 ± 1.5 | 21.9 ± 1.5 | 24.8 ± 1.7 | 0.090 | 20.8 ± 1.1 | 0.070 |
| FFM (kg) | 50.7 ± 2.6 | 51.3 ± 2.2 | 55.2 ± 3.5 | 0.505 | 51.0 ± 1.7 | 0.244 |
| PA consistency | 2.2 ± 0.1 | 2.2 ± 0.1 | 2.1 ± 0.2 | 0.948 | 2.2 ± 0.1 | 0.818 |

Abbreviations: BMI, body mass index; FFM, fat free mass; PA, physical activity

* Significantly different than RR and XX genotypes in 3 genotype model

† Significantly different than X/X genotypes in dominant allele model

‡ The second P-value in Table 1 reflects the dominant allele comparison (X/X vs. R/R + R/X)

**Table 2** Isokinetic peak torque, WAnT power, and fatigue index across all 3 genotypes and using the dominant allele model.

| | R/R (N = 19) | R/X (N = 24) | X/X (N = 14)§ | *P* | R/R + R/X (N = 43) | *P*‡ |
|---|---|---|---|---|---|---|
| quad 180° PT (N*m) | 49.9 ± 4.9 | 48.7 ± 3.0 | 52.9 ± 5.7 | 0.803 | 49.3 ± 2.7 | 0.528 |
| quad 180° FI (%) | 51.0 ± 1.7 | 54.4 ± 1.8 | 48.6 ± 2.2 | 0.105 | 52.9 ± 1.3 | 0.099 |
| quad 250° PT (N*m) | 29.4 ± 2.5 | 31.4 ± 3.3 | 36.5 ± 4.5 | 0.409 | 30.5 ± 2.1 | 0.205 |
| quad 250° FI (%) | 48.2 ± 3.0 | 51.9 ± 3.4 | 50.8 ± 4.3 | 0.717 | 50.1 ± 2.2 | 0.872 |
| ham 180° PT (N*m) | 29.2 ± 2.8 | 29.3 ± 2.1 | 35.4 ± 3.9 | 0.263 | 29.3 ± 1.7 | 0.101 |
| ham 180° FI (%) | 42.6 ± 2.6 | 43.4 ± 2.3 | 38.6 ± 1.9 | 0.404 | 43.0 ± 1.7 | 0.183 |
| ham 250° PT (N*m) | 25.5 ± 1.8 | 23.9 ± 1.9 | 30.9 ± 3.5 | 0.128 | 24.6 ± 1.3† | *0.050* |
| ham 250° FI (%) | 46.3 ± 2.8 | 49.2 ± 2.9 | 42.4 ± 1.5 | 0.229 | 47.8 ± 2.0 | 0.130 |
| WAnT PP (W) | 600.4 ± 48.8 | 590.0 ± 42.7 | 676.6 ± 53.3 | 0.440 | 594.6 ± 31.7 | 0.202 |
| WAnT PP/BM (W/kg) | 9.1 ± 0.3 | 8.7 ± 0.4 | 8.8 ± 0.4 | 0.822 | 8.9 ± 0.3 | 0.907 |
| WAnT PP/FFM (W/kg) | 11.1 ± 0.4 | 11.2 ± 0.5 | 11.9 ± 0.5 | 0.550 | 11.2 ± 0.3 | 0.278 |
| WAnT MP (W) | 363.5 ± 32.5 | 347.5 ± 25.7 | 407.2 ± 29.2 | 0.382 | 354.6 ± 20.1 | 0.388 |
| WAnT MP/BM (W/kg) | 5.5 ± 0.2 | 5.2 ± 0.3 | 5.4 ± 0.2 | 0.722 | 5.3 ± 0.2 | 0.891 |
| WAnT FI (%) | 62.4 ± 1.4 | 63.7 ± 1.6 | 60.2 ± 2.0 | 0.378 | 63.1 ± 1.1 | 0.201 |

Abbreviations: Quad, quadriceps; Ham, hamstring; PT, peak torque; FI, fatigue index; WAnT, Wingate anaerobic cycling test; PP, peak power; MP, mean power; FFM, fat free mass; BM, body mass

† Significantly different than X/X genotypes in dominant allele model

‡ The second P-value in Table 2 reflects the dominant allele comparison (X/X vs. R/R + R/X)

§ Data from 2 X/X participants were lost due to velocity errors during the 250° $s^{-1}$ trials

ent variables included participant characteristics and the primary phenotype measures of isokinetic peak torque and WAnT power outputs. 2-way ANOVA was used to compare *ACTN3* genotype across repetition or time in relation to isokinetic torques and WAnT power output. Correction for body mass differences among genotype groups was performed as appropriate. Data are expressed as means ± SEM. All analyses were performed using SPSS v. 15.0 statistical software (SPSS, Chicago, IL, USA). Statistical significance was accepted at $P < 0.05$.

## Results

Subject characteristics are described in **Table 1**. R/X individuals were significantly older ($P = 0.002$) than RR and XX individuals. Including age as a covariate in statistical models did not alter any genotype-phenotype associations. When the dominant model analysis was performed, X/X homozygotes exhibited significantly greater body mass than R carriers ($P = 0.044$).

Peak isokinetic torque and the corresponding fatigue indices are presented in **Table 2**. There were no significant differences among genotypes when analyzed using the 3-genotype model. The dominant model analysis (X/X vs. R-allele carriers) revealed significantly higher isokinetic hamstring peak torque at 250° $s^{-1}$ ($P = 0.050$) in X/X individuals, but not after correction for body mass differences ($P = 0.163$). Similarly, normalization of torque values to body mass in all cases led to higher *P*-values as the adjustment resulted in nearly identical mean values. As there was only one significant genotype difference (in the dominant model only), the non-normalized raw values are shown in **Table 2** and elsewhere.

The quadriceps and hamstring torque values during the isokinetic fatigue test are depicted in **Fig. 1a, b**. Torque at both 180° $s^{-1}$ and 250° $s^{-1}$ was not associated with R577X genotype; however, there was a significant main effect of repetition ($P < 0.001$) such that quadriceps and hamstring torque at both velocities significantly decreased every 5 repetitions throughout the tests.

No significant R577X genotype differences in any measure of peak or mean WAnT power were observed (all $P > 0.05$; **Fig. 2a, b**, **Table 2**). There was a significant main effect of time, such that WAnT power significantly decreased every 5 s throughout the WAnT test ($P < 0.001$).

## Discussion

Our main finding is that no associations between *ACTN3* genotype and isokinetic muscle performance or WAnT performance were observed. These findings conflict with the reports using

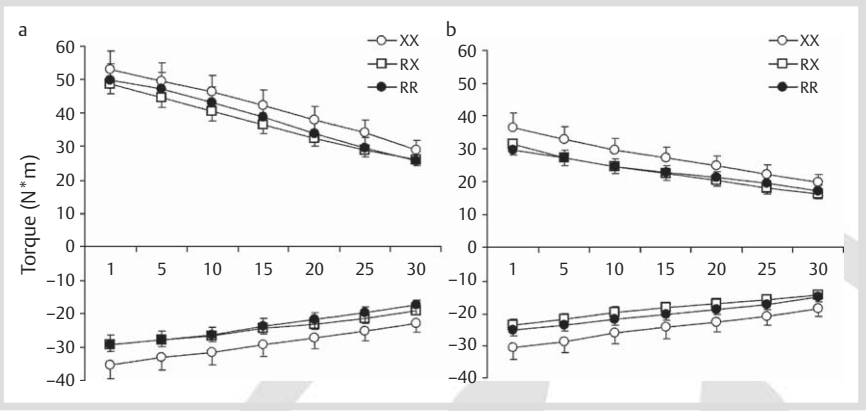


**Fig. 1** **a**) Isokinetic concentric torque at 180° $s^{-1}$ and **b**) isokinetic concentric torque at 250° $s^{-1}$. Repetition number is plotted along the X axis and each point is the average of the 3 consecutive values at 5 repetition intervals. There was a significant main effect of repetition, such that each averaged torque was significantly less than all previous values ($P<0.001$). No significant genotype differences were observed.

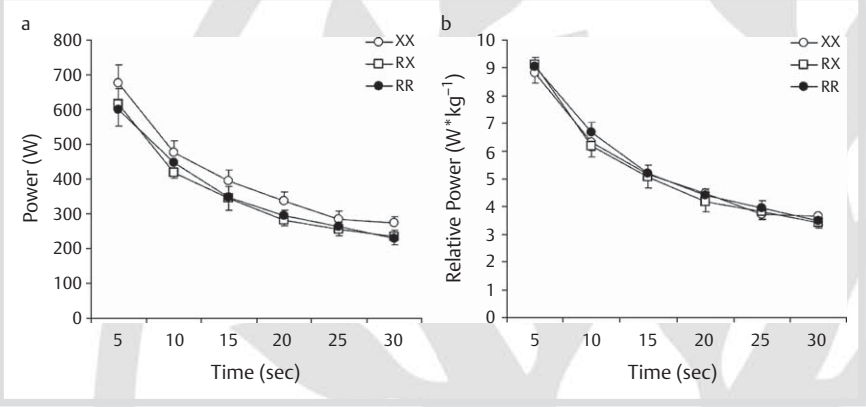


**Fig. 2** **a**) WAnT peak power and **b**) relative WAnT peak power. There was a significant main effect of time, such that power output at each time point was significantly less than all previous values ($P<0.001$). No significant genotype differences were found.

elite power athletes but support a growing body of literature suggesting that the lack of ACTN3 does not appear to influence muscle power within a single bout of acute exercise.

The initial associations of *ACTN3* genotype with muscle performance examined elite athletes engaged in sprint and power sports [18, 30] and subsequent studies using different populations of elite athletes confirmed these results [5–8, 22–25]. These associations involve activities that require multiple high velocity contractions in highly trained individuals. Given that the X/X genotype tends to appear in lower frequencies in elite sprint and power athletes, the possibility exists that the presence of ACTN3 may facilitate greater adaptation to training. This effect would not be seen in untrained individuals, such as those studied presently. However, the *ACTN3* R577X polymorphism may be a subtle yet decisive genetic factor that helps separate the best performers from all others. Differences in adaptation to training could propagate over time, leading to altered athletic performance that cannot be detected in a single session. Moreover, power trained athletes produce greater normalized maximal force than endurance trained athletes [9] and untrained individuals [11]. These forces may result in greater damage to the sarcomere during explosive muscle contractions, which could be exacerbated by the absence of ACTN3. The impending muscle damage may alter the trajectory of muscle regeneration, adaptation and ultimately performance. Interestingly, the R577X polymorphism was not associated with exercise-induced muscle damage [3], however, the subjects in that study were untrained and displayed a highly variable muscle damage response, potentially masking any influence of *ACTN3* genotype.

Because of the hypothesized structural role of ACTN3, we anticipated a greater decrease in peak torque, peak power and increased fatigue response to testing in X/X homozygotes. Instead, the responses were independent of genotype, particularly after correcting for body mass differences, which confirm previous findings using isokinetic and WAnT testing measures [19]. While our data provide partial replication of previous work [19], we extend those findings by studying an untrained population, using higher velocity isokinetic fatigue testing speeds, and including women in the isokinetic testing, as previous results suggest that *ACTN3* genotype may be more influential in females [2, 4, 29, 30]. Other investigations examining isokinetic torque have demonstrated conflicting findings [13, 14, 28, 29], but these associations used a low number of repetitions per testing set and did not investigate the role of genotype on fatigue.

The suitability of some of the previously studied phenotypes for examining the role of *ACTN3* have recently been questioned because most athletic performances incorporate multi-joint movements [26]. However, the WAnT is a multi-joint, maximal effort functional task and is correlated with isokinetic, sprinting, and vertical jump performance [15, 27]. But such tests are challenging for identifying the key underlying phenotype(s) impacted by *ACTN3* in vivo, which argues for more specific tests of muscle phenotypes, such as isokinetic testing, thus partially mimicking the conditions under which *ACTN3* genotype has been most consistently associated with sprint and power performance. Interestingly, despite using multi-joint athletic movements in untrained individuals, sprint and vertical jump performance were not influenced by *ACTN3* genotype in a recent study [26] pointing to the complex (i. e., multigenic) nature of skeletal muscle performance phenotypes.

Several limitations exist in the present study including recruitment based on genotype, sample size, and the preliminary nature of these findings. The method of recruitment resulted in a genotype distribution different from that of the general public,

but this was done to increase the number of X/X individuals to balance the genotype groups. To control for the potential bias in this method, all subjects met the physical activity criteria and the researchers were blinded to genotype during testing. Post-hoc power analyses revealed that for the observed genotype differences to be considered statistically significant, in excess of 5 000 subjects would be required per group. Therefore, while our study is underpowered, this reinforces our conclusion that *ACTN3* genotype does not appear to be important in this population. Although the results are preliminary, they support recent studies examining similar phenotypes.

In summary, the present study found no significant associations of *ACTN3* R577X genotype with isokinetic fatigue or WAnT performance in recreationally active individuals. These findings support recent work in non-athletes but contrast the previous findings in sprint and power athletes. The lack of association between *ACTN3* genotype and muscle performance in the general population indicates that *ACTN3* alone does not identify individuals with predisposition for enhanced sub-elite performance. The emerging use of direct-to-consumer genetic tests that emphasize the use of *ACTN3* and other genes for prediction of future sport performance potential appears to be scientifically (and perhaps ethically) questionable.

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