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Association of the *ACTN3* Genotype and Physical Functioning With Age in Older Adults

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Abstract

Objective—The purpose of this study was to examine the association of the alpha-actinin-3 (*ACTN3*) R577X polymorphism on muscle function and physical performance in older adults.

Methods—We measured knee extensor torque, midthigh muscle cross-sectional area, muscle quality, short physical performance battery score, and 400-meter walk time at baseline and after 5 years in white older adults aged 70–79 years in the Health, Aging and Body Composition Study cohort (n = 1367). Incident persistent lower extremity limitation (PLL) over 5 years was additionally assessed. We also examined white men in the Osteoporotic Fractures in Men Study, a longitudinal, observational cohort (n = 1152) of men 65 years old or older as a validation cohort for certain phenotypes.

Results—There were no significant differences between genotype groups in men or women for adjusted baseline phenotypes. Male X-homozygotes had a significantly greater adjusted 5-year increase in their 400-meter walk time compared to R-homozygotes and heterozygotes (p = .03). In women, X-homozygotes had a ~35% greater risk of incident PLL compared to R-homozygotes (hazard ratio = 0.65, 95% confidence interval = 0.44–0.94). There were no other significant associations between any of the phenotypes and *ACTN3* genotype with aging in either cohort.

Conclusions—The *ACTN3* polymorphism may influence declines in certain measures of physical performance with aging in older white adults, based on longitudinal assessments. However, the influence of the *ACTN3* R577X polymorphism does not appear to have a strong effect on skeletal muscle–related phenotypes based on the strength and consistency of the associations and lack of replication with regard to specific phenotypes.

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Keywords

Genetics; Elderly; Sarcopenia; Skeletal muscle

Twin studies indicate that muscle function phenotypes are highly heritable (1,2), and various candidate genes have been studied to explain some of the high inter-individual variability observed in these phenotypes (3). However, only a small number of genes containing single nucleotide polymorphisms (SNPs) have been identified as candidate genes for explaining this variability.

Alpha-actinin-3 (ACTN-3), a structural protein in type II skeletal muscle fibers, is associated with physical performance (4–8). Recent data suggest that the R577X SNP in the ACTN-3 gene (*ACTN3*) explains some of the inter-individual variability in muscle functioning in older adults (9), although not all studies agree (10). The R577X SNP results from a C-to-T transition at position 1747 in exon 16 that substitutes an arginine residue at codon 577 for a premature stop codon (11). X-homozygotes fail to express ACTN-3, but this is not known to be associated with any disease phenotype (12). Nevertheless, the lack of ACTN-3 expression has been associated with athletic performance (5,13).

Although few studies have been reported that have examined the association of the *ACTN3* R577X polymorphism in older adults, studies in younger athletes show that ACTN-3 is associated with better performance in athletes who are engaged in muscle power–dependent sports (5,7,8,13). In addition, data from cross-sectional studies show that young adult X-homozygotes have lower strength than heterozygotes (4) and R-homozygotes (14). Moreover, we recently reported that the R577X polymorphism is associated with muscle power response to strength training in older adults (9). However, there were no differences in muscle size, strength, or muscle power at baseline; these findings agreed with those of a previous report (10). Nevertheless, that study was limited by a relatively small sample size.

The influence of the *ACTN3* R577X polymorphism on skeletal muscle and physical functioning in older adults has not been thoroughly examined in a large epidemiologic cohort. Additionally, no reports have addressed the potential impact of this polymorphism on age-related changes in these phenotypes. Thus, the purpose of this study was to determine the association of the *ACTN3* R577X polymorphism with muscle traits and physical functioning in a large cohort of older adults and to determine the association of this polymorphism with age-related declines in these phenotypes.

Methods

Participants

The Health, Aging and Body Composition (Health ABC) Study is a longitudinal, observational study of 3075 well-functioning men and women between the ages of 70 and 79 years. White participants were recruited in 1997–1998 from a random sample of Medicare enrollees in Memphis, Tennessee, and Pittsburgh, Pennsylvania. Fifty-two percent of the participants were women, and 41% were black. Eligible participants had no self-reported difficulty walking one-quarter mile, climbing 10 steps, and performing activities of daily living; did not report using a walking aid; and were free of cancer under active treatment. Each institutional review board (IRB) approved the protocol, and all participants gave written informed consent for study participation.

Although we performed preliminary analyses on all participants, there was a very strong racial influence on many of the phenotypes of interest in both men and women. Combining black

and white participants appeared to result in spurious associations between the association of the *ACTN3* R577X polymorphism and some skeletal muscle phenotypes. This racial difference in skeletal muscle phenotypes has previously been observed in the Health ABC cohort (15). Moreover, of the 868 black participants, there were only 38 X-homozygotes for baseline analyses and 19 X-homozygotes for 5-year changes. The exclusion of blacks from the present analysis resulted in a sample size of 1794 white participants.

Of the 1794 remaining participants, some were excluded from the present analysis because of missing genotype ($n = 234$) or phenotype ($n = 193$) data. Thus, baseline analysis was conducted on the remaining 1367 participants (726 men and 641 women) who had complete data. Because these measures required a 5-year follow-up visit, there was some loss to follow-up ($n = 372$).

A second cohort of men from the Osteoporotic Fractures in Men (MrOS) Study was also studied. The MrOS Study is a multicenter, observational, longitudinal study of 5995 community dwelling, ambulatory men 65 years old or older (16,17). To be eligible, men had to be able to give informed consent, walk without assistance, not have a bilateral hip replacement, be able to give self-reported data, and not have a medical condition that would have resulted in imminent death (16,17). A subset of men ($n = 1201$) from the Pittsburgh and Minneapolis centers form the basis of the current analysis. Although there were some nonwhite participants in the current MrOS sample ($n = 49$), including only one X-homozygote, we decided to exclude these participants because of their small number. The MrOS Study was approved by the University of Pittsburgh and the University of Minnesota IRBs, and written informed consent was obtained from all participants. The MrOS Study included a 4-year follow-up visit, so there was some loss to follow-up ($n = 124$).

Outcomes—Health ABC Study

Thigh cross-sectional area—In the Health ABC Study cohort, midthigh cross-sectional area (CSA) of the right leg was measured at baseline and after 5 years at the level of the midfemur using computed tomography (CT) as previously described (18). Briefly, a single 10 mm-thick axial image (120 kVp, 200–250 mAs) of the right thigh was acquired at the midpoint of the distance between the medial edge of the greater trochanter and the intercondyloid fossa. The total area of nonadipose and nonbone tissues within fascial border was used as a quantification of muscle area (cm^2).

Knee extensor torque—Average isokinetic knee extensor muscle torque (MT, N-m), was measured at baseline and after 5 years using a Kin-Com 125 AP Dynamometer (Chattanooga, TN) at 60 degrees per second on the right leg, and the mean of the three most replicable and satisfactory trials of a limit of six attempts was used. When MT of the right leg was not available or valid because of knee replacement or pain, MT of the left leg was used in all analyses and was matched with the left leg thigh CSA for calculation of muscle area and muscle quality. Muscle quality was defined as MT/midthigh muscle CSA and was calculated at baseline and after 5 years.

Self-reported functional limitation—Incident persistent lower extremity limitation (PLL) was assessed and defined by self-reported difficulty walking one-quarter mile or climbing 10 steps without resting at two consecutive 6-month intervals. Incident PLL was assessed over a 5-year follow-up period by telephone interviews and annual clinic visits. Because of the study exclusion criteria, no participants had baseline lower extremity limitation.

Physical performance—Physical performance was evaluated at baseline and after 5 years using the Established Populations for Epidemiologic Studies of the Elderly (EPESE) short

physical performance battery (SPPB) using previously described methods (19,20). The SPPB included five chair stands and tests of gait speed and standing balance.

In addition, participants were also asked to walk 400 meters after a 2-minute warm-up using methods described elsewhere (21). Standard vocal support was given during the test, and time to complete the test(s) was recorded.

Outcomes—MrOS

In the MrOS cohort, thigh fat-free mass (FFM, kg) was measured using dual-energy x-ray absorptiometry (QDR 4500; Hologic, Waltham, MA). Physical performance was assessed during the baseline examination, during a single baseline visit. Rigorous centralized training, examiner certification in protocol administration, and periodic protocol review during the course of the study were used to ensure consistency in the measures of physical performance.

Grip strength (kg) was measured in both hands using a Jamar handheld dynamometer (Sammons Preston Rolyan, Bolingbrook, IL) (22). The maximum effort from two trials of both hands was analyzed. Participants with a recent injury or new weakness in the hands or wrists could elect to skip this assessment, in which case they were considered unable to complete the grip strength assessment.

Leg power (W) was measured using the Nottingham Power Rig (23,24). Participants completed up to nine measurements on each leg separately; the overall maximal leg power from both legs was analyzed. In an analysis of a small subsample of the MrOS participants ($n = 55$), test–retest reliability was estimated. Coefficients of variation (CVs) for between-examiner consistency ranged from 2.6% to 3.5%, and the CVs representing the combination of within-examiner variance, within-participant variance, and machine variance were <11%. Leg muscle power quality was calculated as power/thigh FFM (W/kg).

Time to complete a walking course (s) was determined from the better of two attempts of usual walking pace over 6 meters. The walking attempts were completed consecutively without a rest between attempts. Finally, the time to complete a five-chair-stand test without using the arms was measured (16). Each participant was asked to rise from a standard chair once without using his arms to stand. If the participant was unable to do this, he was considered unable to complete a single chair stand. If he was able to rise one time successfully, he was then asked to rise from a chair five times without using his arms; time to complete the five chair stands was recorded.

Genotyping

Genotyping for the *ACTN3* R577X variant (dbSNP rs 1815739) was done using a TaqMan allele discrimination assay that used the 5′ nuclease activity of Taq polymerase to detect a fluorescent reporter signal generated during polymerase chain reactions (PCRs) as previously described (4). Both alleles were detected simultaneously using allele-specific oligonucleotides labeled with different fluorophores, and R577X genotype was determined by the ratio of the two fluorophores used.

Potential Confounders and Effect Modifiers

In both cohorts, potential confounders and effect modifiers of the association between *ACTN3* R577X genotype group and muscle function, physical performance, and incident PLL were assessed. These included baseline age, body mass index, smoking status, alcohol use, comorbidity, level of physical activity, study site, baseline values, and change in body weight (for longitudinal analyses). In addition, cross-sectional data were adjusted for medications (ace

inhibitor, diuretic, androgen, and anti-inflammatory use) that could have had an influence on muscle phenotypes.

Smoking status was defined as never, previous, or current smoking at baseline. In the Health ABC cohort, alcohol use was defined as self-report at baseline of less than one drink per week, one to seven drinks per week, more than one drink per day, or none. In the MrOS cohort, alcohol use was defined by self-report at baseline of none, less than two drinks per week, or two or more drinks per week. Comorbidity in the Health ABC cohort was examined by summing the total of 11 conditions at baseline, assessed by self-report and validated with medication review, and grouping those with none, one, two, or three or more conditions. Comorbidity in the MrOS cohort was determined by summing eight conditions at baseline with a grouping that was the same as in the Health ABC Study. In the Health ABC cohort, physical activity was defined using the caloric expenditure (25) in the past week at baseline for self-reported walking, climbing stairs, and exercise. In the MrOS cohort, physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (26). Additional physical activity questions were used to assess walking for exercise, inactive time, and volunteer or paid employment (16).

Data Analysis

Descriptive statistics (mean [standard deviation]) were used to describe demographic and key clinical characteristics of the study population at baseline by *ACTN3* genotype groups. Because several reports have shown that the effect of this polymorphism may be sex specific (4,5), men and women were analyzed separately. For longitudinal change analyses, baseline values were subtracted from follow-up values (4 year [MrOS] or 5 year [Health ABC]). Analysis of variance (ANOVA) was used to test for overall group differences and the differences between R-homozygotes and heterozygotes versus X-homozygotes in the distribution of continuous variables. The chi-square test was used to test for differences in the distribution of categorical variables. Adjusted least-square mean values by *ACTN3* R577X genotype for muscle and physical performance phenotypes were estimated in both cohorts using analysis of covariance (ANCOVA). For incident PLL, Cox's proportional hazards models were used while adjusting for potential confounders. Statistical significance was considered when the alpha was <0.05. Analyses were conducted with SAS (version 9.1; SAS Institute Inc., Cary, NC).

Results

Genotype Results

In the Health ABC cohort, genotype distribution for all participants with genotype data fit Hardy–Weinberg equilibrium with a distribution of RR = 473 (30%), RX = 777 (50%), XX = 301 (19%) (χ^2 = 0.32, *df* =1, *p* = .570). In the MrOS cohort, the genotype distribution of the white participants met the expectations of Hardy–Weinberg equilibrium with a genotype distribution of RR = 361 (31%), RX =551 (48%), XX =240 (21%) (χ^2 =1.23, *df* =1, *p* = .540).

Characteristics of the 1367 Health ABC participants by sex and *ACTN3* genotype group are shown in Table 1. In men, there was a significant difference between the three genotype groups only for physical activity (*p* = .020). There were no differences between any of the other characteristics in men, and there were no differences in participant characteristics by *ACTN3* genotype group in women. Table 2 shows the baseline participant characteristics of the 1152 men from the MrOS cohort by *ACTN3* genotype group. There was an overall between-genotype difference only in weight, with heterozygotes weighing slightly less than R- and X-homozygotes (*p* = .039). There were no other baseline characteristic differences between genotype groups in the MrOS cohort.

Table 3 shows the adjusted baseline differences in muscle and performance phenotypes by sex and *ACTN3* genotype in the Health ABC cohort. There were no adjusted differences between genotype groups in men or women for these phenotypes (all $p > .05$). Table 4 shows the mean baseline differences between *ACTN3* genotype groups for muscle and performance phenotypes at baseline in the MrOS cohort. There were no adjusted differences between genotype groups for any of the phenotypes.

Five-year changes in muscle and performance phenotypes by sex and *ACTN3* genotype in the Health ABC cohort are shown in Table 5. In men, there was a significant difference across genotypes ($p = .030$) for adjusted increases in 400-meter walk time. Individual genotype group comparisons show that adjusted 400-meter walk time in X-homozygotes increased to a greater extent than in R-homozygotes ($p = .008$) and heterozygotes ($p = .075$). These associations were not observed in women. There were no other differences between genotype groups for age-related changes in muscle or performance phenotypes in men or women (Table 5).

Incident PLL risk in men and women in the Health ABC cohort by *ACTN3* genotype group are shown in Table 6. In women, R-homozygotes had a ~35% lower risk of adjusted incident PLL compared to X-homozygotes (hazard ratio = 0.65, 95% confidence interval = 0.44–0.94). There were no other adjusted or unadjusted differences for the risk of incident PLL between *ACTN3* genotype groups in men or women.

Four-year changes in muscle and performance phenotypes by *ACTN3* genotype in the MrOS cohort are shown in Table 7. There were no differences between genotype groups for age-related adjusted changes in these phenotypes.

Discussion

To our knowledge, this is the first study to examine the influence of the *ACTN3* R577X polymorphism on a diverse array of important skeletal muscle and performance phenotypes in two large, well-characterized cohorts of older adults. Moreover, this study was also able to determine the influence of the *ACTN3* R577X genotype on changes in these key phenotypes with at least 4 years of aging. Although the *ACTN3* R577X polymorphism does not appear to influence baseline skeletal muscle phenotypes, our results indicate that the *ACTN3* X-homozygous genotype may play a small role in hastening the decline in 400-meter walk time in men with age and may increase risk of functional limitation in women. Our findings do not support an extensive influence of *ACTN3* genotype on typical muscle phenotypes and provide only weak support for a potential age-related influence on the decline of physical function in late life.

It is unclear why there were only differences in 400-meter walk time in men by *ACTN3* genotype. Previous reports have shown that the *ACTN3* genotype may be sex specific, with greater effects observed on skeletal muscle–related phenotypes in women (4,5). The results of the present investigation showing a difference in incident functional limitation in only women by *ACTN3* genotype is consistent with the findings of those previous investigations. However, there were no other associations observed in women, which suggests that the influence of the *ACTN3* genotype does not have a strong effect on these phenotypes. One possible explanation for the unexpected 400-meter-walk finding in men could be that there were a host of phenotypes examined, which could have led to a spurious association due to chance. Moreover, the 400-meter-walk results by genotype, although not significant, were in the opposite direction in women, and there was not a similar phenotype in the MrOS cohort to confirm the results in men. However, the association between changes in 400-meter walk time and *ACTN3* genotype was in the expected direction, with X-homozygotes showing greater increases in walk time.

The lack of an association between the *ACTN3* R577X genotype and baseline skeletal muscle traits is somewhat surprising given the recent findings that the *ACTN3* R577X genotype has a significant influence on physical and muscle performance in younger cohorts and in athletes (5,7,8,27) and based on the large sample size of the current study. However, the previously observed associations between the *ACTN3* polymorphism and skeletal muscle-related phenotypes have been observed primarily in the presence of interventions such as exercise training (4,9). Although some cross-sectional reports also indicate an association between athletic performance and the *ACTN3* genotype, these participants were highly trained athletes and may not be representative of the general population (5–8,28). Nevertheless, our findings support those from smaller cross-sectional cohorts that the *ACTN3* polymorphism does not explain a significant proportion of the variability in muscle phenotypes in older adults (9,10).

The considerable changes in skeletal muscle structure and physiology that occur with age may be at least a partial explanation for the lack of a significant relationship between skeletal muscle phenotypes and the *ACTN3* R577X polymorphism. For example, there are many structural changes in skeletal muscle that occur with age, including increased fat and connective tissue within skeletal muscle, loss of motor units, and the loss of type II muscle fibers (29). This loss of type II muscle fibers may be particularly important with regard to the influence of the *ACTN3* R577X SNP in elderly persons, as ACTN-3 is expressed in this fiber type only. A significant loss of type II fibers would have a much greater influence on muscle function than would merely a lack of ACTN-3 expression alone, and would amplify the importance of type I skeletal muscle fibers in physical functioning. In addition, recent research has found that type IIx fiber number is lower in X-homozygotes than in R-homozygotes (14). Other recent findings (30) in *ACTN3* knockout mice indicate that metabolic and structural properties of type II skeletal muscle fibers change to favor endurance performance. These data suggest a mechanistic pathway by which the *ACTN3* genotype may influence muscle performance. However, these findings have not been confirmed in older adults. Further exploration of the functional contributions of the ACTN-3 protein would help to clarify whether this polymorphism should continue to be investigated with regard to its association with physical performance.

Although there are numerous strengths of the current investigation, there are several potential limitations that should be addressed. First, the MrOS cohort should not be considered a true validation cohort for the Health ABC cohort based on current standards (31), as not all of the phenotypes were the same or measured in the same way and the MrOS sample did not include women. However, a meaningful genetic influence should be strong enough to capture closely related phenotypes. Second, there was some loss to follow-up in both cohorts that may have biased our results. However, the X-homozygote genotype frequency in both the baseline and follow-up subsamples were ~20%, suggesting that this loss to follow-up was unlikely related to *ACTN3* genotype. Third, skeletal muscle and performance phenotypes are complex phenotypes that are influenced by environmental/lifestyle factors and numerous genetic factors. We did not consider the entire complement of candidate gene polymorphisms in the present analysis. There are likely complex Gene × Gene and Gene × Environment interactions not yet explored that could help to explain inter-individual variability in muscle phenotypes. Finally, although the length of follow-up observed in the present investigation has been shown to be long enough to observe significant phenotype changes in older adults (21,32,33), a longer follow-up interval may be necessary.

Summary

Although the *ACTN3* R577X polymorphism was associated with two longitudinal measures of physical functioning, it does not appear to play a strong or consistent role in the age-related declines in physical functioning in older adults. Additionally, the *ACTN3* R577X

polymorphism does not appear to play a significant role in baseline skeletal muscle phenotypes in the general population of older adults. Continued examination of this candidate gene is warranted for intervention studies, as this gene has been shown to explain a greater proportion of trait variance in response to interventions such as resistance training (4,9). Additional studies with a longer follow-up in older adults and with measures that are more specific to type II muscle fiber functioning, such as peak movement velocity, may also help to determine if this polymorphism plays a significant role in muscle function in the aging process.

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References

1. Arden NK, Spector TD. Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J Bone Miner Res 1997;12:2076–2081. [PubMed: 9421240]
2. Huygens W, Thomis MA, Peeters MW, Vlietinck RF, Beunen GP. Determinants and upper-limit heritabilities of skeletal muscle mass and strength. Can J Appl Physiol 2004;29:186–200. [PubMed: 15064427]
3. Buchner DM, Cress ME, de Lateur BJ, Wagner EH. Variability in the effect of strength training on skeletal muscle strength in older adults. Facts Res Gerontol 1993;7:143–153.
4. Clarkson PM, Devaney JM, Gordish-Dressman H, et al. ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. J Appl Physiol 2005;99:154–163. [PubMed: 15718405]
5. Yang N, MacArthur DG, Gulbin JP, et al. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet 2003;73:627–631. [PubMed: 12879365]
6. Santiago C, Gonzalez-Freire M, Serratosa L, et al. ACTN3 genotype in professional soccer players. Br J Sports Med 2008;42:71–73. [PubMed: 17550918]
7. Papadimitriou ID, Papadopoulos C, Kouvatsi A, Triantaphyllidis C. The ACTN3 gene in elite Greek track and field athletes. Int J Sports Med 2008;29:352–355. [PubMed: 17879893]Epub 2007 Sep 18
8. Roth SM, Walsh S, Liu D, Metter EJ, Ferrucci L, Hurley BF. The ACTN3 R577X nonsense allele is under-represented in elite-level strength athletes. Eur J Hum Genet 2008;16:391–394. [PubMed: 18043716]
9. Delmonico MJ, Kostek MC, Doldo NA, et al. Alpha-actinin-3 (ACTN3) R577X polymorphism influences knee extensor peak power response to strength training in older men and women. J Gerontol A Biol Sci Med Sci 2007;62:206–212. [PubMed: 17339648]
10. San Juan AF, Gomez-Gallego F, Canete S, Santiago C, Perez M, Lucia A. Does complete deficiency of muscle alpha actinin 3 alter functional capacity in elderly women? A preliminary report. Br J Sports Med 2006 Jan;40(1):e1. [PubMed: 16371478]
11. North KN, Yang N, Wattanasirichaigoon D, Mills M, Easteal S, Beggs AH. A common nonsense mutation results in alpha-actinin-3 deficiency in the general population. Nat Genet 1999;21:353–354. [PubMed: 10192379]
12. Vainzof M, Costa CS, Marie SK, et al. Deficiency of alpha-actinin-3 (ACTN3) occurs in different forms of muscular dystrophy. Neuro-pediatrics 1997;28:223–228.
13. Mills MA, Yang N, Weinberger RP, et al. Differential expression of the actin-binding proteins, α-actinin-2 and -3, in different species: implications for the evolution of functional redundancy. Hum Mol Gen 2001;10:1335–1346. [PubMed: 11440986]

14. Vincent B, De Bock K, Ramaekers M, et al. ACTN3 (R577X) genotype is associated with fiber type distribution. Physiol Genomics 2007;32:58–63. [PubMed: 17848603]
15. Newman AB, Haggerty CL, Goodpaster B, et al. Strength and muscle quality in a well-functioning cohort of older adults: the Health, Aging and Body Composition study. J Am Geriatr Soc 2003;51:323–330. [PubMed: 12588575]
16. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study—a large observational study of the determinants of fracture in older men. Contemp Clin Trials 2005;26:569–585. [PubMed: 16084776]
17. Blank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). Contemp Clin Trials 2005;26:557–568. [PubMed: 16085466]
18. Visser M, Kritchevsky SB, Goodpaster BH, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition study. J Am Geriatr Soc 2002;50:897–904. [PubMed: 12028178]
19. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–561. [PubMed: 7838189]
20. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94. [PubMed: 8126356]
21. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA 2006;295:2018–2026. [PubMed: 16670410]
22. Harkonen R, Harju R, Alaranta H. Accuracy of the Jamar dynamometer. J Hand Ther 1993;6:259–262. [PubMed: 8124439]
23. Bassey EJ, Short AH. A new method for measuring power output in a single leg extension: feasibility, reliability and validity. Eur J Appl Physiol 1990;60:385–390.
24. Bassey EJ, Fiatarone MA, O'Neill EF, Kelly M, Evans WJ, Lipsitz LA. Leg extensor power and functional performance in very old men and women. Clin Sci 1992;82:321–327. [PubMed: 1312417]
25. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exer 2000;32:S498–S516.
26. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153–162. [PubMed: 8437031]
27. Moran CN, Yang N, Bailey ME, et al. Association analysis of the ACTN3 R577X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks. Eur J Hum Genet 2007;15:88–93. [PubMed: 17033684]
28. Niemi AK, Majamaa K. Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes. Eur J Hum Genet 2005;13:965–969. [PubMed: 15886711]
29. Lexell J. Human aging, muscle mass, and fiber-type composition. J Gerontol A Biol Sci Med Sci 1995;50:11–16. [PubMed: 7493202]
30. MacArthur DG, Seto JT, Chan S, et al. An Actn3 knockout mouse provides mechanistic insights into the association between {alpha}-actinin-3 deficiency and human athletic performance. Hum Mol Genet 2008;17:1076–1086. [PubMed: 18178581]Epub 2008 Jan 4
31. Chanock SJ, Manolio T, Boehnke M, et al. Replicating genotype-phenotype associations 1. Nature 2007;447:655–660. [PubMed: 17554299]
32. Kritchevsky SB, Nicklas BJ, Visser M, et al. Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. JAMA 2005;294:691–698. [PubMed: 16091571]
33. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61:72–77. [PubMed: 16456196]

Table 1

Baseline Characteristics of White Health, Aging and Body Composition Study Participants by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group (*N* = 1367)

	Men (*N* = 726)				Women (*N* = 641)			
Characteristic	**RR (*n* = 234)**	**RX (*n* = 348)**	**XX (*n* = 144)**	***p* Value**	**RR (*n* = 186)**	**RX (*n* = 330)**	**XX (*n* = 125)**	***p* Value**
Age, y	73.7 (3.0)	73.9 (2.7)	74.2 (3.0)	.228	73.6 (2.6)	73.6 (2.8)	73.4 (3.1)	.909
Height, cm	174.1 (6.4)	173.5 (6.7)	173.6 (5.7)	.524	159.6 (6.3)	159.4 (5.5)	159.0 (6.1)	.681
Weight, kg	82.3 (12.9)	81.1 (12.2)	81.9 (12.7)	.512	66.4 (12.9)	65.8 (11.3)	66.5 (12.0)	.787
Body mass index, kg/m^2	27.1 (3.9)	26.9 (3.6)	27.1 (3.7)	.762	26.0 (4.9)	25.9 (4.3)	26.3 (4.5)	.693
Fat-free mass, kg	58.3 (7.3)	57.1 (6.8)	58.3 (7.2)	.084	40.2 (5.4)	39.5 (5.1)	40.0 (5.2)	.289
Fat mass, kg	24.0 (7.0)	23.9 (6.8)	23.5 (6.7)	.824	26.3 (8.5)	26.3 (7.3)	26.7 (7.6)	.880
Body fat, %	27.8 (4.6)	29.1 (4.9)	28.2 (4.5)	.226	38.7 (6.0)	39.2 (5.4)	39.3 (5.4)	.500
Physical activity, kcal/wk	7630 (6416)	6290 (5165)	7021 (5632)	.020	5722 (4233)	5743 (4271)	6102 (4544)	.693

Note: Values are means (standard deviation).

Table 2

Baseline Characteristics of White Osteoporotic Fractures in Men Study Participants by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group (*N* = 1152)

Characteristic	RR (*N* = 361)	RX (*N* = 551)	XX (*N* = 240)	*p* Value
Age, y	73.4 (5.8)	73.9 (5.7)	73.9 (5.5)	.410
Height, cm	173.5 (6.6)	173.0 (6.6)	173.6 (6.8)	.306
Weight, kg	85.1 (14.6)	83.4 (12.7)	85.8 (13.2)	.039
Body mass index, kg/m^2	28.2 (4.4)	27.9 (3.9)	28.5 (4.1)	.142
Fat-free mass, kg	60.5 (7.8)	59.9 (7.3)	61.1 (7.4)	.109
Fat mass, kg	22.9 (7.7)	22.0 (6.8)	23.0 (7.0)	.092
Body fat, %	26.9 (5.5)	26.4 (5.2)	26.9 (5.2)	.334
Physical activity (PASE) score	151.5 (63.9)	149.1 (62.3)	154.2 (62.3)	.563

Notes: Values are means (standard deviation). PASE = Physical Activity Scale for the Elderly.

Table 3

Baseline Differences in Grip Strength, Knee Extensor Torque, Thigh Muscle Area, Muscle Quality, SPPB Score, 400-Meter Walk Time, and Ability to Complete 400-Meter Walk Measures in White Health, Aging and Body Composition Study Participants (*N* = 1367) by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group and Sex

	Men (*N* = 726)				Women (*N* = 641)			
Characteristic	**RR (*n* = 234)**	**RX (*n* = 348)**	**XX (*n* = 144)**	***p* Value**	**RR (*n* = 186)**	**RX (*n* = 330)**	**XX (*n* = 125)**	***p* Value**
Average quadriceps torque, N-m*	128 ± 4	129 ± 4	133 ± 4	.318	78 ± 2	77 ± 2	78 ± 2	.901
Midthigh muscle area, cm^{2}†	127 ± 2	125 ± 2	128 ± 2	.205	86 ± 1	86 ± 1	85 ± 1	.683
Muscle quality, N-m/cm^{2}‡	2.15 ± 0.05	2.14 ± 0.05	2.20 ± 0.06	.329	1.94 ± 0.05	1.95 ± 0.04	1.98 ± 0.05	.680
Grip strength, kg	37 ± 0.9	37 ± 0.9	37 ± 1.0	.977	22 ± 0.6	22 ± 0.5	23 ± 0.6	.529
SPPB score	10.3 ± 0.2	10.2 ± 0.2	10.3 ± 0.2	.515	10.0 ± 0.2	9.9 ± 0.1	10.0 ± 0.2	.481
400-meter walk, s	325 ± 6	322 ± 6	323 ± 6	.829	343 ± 6	340 ± 6	338 ± 7	.726
Inability to complete 400-meter walk, *n* (%)	26 (11.1)	48 (13.8)	23 (16.0)	.381	36 (19.4)	66 (20.0)	22 (17.6)	.828

Notes: Values are least square means ± standard error of the mean adjusted for baseline age, body mass index, alcohol use, comorbidity, smoking, study site, physical activity, ace inhibitor use, diuretic use, and antiinflammatory medication use.

* Isokinetic torque at an angular velocity of 60 degrees/s.

† Midthigh cross-sectional area measured from computed tomography.

‡ Peak torque/quadriceps muscle area.

SPPB = short physical performance battery (sum of three subscores).

Table 4

Baseline Leg Muscle Power, Thigh Fat-Free Mass (FFM), Muscle Power Quality, Grip Strength, and Measures of Physical Functioning Measures in White Osteoporotic Fractures in Men Study Participants (*N* = 1152) by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group

Characteristic	RR (*N* = 361)	RX (*N* = 551)	XX (*N* = 240)	*p* Value
Peak power, W*	205 ± 20	197 ± 21	199 ± 21	.298
Thigh muscle FFM, kg	20.0 ± 7.6	19.8 ± 7.7	20.0 ±7.8	.393
Muscle power quality, W/kg†	10.5 ± 1.0	10.2 ± 1.0	10.2 ± 1.0	.379
Grip strength, kg	43 ± 3	42 ± 3	43 ± 3	.504
Five-chair-stand time, s	11.6 ± 1.2	11.7 ± 1.3	12.0 ± 1.3	.403
6-Meter walk, m/s	1.22 ± 0.1	1.20 ± 0.1	1.25 ± 0.1	.123

Notes: Values are least square means ± standard error of the mean adjusted for baseline age, study site, comorbidity, body mass index, alcohol use, smoking status, physical activity, androgen use, ace inhibitor use, diuretic use, and antiinflammatory medication use.

* Peak power of both legs using the Nottingham Power Rig.

† Peak muscle power/thigh FFM.

Table 5

Five-Year Follow-Up Changes in Grip Strength, Knee Extensor Torque, Thigh Muscle Area, Muscle Quality, SPPB Score, and 400-Meter Walk Time in White Health, Aging and Body Composition Study Participants (*N* = 995) by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group and Sex

	Men (*N* = 529)				Women (*N* = 466)			
Characteristic	**RR (*n* = 171)** *	**RX (*n* = 258)** †	**XX (*n* = 100)** ‡	***p* Value**	**RR (*n* = 137)** §	**RX (*n* = 242)**‖	**XX (*n* = 89)**¶	***p* Value**
Average quadriceps torque, N-m#	−25 ± 3	−27 ± 2	−25 ± 3	.708	−10 ±1	−13 ± 1	−13 ± 2	.119
Midthigh muscle area, cm^2	−6.1 ± 0.9	−6.8 ± 0.8	−6.8 ± 1.1	.690	−1.3 ± 0.6	−1.4 ± 0.5	−2.0 ± 0.7	.662
Muscle quality, N-m/cm^2**	−0.31 ± 0.04	−0.36 ± 0.04	−0.33 ± 0.05	.491	−0.23 ± 0.03	−0.27 ± 0.03	−0.31 ± 0.04	.184
Grip strength, kg	−2.7 ± 0.7	−3.5 ± 0.6	−2.7 ± 0.8	.369	−1.5 ± 0.5	−1.4 ± 0.5	−2.2 ± 0.6	.468
SPPB score	−0.7 ± 0.2	−0.8 ± 0.1	−0.6 ± 0.2	.664	−0.6 ± 0.2	−0.8 ± 0.2	−0.6 ± 0.2	.597
400-Meter walk, s	20.6 ± 7.5	29.2 ± 6.6	43.4 ± 8.7	.030	32.9 ± 5.9	26.0 ± 5.2	24.7 ± 7.0	.417

Notes: Values are LS least square means ± standard error of the mean adjusted for baseline age, body mass index, alcohol use, comorbidity, smoking status, study site, physical activity, body weight change, and baseline values.

* Missing data points: 9 for muscle area, 2 for grip strength, 23 for muscle quality, 71 for 400-m walk, and 4 for SPPB.

† Missing data points: 11 for muscle area, 6 for peak torque, 33 for muscle quality, 75 for 400-m walk, and 6 for SPPB.

‡ Missing data points: 1 for muscle area, 14 for muscle quality, 30 for 400-m walk, and 1 for SPPB.

§ Missing data points: 6 for muscle area, 3 for peak torque, 5 for grip strength, 27 for muscle quality, 59 for 400-m walk.

‖ Missing data points: 5 for muscle area, 9 for peak torque, 43 for muscle quality, 90 for 400-m walk, and 2 for SPPB.

¶ Missing data points: 3 for muscle area, 8 for peak torque, 18 for muscle quality, 34 for 400-m walk, and 2 for SPPB.

Isokinetic torque at an angular velocity of 60 degrees/s.

** Peak torque/quadriceps muscle area.

SPPB = short physical performance battery (sum of three subscores).

Table 6

Incident Persistent Lower Extremity Limitation (PLL) in White Health, Aging and Body Composition Study Participants by Sex and Alpha-Actinin-3 (*ACTN3*) R577X Genotype (*N* = 1367)

Incident PLL	*N*	Number of Events	Events/100 Person-Years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Men (*n* = 726)					
RR	234	70	8.2	1.02 (0.70–1.50)	1.03 (0.76–1.66)
RX	348	93	7.2	0.90 (0.63–1.30)	0.95 (0.65–1.37)
XX	144	42	8.1	1.00	1.00
Women (*n* = 641)					
RR	186	57	8.5	0.64 (0.44–0.93)	0.65 (0.44–0.94)
RX	330	126	11.0	0.82 (0.60–1.12)	0.89 (0.65–1.23)
XX	125	55	13.5	1.00	1.00

Notes: Data presented are raw and adjusted hazard ratios (HR) and 95% confidence intervals (CI).

*Data adjusted for baseline age, body mass index, comorbidity, smoking status, alcohol use, study site, and physical activity.

Table 7

Four-Year Changes in Grip Strength, Leg Muscle Power, Thigh Fat-Free Mass, Muscle Quality, and Physical Functioning Measures in White Osteoporotic Fractures in Men Study Participants by Alpha-Actinin-3 (*ACTN3*) R577X Genotype Group

Characteristic	RR (*N* = 274)*	RX (*N* = 392)†	XX (*N* = 185)‡	*p* Value
Peak power, W§	−37 ± 4	−45 ± 4	−41 ± 54	.181
Thigh muscle FFM, kg	−0.6 ± 0.1	−0.7 ± 0.1	−0.6 ± 0.1	.573
Muscle power quality, W‖	−1.7 ± 0.2	−2.1 ± 0.2	−1.8 ± 0.2	.303
Grip strength, kg	−2.9 ± 0.4	−2.8 ± 0.4	−1.7 ± 0.5	.092
Five-chair-stand time, s	1.0 ± 0.3	1.1 ± 0.2	1.2 ± 0.3	.798
6-Meter walk, m/s × 10^{-1}	−1.4 ± 0.1	−1.4 ± 0.1	−1.6 ± 0.2	.568

Notes: Values are LS means ± standard error of the mean adjusted for baseline age, body mass index, comorbidity, alcohol use, smoking status, physical activity, study site, baseline values, and body weight change.

*Missing data points: 100 for peak power, 103 for muscle power quality, 12 for grip strength, 39 for five chair stands, and 7 for 6-meter walk.

†Missing data points: 172 for peak power, 173 for muscle power quality, 22 for grip strength, 52 for five chair stands, and 18 for 6-meter walk.

‡Missing data points: 71 for peak power, 72 for muscle power quality, 13 for grip strength, 38 for five chair stands, and 11 for 6-meter walk.

§Peak power of both legs using the Nottingham Power Rig.

‖Peak muscle power/thigh FFM.

FFM = fat-free mass.