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ORIGINAL ARTICLE

History-dependent force, angular velocity and muscular endurance in *ACTN3* genotypes

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Abstract
Purpose This study aimed at determining the influence of the *ACTN3* R577X polymorphism on muscle strength and muscle endurance in non-athletic young men.
Methods 266 healthy young men were included in this study. Each subject performed maximal isometric, concentric and eccentric contractions of the knee extensor muscles on an isokinetic dynamometer. Force depression, force enhancement and the fatigue index were derived from these data. In addition, handgrip strength, squat jump (SJ) and counter movement jump (CMJ) height were obtained.
Results Our group included 83 RR (31 %), 131 RX (49 %) and 52 XX (20 %) individuals. The muscle bone cross-sectional area of the thigh was 5 % higher in RR compared to XX individuals ($P = 0.033$). RR genotypes showed 6 % higher handgrip strength compared to the XX group ($P = 0.047$). They also jumped 5 % higher in both the SJ and CMJ tests ($P = 0.029$; $P = 0.031$). No differences were found in force depression, force enhancement, isometric or eccentric strength. The relative concentric knee torque at 200°/s and at 300°/s was 7 and 8 % higher in RR compared to XX genotypes, respectively ($P = 0.049$; $P = 0.048$). Also, the fatigue index was found to be 4 % lower in XX genotypes ($P = 0.037$).
Conclusions Our findings are in agreement with the higher prevalence of the RR genotype in power-oriented activities. The better fatigue index of XX genotypes may be beneficial in endurance-type activities.

Keywords Force enhancement · Force depression · α-Actinin-3 · Association study

Abbreviations

ANOVA	Analysis of variance
CMJ	Counter movement jump
DNA	Deoxyribonucleic acid
EDTA	Ethylene-diamineteraacetic acid
FD	Force depression
FE	Force enhancement
FI	Fatigue index
KO	Knock-out
MBA	Cross-sectional muscle and bone area
SJ	Squat jump
yr	Year

Introduction

To date, over 200 genes have been associated with different aspects of physical performance. One of the most promising genes is *ACTN3* as it shows a genotype and performance association across several athletic and non-athletic cohorts. This gene encodes for α-actinin-3, which is a major structural protein of the Z-disk where it crosslinks

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actin filaments to maintain the myofibrillar array of the sarcomere and interacts with a large number of signaling, metabolic and structural proteins such as titin (Calura et al. 2008). While the homologous α-actinin-2 is expressed in all muscle fibers, α-actinin-3 is only present in fast muscle fibers, which are responsible for producing rapid powerful contractions, but are less resistant to fatigue. A deficiency in α-actinin-3 might, therefore, alter the performance of type II fibers and consequently muscle force generation and resistance to fatigue.

In humans, α-actinin-3-deficiency is common due to the *ACTN3* R577X polymorphism (North et al. 1999). Individuals homozygous for the X-allele lack α-actinin-3 in their skeletal muscles, while carriers of the functional R-allele show normal expression of this protein. This mutation does not lead to a disease phenotype, likely due to compensation by α-actinin-2. However, the high degree of conservation of the *ACTN3* gene points towards functions independent of α-actinin-2.

Several independent studies show a reduced frequency of the XX genotype in sprint and power athletes [reviewed in (Eynon et al. 2013; Ma et al. 2013)]. In line, non-athletic RR individuals show faster sprint times, higher maximal strength production during high-velocity movements, higher muscle mass and fast fiber area than XX individuals (Vincent et al. 2007; Zempo et al. 2010). Extra evidence is provided by the *Actn3* KO mouse model which mimics the phenotype of human α-actinin-3 deficiency. KO mice have decreased muscle mass, type II_b fiber diameter, grip strength and absolute muscle force compared to wild-type mice (Chan et al. 2011; MacArthur et al. 2008). These data suggest that loss of α-actinin-3 is detrimental to the generation of rapid forceful contractions.

However, most studies did not find a decreased muscle force in XX participants during concentric movements (Hanson et al. 2010; Norman et al. 2009). Yet, the contraction speed in the majority of these studies was limited, while the angular velocity of the knee during activities such as sprinting can reach more than 1000°/s with both concentric and eccentric components (Kivi et al. 2002). Vincent et al. (2007) reported a higher relative torque at 300°/s in RR compared to XX genotypes. Measurements at 400°/s were not reliable due to the inability of 15 % of the total group to perform the muscle extensions qualitatively correct at this speed. Therefore, concentric torques at velocities up to 300°/s will be measured in this study. In addition, handgrip strength, squat jump height, counter movement jump height and isometric torque at three knee angles (5°, 45° and 85°) will be determined. As α-actinin-3 is thought to protect the muscle during eccentric movements, the maximal force during eccentric contractions will be tested (Seto et al. 2011; Vincent et al. 2010).

Muscle force is known to be contraction-history dependent. History dependence is the effect that the history of contraction has on the steady-state (isometric) force. The force that a muscle can produce at a final length depends on the type of contraction to reach this final length. Force enhancement (FE) and force depression (FD) describe the higher and lower isometric force depending on the preceding contraction history (eccentric versus concentric, respectively). The cellular mechanisms behind these phenomena are still unclear and under debate. Stress-induced inhibition of cross-bridge attachment is proposed to contribute to FD, although other factors may be involved (Joumaa et al. 2012). Whether the Z-line plays a mechanistic role in explaining these observations has not been investigated yet. Therefore, we want to explore if variation observed in FE and FD can partially be explained by *ACTN3* R577X genotype.

Although the XX genotype is detrimental during power activities, the loss of α-actinin-3 may be advantageous during endurance events. An over-representation of the XX genotype was found in endurance athletes, yet not consistent in all studies [reviewed in (Eynon et al. 2013; Ma et al. 2013)]. XX individuals show a higher skeletal muscle metabolic efficiency, a higher resistance to fatigue and higher rates of VO_{2max}, all factors that are beneficial during endurance activities (MacArthur et al. 2007; Pimenta et al. 2013). The KO mouse model also shows evidence for a beneficial effect of the X-allele on endurance capacity. *Actn3* KO mice can run 33 % further prior to exhaustion and have enhanced adaptive response to endurance training compared to wild-type mice (MacArthur et al. 2007). Fast muscle fibers of KO mice have enhanced recovery from fatigue, longer twitch half-relaxation times, a reduced use of the anaerobic pathway and increased activity of oxidative enzymes (Chan et al. 2008; MacArthur et al. 2008).

As the overall endurance has already been associated with the *ACTN3* R577X polymorphism in young men, we will focus on muscular endurance specifically in the leg muscles by completing a fatiguing protocol on the isokinetic dynamometer. Avoiding or delaying the decline in the capacity to generate force over repeated contractions in time can result in an improved performance. When compared to power athletes, endurance athletes showed better results on fatigue parameters assessed in isokinetic knee flexion and extension fatiguing protocols (Rainoldi et al. 2008). Thus, fatigue index, which reflects the percentage of force drop caused by the fatiguing protocol, is hypothesized to be lower in XX genotypes.

Methods

Participants

In total, 266 healthy male students/volunteers (age 20.9 ± 2.5 years) gave written consent to participate in this

study after being fully informed of the study protocol and procedures. The Ethics Committee of the Faculty of Medicine of KU Leuven approved the study protocol. All experiments were conducted in conformity with the principles of the 1964 declaration of Helsinki and its later amendments. The participants were recruited by announcements among the local student population. Inclusion criteria on admission were male, non-smokers, ages 18–25 years and in good health. Exclusion criteria were acute or chronic disease, consistent intake of medication or nutrition supplements of any kind during a period of 6 months before the study, any medical condition that might contra-indicate high-intensity exercise and a history of consistent resistance training in a period of 12 months before the study.

Measurements

Anthropometric measurements were taken from all participants to calculate fat-free mass and percentage body fat. Skinfolds of the triceps, biceps, subscapular and suprailiacal region were measured to the nearest 0.1 mm using a Harpenden skinfold calliper (Baty, British Indicators RH15 9LB England) to estimate fat-free mass using the standard Durnin and Womersley equation. The Siri-equation was used to assess percentage body fat. Cross-sectional muscle and bone area (MBA) of the thigh (cm^2) was estimated based on the circumference of the mid-thigh corrected for subcutaneous fat at this location. After the anthropometric measurements, handgrip strength, squat jump and counter movement jump height were determined using a handgrip dynamometer (Saehan Corporation, Masan, Korea) and a contact mat (Schmerzal, Wuppertal, Germany), respectively. The SJ tests were performed with both hands on the hips. The best score of three trials was retained for analysis. Further static and dynamic torques of the knee-extensor muscles were determined on a self-constructed computerized active isokinetic dynamometer (servomotor SEW Eurodrive CM90, Bruchsol, Germany) as described in Vincent et al. (2007). The participant was positioned in a backward inclined chair (30°) and alignment of the knee was controlled. The lower leg was fixed to the lever arm at the level of the ankle. After a short familiarization session, maximal isometric extensions at 5°, 45° and 85° knee flexion were registered as static torques (with 0° knee in full extension), with 45 s of rest between contractions. Dynamic torques at 100°, 200° and 300°/s were defined as the registered torque (at 45°) during one extension movement over the complete range of motion (from 85° to 5° knee angle) at each contraction speed. Dynamic torques are expressed in N·m as well as relative to the maximal isometric torque (%). Eccentric torque was measured at the same 45° knee angle during a single maximal knee extension contraction, while knee flexion was forced by the dynamometer at an angular velocity of −100°/s or −200°/s. Force depression was defined as the torque difference between the pure isometric force at 85° and the isometric force at 85° knee angle after a concentric movement at a speed of 100°/s. The torque difference between the isometric force at 5° knee angle after 45 s rest and the isometric force at 5° after an eccentric movement at a speed of 100°/s was defined as force enhancement. At the end of the test protocol, the participants performed a fatiguing protocol existing out of three series of ten concentric contractions at 100°/s. One minute of rest was given between series. Maximal isometric force at 45° knee angle was measured before and after each series to determine the decay in force. The percentage loss of force between the isometric torque at 45° before and after the fatiguing protocol was calculated as the fatigue index (FI). Participants were verbally encouraged to perform at their maximum effort and verbal feedback of their performance was presented after each test. All experiments were performed double-blind as the *ACTN3* R577X genotype of the participants was still unknown during the measurements.

DNA collection and genotyping

DNA was extracted from EDTA blood samples at UZ Leuven using chemagic Magnetic Separation Module I following the protocol of the manufacturer (PerkinElmer, Baesweiler, Germany). The *ACTN3* R577X polymorphism (rs1815739) genotyping was performed using a TaqMan SNP genotyping assay (ID C_590093_1, Applied Biosystems). All reactions were set up manually, and allele calling was done using SDS 1.3 software and visually checked. Genotyping was successful in all 266 participants.

Statistical analyses

A χ^2 test ($df = 1$) was performed to determine deviations of genotype distribution from Hardy–Weinberg equilibrium. Anthropometric and strength measurements were compared between RR and XX homozygotes using Student *t* tests in SAS 9.1. Three-genotype comparisons applying ANOVA are reported in Supplemental Table 1 (see Supplemental Digital Content 1 which presents the results of all variables compared between RR and XX genotypes in this paper with the inclusion of the RX group).

Results

Prevalence of the ACTN3 R577X polymorphism

Our sample included 83 RR (31 %), 131 RX (49 %) and 52 XX (20 %) individuals. This corresponds to an allele

Table 1 Anthropometric characteristics in *ACTN3* 577RR versus 577XX genotypes

	RR	XX	*P* value
N	83	52	
Age (years)	23.5 ± 1.1	22.8 ± 0.3	0.60
Stature (cm)	180.6 ± 0.6	180.3 ± 0.9	0.72
Weight (kg)	73.6 ± 0.8	72.5 ± 1.3	0.46
Body fat (%)	11.7 ± 0.4	11.6 ± 0.5	0.85
MBA (cm^2)	176.7 ± 3.4	167.6 ± 2.6	<0.05

Values are mean ± SE

MBA muscle bone cross-sectional area of the thigh

frequency of 0.56 for the R-allele and 0.44 for the X-allele. The genotype distribution was in agreement with Hardy–Weinberg equilibrium ($\chi^2 = 0.0001$; $P = 0.98$).

Body composition

Somatic characteristics were similar across the XX and RR genotype groups (Table 1) except for the estimated muscle bone cross-sectional area of the thigh (MBA) which was 5 % higher in RR individuals compared to XX genotypes ($P = 0.033$).

Strength characteristics

Analyses of the field strength tests showed that RR individuals on average jumped 5 % higher during both squat jumps ($P = 0.028$) and counter movement jumps ($P = 0.031$). They also had a 6 % higher handgrip strength ($P = 0.046$) compared to XX individuals (Table 2).

No genotype-dependent differences were found in isometric knee force at any angle. The maximal torque during concentric movements was similar between both groups at 100°/s ($P = 0.27$), tended to be higher at 200°/s ($P = 0.099$) and was significantly higher at 300°/s ($P = 0.039$) in the RR group. Expressed relative to their maximal isometric force, dynamic concentric contractions were higher in RR versus XX participants at both 200°/s and 300°/s (Fig. 1). According to the torque–velocity relationship, torque production decreased as contraction velocity increased (test for main effect of velocity: $P < 0.0001$). In contrast, eccentric force was similar in RR and XX individuals at every speed ($0.66 < P < 0.93$).

Of the total group, 242 participants showed a lower muscle force after active shortening, although no differences were found between RR and XX genotypes. This force depression (FD) ranged up to 58 % of the isometric force. On the other hand, only 164 participants had a greater isometric force after an eccentric movement. The highest force enhancement (FE) was 43 %. No differences were found in FE between RR and XX genotypes. In contrast, the fatigue index was 4 % lower in XX homozygotes ($P = 0.037$), indicating that they were able to retain their strength better than RR individuals during the fatiguing protocol.

Table 2 Strength measurements in *ACTN3* 577RR versus 577XX genotypes

	RR	XX	*P* value
Squat jump (cm)	37.4 ± 0.6	35.5 ± 0.6	<0.05
Counter movement jump (cm)	38.3 ± 0.6	36.4 ± 0.6	<0.05
Handgrip strength (kg)	52.6 ± 1.1	49.3 ± 1.2	<0.05
Static			
5° (N·m)	194.3 ± 3.7	191.4 ± 6.0	0.68
45° (N·m)	217.9 ± 4.3	212.7 ± 7.0	0.53
85° (N·m)	111.7 ± 2.3	111.2 ± 3.4	0.90
Concentric			
100°/s (N·m)	140.8 ± 3.3	134.9 ± 4.4	0.27
200°/s (N·m)	102.0 ± 2.7	93.9 ± 4.4	0.10
300°/s (N·m)	82.6 ± 2.6	73.9 ± 3.3	<0.05
Eccentric			
−100°/s (N·m)	235.7 ± 4.7	232.3 ± 6.3	0.66
−200°/s (N·m)	194.3 ± 7.8	195.3 ± 8.7	0.93
Force depression			
Absolute difference (N·m)	−11.9 ± 1.3	−14.2 ± 1.8	0.29
Relative difference (%)	−11.2 ± 1.3	−13.7 ± 1.9	0.25
Force enhancement			
Absolute difference (N·m)	7.5 ± 2.4	4.5 ± 2.2	0.36
Relative difference (%)	4.7 ± 1.3	3.4 ± 1.3	0.51
Fatigue index (%)	16.7 ± 1.1	12.7 ± 1.6	<0.05

Values are mean ± SE

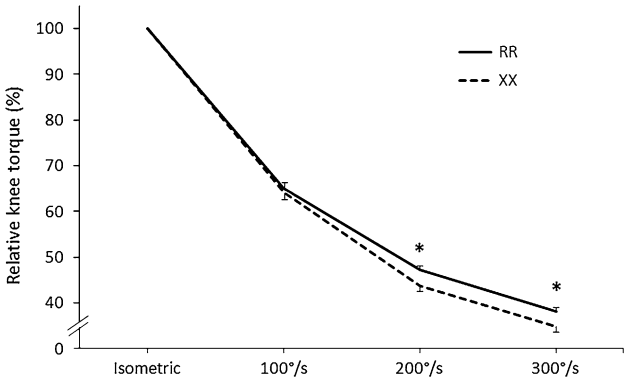

Fig. 1 Relative knee torque production of *ACTN3* 577RR (*solid line*) and 577XX (*dashed line*) genotypes during isometric contraction at 45° and concentric movements at 100°, 200° and 300°/s. Values are mean ± SE of 135 observations and are expressed as the ratio of the torque over maximal static torque at 45°. *$P < 0.05$

Discussion

The main objective of this study was to establish the effect of the *ACTN3* R577X polymorphism on several strength measurements in the lower and upper limbs of non-athletic young men. In our non-athletic cohort, 577XX genotypes were able to retain a higher force after a fatiguing protocol. RR individuals presented higher handgrip strength and higher squat and counter movement jump rates compared to 577XX. Also, the benefit of the R-allele extended with increasing velocities. No genotype-related differences were observed for isometric knee contractions or slow-velocity concentric contraction speed (100°/s). Yet the relative knee extension torque was significantly higher in RR genotypes during concentric movements at 200°/s and at 300°/s.

Although handgrip strength is a frequently used field test and is a simple way to determine the isometric force of the upper limbs, only a few studies investigated the *ACTN3* R577X polymorphism related to handgrip strength. A trend for a higher handgrip strength in 577RR genotypes ($P = 0.09$) was found in a meta-analysis including seven cohorts, although a high proportion of the participants were elderly and children (Alfred et al. 2011). In the adolescent cohort, the RR individuals did have a higher handgrip strength compared to XX individuals (Shang et al. 2012). The higher grip strength in young male RR genotypes found here is in line with those previous studies.

The 577RR group also performed on average 5 % higher squat jumps and counter movement jumps compared to 577XX participants. Similarly, Pimenta et al. (2013) found jump heights to be higher in the RR group in professional soccer players, with a similar difference as found in this study (Pimenta et al. 2013). Other studies were unable to find differences in jump height in relation to the *ACTN3* R577X polymorphism in athletic and non-athletic young men (Ruiz et al. 2010; Santiago et al. 2010).

In contrast, the XX group was able to retain a higher percentage of their force after a fatiguing protocol compared to the RR genotypes. It has been shown that RR individuals have a higher percentage of type II_x fibers, which are less resistant to fatigue than type I fibers (Vincent et al. 2007). Therefore, it is logical that the decline in force is lower in XX genotypes during a fatiguing protocol. As a result, the XX genotype will offer an advantage in endurance type activities.

No difference was found in FE nor in FD between the knee extensor muscles of the RR and XX group. Although the study of FE in human muscle is limited, it has already been observed in the knee extensor muscles using a Biodex machine with mean values ranging from 0 to 5 % (Shim and Garner 2012). These results are similar to the FE values of our RR (4.7 %) and XX group (3.4 %). The isometric force following active shortening of the knee extensor muscles was found to be decreased in 91 % of the total group. This FD was on average −11.9 % with scores ranging from −57.7 to 35.8 % in our group of non-athletic young men, which is higher than the average FD observed by Herzog et al. (Lee et al. 1999). As the mechanisms responsible for this phenomenon are still illusive, it would be too speculative to explain the high variability in FD response observed in this testgroup.

We did find a lower torque production in the knee extensors of XX participants during concentric contractions at high velocities. Vincent et al. (2007) found similar results in the knee extensor muscles (Vincent et al. 2007). The importance of α-actinin-3 during high angular contraction speeds is logical in regard to its function in skeletal muscle. Alpha-actinin-3 protein is only expressed in type II fibers, with the highest expression in the anaerobic type II_x fibers (Vincent et al. 2007). These fibers are responsible for producing forceful contractions at high velocity. Loss of α-actinin-3 could result in altered contractile properties in fast fibers, which could explain the lower maximal torque production of the knee muscles at high velocities in XX genotypes. In the *Actn3* KO mice, loss of α-actinin-3 results in a shift towards slow twitch characteristics in their fast fibers, including a slower contraction speed and a reduced force output (Chan et al. 2008, 2011; MacArthur et al. 2008).

The maximal force output of a muscle or muscle fiber depends highly on the amount of sarcomeres in parallel and thus on the muscle (fiber) diameter. *Actn3* KO mice show a 30 % decrease in diameter of type II_b fibers (which are homological to type II_x fibers in humans). In line, the 577RR group had significantly higher estimated muscle bone areas of the thigh compared to the XX group. This is in accordance with Erskine et al. (2013) who found a significant higher volume of the quadriceps femoris muscle in RR compared to XX genotypes in a testgroup of untrained young men. Interestingly, the higher 1-RM and maximal power observed in R-allele carriers were no longer significant when controlled for the higher muscle volume (Erskine et al. 2013). This was also the case when the concentric torque measurements in our study were controlled for MBA of the thigh ($0.21 < P < 0.99$). These results suggest that the influence of the *ACTN3* R577X polymorphism on dynamic strength measurements may be at least partially due to an alteration in muscle volume. Regrettably, only a small number of studies have reported CSA or muscle volume in relation to torque or strength measurements in the contributing muscles (Delmonico et al. 2008; Zempo et al. 2010). Strong correlations have been described between muscle CSA and isometric strength (Schantz et al. 1983) and, therefore, it is somehow surprising that the greater MBA of the thigh in RR genotypes does not lead to a higher isometric leg extension strength. However, given the restricted expression of

α-actinin-3 to type II fibers, this effect might selectively be picked up at higher contraction speeds. In addition, early studies have shown type II fibers to produce relatively higher force at higher velocities and that this effect is present in the arm flexors at relatively low contraction velocities (60°/s) (Nygaard 1981), however, only at higher velocities in the knee extensors (180°/s) (Thorstensson et al. 1976). This muscle-group specific characteristic might be related—amongst other factors—to our observation of a genotype–phenotype association in handgrip strength while it was not observed in isometric knee extension strength and only at the higher contraction speeds.

The higher volume of skeletal muscle in mice and humans expressing α-actinin-3 in their fast fibers could be the result of a change in muscle fiber composition. Vincent et al. (2007) showed an higher number and percentage surface area of type II_x fibers in RR individuals (Vincent et al. 2007). In line, the XX individual was the only one with type I fibers and completely lacked type II_x fibers in the vastus lateralis in a study of three men with spinal cord injury (1 RR, 1 RX and 1 XX), an injury that leads to immobilization of the lower limb muscles (Broos et al. 2012). Normally, slow fibers undergo a transformation to fast fibers in the immobilized muscle. When the muscles of mice were immobilized, this shift was observed in the muscles of wild-type mice, while there was no evidence for fiber-type conversion in the KO mice (Garton et al. 2013). These data indicate that *Actn3*$^{-/-}$ KO mice and XX genotypes have a higher threshold for fiber conversion towards fast fiber type. Thus, it is possible that the influence of α-actinin-3 on fiber type transformation threshold steers the higher muscle volume and the higher force output (at high velocities) in RR genotypes and as a result the higher frequency of the R-allele in power oriented athletes.

Conclusions

In conclusion, our data show an influence of the *ACTN3* R577X polymorphism on muscle strength phenotypes in non-athletic young men. The improved strength performance of RR compared to XX genotype may be beneficial during power-oriented sports. In contrast, the ability to retain a higher percentage of force over time can be beneficial during long lasting events. Although the differences between the two groups are relatively small, carrying the beneficial allele may give an athlete just that extra bit needed to perform at a higher level.

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Conflict of interest The authors report no conflict of interest.

References

Alfred T, Ben-Shlomo Y, Cooper R, Hardy R, Cooper C, Deary IJ, Gunnell D, Harris SE, Kumari M, Martin RM, Moran CN, Pitsiladis YP, Ring SM, Sayer AA, Smith GD, Starr JM, Kuh D, Day IN (2011) ACTN3 genotype, athletic status and lifecourse physical capability: meta-analysis of the published literature and findings from nine studies. Hum Mutat 32:1008–1018

Broos S, Malisoux L, Theisen D, Francaux M, Deldicque L, Thomis MA (2012) Role of alpha-actinin-3 in contractile properties of human single muscle fibers: a case series study in paraplegics. PLoS One 7:e49281

Calura E, Cagnin S, Raffaello A, Laveder P, Lanfranchi G, Romualdi C (2008) Meta-analysis of expression signatures of muscle atrophy: gene interaction networks in early and late stages. BMC Genomics 9:630

Chan S, Seto JT, MacArthur DG, Yang N, North KN, Head SI (2008) A gene for speed: contractile properties of isolated whole EDL muscle from an alpha-actinin-3 knockout mouse. Am J Physiol Cell Physiol 295:C897–C904

Chan S, Seto JT, Houweling PJ, Yang N, North KN, Head SI (2011) Properties of extensor digitorum longus muscle and skinned fibers from adult and aged male and female Actn3 knockout mice. Muscle Nerve 43:37–48

Delmonico MJ, Zmuda JM, Taylor BC, Cauley JA, Harris TB, Manini TM, Schwartz A, Li R, Roth SM, Hurley BF, Bauer DC, Ferrell RE, Newman AB (2008) Association of the ACTN3 genotype and physical functioning with age in older adults. J Gerontol A Biol Sci Med Sci 63:1227–1234

Erskine RM, Williams AG, Jones DA, Stewart CE, Degens H (2013) The individual and combined influence of ACE and ACTN3 genotypes on muscle phenotypes before and after strength training. Scand J Med Sci Sports. doi:10.1111/sms.12055

Eynon N, Hanson ED, Lucia A, Houweling PJ, Garton F, North KN, Bishop DJ (2013) Genes for elite power and sprint performance: ACTN3 leads the way. Sports Med 43:803–817

Garton FC, Seto JT, Quinlan KG, Yang N, Houweling PJ, North KN (2013) alpha-Actinin-3 deficiency alters muscle adaptation in response to denervation and immobilization. Hum Mol Genet 23:1879–1893

Hanson ED, Ludlow AT, Sheaff AK, Park J, Roth SM (2010) ACTN3 genotype does not influence muscle power. Int J Sports Med 31:834–838

Joumaa V, Macintosh BR, Herzog W (2012) New insights into force depression in skeletal muscle. J Exp Biol 215:2135–2140

Kivi DM, Maraj BK, Gervais P (2002) A kinematic analysis of high-speed treadmill sprinting over a range of velocities. Med Sci Sports Exerc 34:662–666

Lee HD, Suter E, Herzog W (1999) Force depression in human quadriceps femoris following voluntary shortening contractions. J Appl Physiol (1985) 87:1651–1655

Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, Gao L (2013) The association of sport performance with ACE and ACTN3 genetic polymorphisms: a systematic review and meta-analysis. PLoS One 8:e54685

MacArthur DG, Seto JT, Raftery JM, Quinlan KG, Huttley GA, Hook JW, Lemckert FA, Kee AJ, Edwards MR, Berman Y, Hardeman EC, Gunning PW, Easteal S, Yang N, North KN (2007) Loss of ACTN3 gene function alters mouse muscle metabolism and shows evidence of positive selection in humans. Nat Genet 39:1261–1265

MacArthur DG, Seto JT, Chan S, Quinlan KG, Raftery JM, Turner N, Nicholson MD, Kee AJ, Hardeman EC, Gunning PW, Cooney GJ, Head SI, Yang N, North KN (2008) An Actn3 knockout mouse provides mechanistic insights into the association between

alpha-actinin-3 deficiency and human athletic performance. Hum Mol Genet 17:1076–1086

Norman B, Esbjornsson M, Rundqvist H, Osterlund T, von Walden F, Tesch PA (2009) Strength, power, fiber types, and mRNA expression in trained men and women with different ACTN3 R577X genotypes. J Appl Physiol 106:959–965

North KN, Yang N, Wattanasirichaigoon D, Mills M, Easteal S, Beggs AH (1999) A common nonsense mutation results in alpha-actinin-3 deficiency in the general population. Nat Genet 21:353–354

Nygaard E (1981) Skeletal muscle fibre characteristics in young women. Acta Physiol Scand 112:299–304

Pimenta EM, Coelho DB, Barros Coelho EJ, Cruz IR, Morandi RF, de Azambuja PG, Santos Carvalho MR, Silami-Garcia E, De Paz Fernandez JA (2013) Effect of gene ACTN3 on strength and endurance in soccer players. J Strength Cond Res 27:3286–3292

Rainoldi A, Gazzoni M, Merletti R, Minetto MA (2008) Mechanical and EMG responses of the vastus lateralis and changes in biochemical variables to isokinetic exercise in endurance and power athletes. J Sports Sci 26:321–331

Ruiz JR, Fernández del Valle M, Verde Z, Diez-Vega I, Santiago C, Yvert T, Rodriguez-Romo G, Gomez-Gallego F, Molina JJ, Lucia A (2010) ACTN3 R577X polymorphism does not influence explosive leg muscle power in elite volleyball players. Scand J Med Sci Sports 21:e34–e41

Santiago C, Rodriguez-Romo G, Gomez-Gallego F, Gonzalez-Freire M, Yvert T, Verde Z, Naclerio F, Altmae S, Esteve-Lanao J, Ruiz JR, Lucia A (2010) Is there an association between ACTN3 R577X polymorphism and muscle power phenotypes in young, non-athletic adults? Scand J Med Sci Sports 20:771–778

Schantz P, Randall-Fox E, Hutchison W, Tyden A, Astrand PO (1983) Muscle fibre type distribution, muscle cross-sectional area and maximal voluntary strength in humans. Acta Physiol Scand 117:219–226

Seto JT, Lek M, Quinlan KG, Houweling PJ, Zheng XF, Garton F, MacArthur DG, Raftery JM, Garvey SM, Hauser MA, Yang N, Head SI, North KN (2011) Deficiency of {alpha}-actinin-3 is associated with increased susceptibility to contraction-induced damage and skeletal muscle remodeling. Hum Mol Genet 20:2914–2927

Shang X, Zhang F, Zhang L, Huang C (2012) ACTN3 R577X polymorphism and performance phenotypes in young Chinese male soldiers. J Sports Sci 30:255–260

Shim J, Garner B (2012) Residual force enhancement during voluntary contractions of knee extensors and flexors at short and long muscle lengths. J Biomech 45:913–918

Thorstensson A, Grimby G, Karlsson J (1976) Force-velocity relations and fiber composition in human knee extensor muscles. J Appl Physiol 40:12–16

Vincent B, De Bock K, Ramaekers M, Van den Eede E, Van Leemputte M, Hespel P, Thomis MA (2007) ACTN3 (R577X) genotype is associated with fiber type distribution. Physiol Genomics 32:58–63

Vincent B, Windelinckx A, Nielens H, Ramaekers M, Van LM, Hespel P, Thomis MA (2010) Protective role of alpha-actinin-3 in the response to an acute eccentric exercise bout. J Appl Physiol 109:564–573

Zempo H, Tanabe K, Murakami H, Iemitsu M, Maeda S, Kuno S (2010) ACTN3 polymorphism affects thigh muscle area. Int J Sports Med 31:138–142