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The individual and combined influence of ACE and ACTN3 genotypes on muscle phenotypes before and after strength training

The individual and combined influence of *ACE* and *ACTN3* genotypes on muscle phenotypes before and after strength training

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ABSTRACT

Alternative measures of muscle size, strength and power to those used in previous studies could help resolve the controversy surrounding associations between polymorphisms of the angiotensin-I converting enzyme (*ACE*) and alpha-actinin-3 (*ACTN3*) genes and skeletal muscle phenotypes, and the responses to resistance training (RT). To this end we measured quadriceps femoris muscle volume (V_m), physiological cross-sectional area (PCSA), maximum isometric force (F_t), specific force (F_t per unit PCSA), maximum isoinertial strength (1-RM) and maximum power (W_{max}; n=40) before and after 9 wk knee extension RT in 51 previously untrained young men, who were genotyped for the *ACE* I/D and *ACTN3* R577X polymorphisms. *ACTN3* R-allele carriers had greater V_m, 1-RM and W_{max} than XX homozygotes at baseline (all P<0.05) but responses to RT were independent of *ACTN3* genotype (all P>0.05). Muscle phenotypes were independent of *ACE* genotype before (all P>0.05) and after RT (all P>0.01). However, people with the 'optimal' *ACE/ACTN3* genotype combination had greater baseline 1-RM and W_{max} compared to those with the 'sub-optimal' profile (both P<0.0125). We show for the first time that the *ACTN3* R577X polymorphism is associated with human V_m and, independently and in combination with the *ACE* I/D polymorphism, influences 1-RM and W_{max}.

INTRODUCTION

There has been widespread interest in the contribution of genetic differences to the inter-individual variability in human muscle size and strength, and the adaptations to resistance training (RT) (Bray et al. 2009). However, the influence of angiotensin-I converting enzyme (*ACE*) and α-actinin-3 (*ACTN3*) gene polymorphisms remains controversial. The functional *ACE* gene I/D polymorphism is characterised by either the presence (insertion allele, I) or absence (deletion allele, D) of a 287 amino acid base pair fragment within intron 16 on chromosome 17 (Rigat et al. 1990). Accordingly, 3 genotypes exist: II, ID and DD, and D-allele carriers express higher ACE activity than II homozygotes (Rigat, Hubert 1990). ACE converts angiotensin I (Ang I) to Ang II and is expressed in skeletal muscle (Reneland & Lithell 1994), where Ang II has been shown to modulate skeletal muscle hypertrophy in response to mechanical loading (Gordon et al. 2001). Thus, the larger proportion of *ACE* D-allele carriers among elite power athletes compared to endurance athletes and the general population (Nazarov et al. 2001; Woods et al. 2001) suggests that the D-allele may predispose to a larger muscle size and hence greater strength. Yet, in untrained people it is equivocal whether *ACE* I/D genotype is associated with these phenotypes (Charbonneau et al. 2008; McCauley et al. 2009; Pescatello et al. 2006; Thomis et al. 2004; Williams et al. 2005), or the responses to RT (Charbonneau, Hanson 2008; Folland et al. 2000; Pescatello, Kostek 2006; Thomis, Huygens 2004; Williams, Day 2005).

A common single nucleotide polymorphism (SNP) of the human *ACTN3* gene results in either an arginine (R) or a stop codon (X) at amino acid 577 of exon 16 on chromosome 11 (North & Beggs 1996), leading to the existence of 3 genotypes: RR, RX, and XX.

XX homozygotes are unable to produce α-actinin-3, a cytoskeletal protein found only in type II muscle fibres that attaches actin filaments to the Z-line (Beggs et al. 1992; Mills et al. 2001; North et al. 1999). A deficiency in this protein might therefore impair the performance of type II fibres (MacArthur & North 2007) that are larger, able to contract faster and are more powerful than type I fibres (Bottinelli et al. 1996; Gilliver et al. 2009; Widrick et al. 2002), which could explain why XX homozygotes are under-represented among elite power athletes (Yang et al. 2003). However, evidence for an *ACTN3* R577X SNP association with untrained human muscle phenotypes is contentious (Clarkson et al. 2005; McCauley, Mastana 2009; Vincent et al. 2007) and it is unclear which *ACTN3* genotype is associated with the greatest response to RT (Clarkson, Devaney 2005; Delmonico et al. 2007). More comprehensive measures of muscle strength and size, such as maximum force resolved at the tendon, physiological cross-sectional area (PCSA) and specific force (maximum force per unit PCSA), may elucidate associations between muscle phenotype and the *ACE* I/D and *ACTN3* R577X polymorphisms before and/or in response to RT.

Therefore, we aimed to determine whether the *ACE* I/D and *ACTN3* R577X polymorphisms, independently or in combination, were associated with detailed measures of muscle strength, power and size before and after RT. We hypothesised that the *ACE* D-allele and the *ACTN3* R-allele would be associated with greater muscle strength, volume and power in the untrained state, and with greater responses to RT.

MATERIALS AND METHODS

Participants

Fifty-one untrained (no history of strength training in the last 12 mo), healthy Caucasian males [20.3 ± 3.1 years, height 178.1 ± 5.6 cm, body mass 75.4 ± 10.6 kg, body mass index (BMI) 23.7 ± 2.6 $kg \cdot m^{-2}$ (mean ± SD)] provided written informed consent prior to participation in the study, which complied with the Declaration of Helsinki and was approved by the local ethics committee of Manchester Metropolitan University. All participants were recreationally active but did not partake in >3 hours structured physical activity a week, as assessed via interview and questionnaire (Baecke et al. 1982). Participants were instructed to maintain their habitual physical activity levels and dietary behaviour for the duration of the study.

Experimental design

Participants were familiarised with all testing procedures within 14 days before the baseline measurements. Maximum isometric patellar tendon force, quadriceps femoris (QF) muscle volume, PCSA and specific force were determined in the right limb before and after 9 wk unilateral knee extension RT, as previously specified (Erskine et al. 2009; Erskine et al. 2010). Maximum power output (W_{max}) of the same limb was determined before and after RT in a subsample (n = 40) on a modified isokinetic cycle ergometer, as described in detail elsewhere (Erskine et al. 2011). All participants were genotyped for the *ACE* I/D and *ACTN3* R577X polymorphisms.

Progressive resistance training (RT)

Unilateral knee extension RT was performed 3 x wk^{-1} for 9 wk on a standard knee extension machine (Technogym, Gambettola, Italy). The maximum load that could be lifted during one repetition, i.e. the single repetition maximum (1-RM), was not only assessed pre and post 9 wk RT, but also prior to the first session of each week. This enabled us to set the training intensity relative to the 1-RM; thus, the training intensity was increased progressively throughout the 9 wk RT. Each training session consisted of a warm-up set of 10 reps at 40% 1-RM and 4 sets of 10 reps at 80% 1-RM with 2 min rest in between sets. All training sessions were supervised and verbal encouragement was given throughout each session. Compliance with the RT protocol was 100%, i.e. each participant completed all 27 RT sessions.

Maximum isometric patellar tendon force (F_t)

Participants performed maximal voluntary isometric knee extension contractions (MVCs) on a dynamometer (Cybex Norm, Cybex International, Ronkonkoma, USA) at optimum knee joint angle (70-90° knee flexion). Co-contraction torque of the antagonist muscles during MVC was estimated by comparing electromyographic activity of the biceps femoris muscle during MVC knee extension and MVC knee flexion (Reeves et al. 2004). Voluntary QF muscle activation was assessed using the interpolated twitch technique (Erskine, Jones 2009) and the patellar tendon moment arm (d_{PT}) was determined via magnetic resonance imaging (MRI) (Erskine, Jones 2009). True maximal torque (TMT) was calculated by correcting MVC knee extension torque for QF activation and antagonist muscle co-activation. Subsequently, maximum force resolved at the patellar tendon (F_t) was calculated as: $F_t = TMT \cdot d_{PT}^{-1}$

Muscle volume, PCSA and specific force

QF volume (V_m) was calculated by adapting a previously described method that incorporated femur length, the anatomical CSA of each of the 4 constituent QF heads at 40% femur length and a series of regression equations (Morse et al. 2007). Vastus lateralis (VL) muscle fascicle length (L_f) and pennation angle (θ_p) were measured during isometric knee extension MVC using ultrasonography (MyLab25, Esaote Biomedica, Genoa, Italy) at 50% VL length along the mid-sagittal plane. Dividing V_m by L_f provided QF PCSA, which was multiplied by the cosine of VL θ_p to give the reduced QF PCSA. F_t divided by the reduced QF PCSA gave QF muscle specific force (Erskine, Jones 2009).

Maximum power output (W_{max})

W_{max} was assessed on a modified isokinetic cycle ergometer (Lode Standard, Groningen, The Netherlands). The pedals contained strain gauges that registered the foot forces at right angles to the top surface of the pedal (Erskine, Jones 2011). The participant performed a maximal 6 s sprint at five predetermined, randomly assigned isokinetic pedal frequencies (130, 110, 90, 70 and 50 RPM), each separated by 5 min rest. The highest power recorded in the trained limb over all five pedal frequencies was defined as W_{max}.

Blood sampling, DNA extraction and determining *ACE* and *ACTN3* genotype

Automated DNA extraction was performed using a QIAcube (Qiagen, Crawley, UK), following the QIAamp spin protocol for DNA purification from whole blood (drawn from an antecubital vein), as described previously (Erskine et al. 2012). Real-time

polymerase chain reaction (PCR) was used to determine the genotype of the *ACE* and *ACTN3* polymorphisms in each participant. Reactions were carried out on 96-well microtitre plates. Each 10-μL reaction volume contained: 5 μL Genotyping Master Mix (Applied Biosystems, Foster City, USA), 4.3 μL nuclease-free H_2O (Qiagen), 0.5 μL genotyping assay mix (Applied Biosystems), plus 0.2 μL sample DNA at a concentration of ~30 $ng \cdot \mu L^{-1}$ and an A260/A280 ratio of 1.7–1.9. For the *ACTN3* R577X, the respective TaqMan rs1815739 SNP genotyping assay mix (Applied Biosystems) was used, which included the appropriate TaqMan primers and probes. The structures of the three primers (150 nM of each) and VIC (150 nM) and FAM (75 nM) probes contained in the genotyping assay mix for the *ACE* I/D polymorphism were manufactured by Applied Biosystems according to previously described methods (Koch et al. 2005) (Table 1). For control wells, 0.2 μL nuclease-free H_2O replaced the DNA template. Following sealing (Microseal 'B' adhesive seal, BioRad Laboratories, Hercules, USA) and centrifugation at 8000 RPM for 1 min, DNA amplification (Chromo4 Real-Time PCR Detection System, BioRad Laboratories) was performed using the following PCR protocols: *ACE* I/D: 50 cycles of incubation at 92°C for 15 s (denaturation) then annealing and extension at 57°C for 1 min. *ACTN3* R577X: denaturation at 95°C for 10 min, followed by 40 cycles of incubation at 92°C for 15 s then annealing and extension at 60°C for 1 min. *ACE* and *ACTN3* genotypes were ultimately determined using Opticon Monitor 3.1 software (BioRad Laboratories). All samples were analyzed in duplicate and in all cases there was 100% agreement between genotype for samples from the same participant.

Table 1 near here.

Data analysis and statistics

ACE and *ACTN3* genotype frequencies were tested for compliance with the Hardy-Weinberg equilibrium using χ^2 tests. Repeated-measures ANOVAs [within factor: time (pre/post training); between factor: genotype (three levels)] were used to detect genotype associations for each polymorphism separately with all muscle phenotypes (1-RM, F_t, V_m, specific force and W_{max}) and their response to RT. If a significant genotype effect or genotype x training interaction was observed, a one-way ANOVA with Bonferroni post-hoc test was used to locate the genotype difference in baseline values or RT-induced changes. Based on the hypothesis that *ACE* D-allele carriers would express higher baseline values and greater training-induced changes in muscle phenotypes than *ACE* II homozygotes, repeated-measures ANOVAs were performed where the results for DD and ID genotypes were pooled. Similarly, the results for *ACTN3* RR and RX genotypes were pooled and compared with those of XX homozygotes. One-tailed Spearman correlations determined the *ACTN3* genotype-dependent variance in baseline 1-RM and W_{max}; the 3 genotypes for the *ACTN3* polymorphism were coded as follows: *ACTN3* XX = 0, RX = 1, RR = 2. Partial Spearman correlations determined the relationships between V_m and W_{max} and *ACTN3* genotype (controlling for each variable in succession). The combined effect of both polymorphisms on muscle phenotypes and related RT responses was assessed by repeated-measures ANOVAs: individuals with the 'optimal' *ACE/ACTN3* genotype combination, i.e. *ACE* DD or ID *and ACTN3* RR or RX, were compared with individuals who had the 'sub-optimal' combination, i.e. only one or none of the 'preferential' genotypes. In all cases, the level of statistical significance was set at $\alpha = 0.05$ and corrected for multiple genotype-phenotype testing

(Holm 1979). All data are presented as mean ± standard deviation (SD) unless otherwise stated.

RESULTS

ACE and *ACTN3* genotypes

The genotype frequencies for the *ACE* (II = 11.8%; ID = 51.0%; DD = 37.3%) and *ACTN3* (RR = 39.2%; RX = 47.1%; XX = 13.7%) polymorphisms were in Hardy-Weinberg equilibrium ($P \geq 0.811$). The *ACE* and *ACTN3* genotype frequencies for those who completed the W_{max} protocol ($n = 40$) did not differ from those of the main group. The *ACE* I/D (Rigat, Hubert 1990) and *ACTN3* R577X (Yang, MacArthur 2003) allele frequencies were similar to those reported elsewhere for Caucasian populations.

Single repetition maximum (1-RM)

There were no differences in 1-RM between *ACE* genotypes before ($P > 0.05$) or in response to RT ($P > 0.01$; Table 2). Although 1-RM gains were independent of *ACTN3* genotype ($P > 0.05$; Table 3), there was a tendency for *ACTN3* XX homozygotes to have a lower baseline 1-RM compared to their RR and RX counterparts ($P = 0.080$; Table 3). When RR and RX genotypes were combined, baseline 1-RM was lower in XX homozygotes than in R-allele carriers ($P < 0.01$; Table 3). Furthermore, people with the 'optimal' *ACE/ACTN3* genotype combination ($n = 39$) had a higher 1-RM than those with the sub-optimal profile ($n = 12$) at baseline ($P = 0.010$) but not in response to RT ($P > 0.05$; Table 4).

Table 2 near here.

Maximum patellar tendon force and muscle specific force

There were no differences in maximum tendon force between genotype of the *ACE* I/D or *ACTN3* R577X polymorphism, either before (both $P > 0.05$), or in response to RT (both $P > 0.05$; Tables 2 and 3). Similarly, muscle specific force did not differ between genotype of either the *ACE* I/D or the *ACTN3* R577X polymorphism, either before (both $P > 0.05$), or in response to RT (both $P > 0.05$; Tables 2 and 3). The 'optimal' *ACE/ACTN3* genotype combination did not influence maximum patellar tendon force or muscle specific force either at baseline ($P > 0.0167$) or in response to RT ($P > 0.05$; Table 4).

Muscle volume (V_m)

Baseline V_m did not differ between *ACE* genotype ($P > 0.05$; Table 2) and the training-induced V_m gains were independent of *ACE* genotype ($P > 0.05$; Table 2). V_m gains were also independent of *ACTN3* genotype ($P > 0.05$; Table 3) but *ACTN3* genotype was associated with baseline V_m ($P < 0.0167$), and RR homozygotes had a greater V_m than XX ($P = 0.018$) but not RX ($P = 0.159$) genotypes (Table 3). Combining RR and RX genotypes demonstrated that V_m was greater in *ACTN3* R-allele carriers than in XX homozygotes ($P < 0.017$; Table 3). However, V_m was not affected by the 'optimal' *ACE/ACTN3* genotype profile either at baseline ($P > 0.0167$) or in response to RT ($P > 0.05$; Table 4).

Table 3 near here.

Maximum power (W_{max})

There were no differences in W_{max} between the 3 *ACE* genotypes before ($P > 0.05$; Table 2) or in response to RT ($P > 0.05$; Table 2). Although training-induced W_{max} gains were independent of *ACTN3* genotype ($P > 0.05$), R-allele carriers demonstrated greater W_{max} than XX homozygotes before RT ($P < 0.0125$; Table 3). In addition, the 'optimal' *ACE/ACTN3* genotype combination was associated with greater W_{max} at baseline ($P < 0.0125$) but not with the response to RT ($P > 0.05$; Table 4).

Table 4 near here.

Correlation analyses

There was a tendency for *ACTN3* genotype to correlate with baseline 1-RM ($R^2 = 0.053$, $P = 0.059$). Baseline V_m correlated with W_{max} having controlled for *ACTN3* genotype ($R^2 = 0.116$; $P = 0.017$), while *ACTN3* genotype correlated with baseline V_m ($R^2 = 0.144$, $P = 0.003$) and W_{max} ($R^2 = 0.092$; $P = 0.029$). *ACTN3* genotype was still correlated with V_m after controlling for W_{max} ($R^2 = 0.085$; $P = 0.036$), but after controlling for V_m, *ACTN3* genotype no longer correlated with W_{max} ($R^2 = 0.030$; $P = 0.147$).

DISCUSSION

We investigated whether using precise measures of skeletal muscle size, strength and power phenotypes (including measurements of agonist and antagonist muscle activation, muscle-tendon moment arm and muscle architecture, not previously assessed in *ACE* or *ACTN3* genotype studies) could help resolve the controversy surrounding associations between *ACE* and *ACTN3* gene polymorphisms and muscle strength, power and size before, and in response to, resistance training (RT). We found that *ACTN3* R-allele carriers had a greater V_m, W_{max} and 1-RM than XX homozygotes, and that people with the 'optimal' combined *ACE/ACTN3* genotype profile had a higher 1-RM and greater W_{max} in the untrained state than those with the 'sub-optimal' profile.

ACE DD homozygotes have been reported to have larger QF muscles than their II counterparts (Charbonneau, Hanson 2008), while no genotype-dependent differences have been reported for the elbow flexor muscle group (Pescatello, Kostek 2006; Thomis, Huygens 2004). In correspondence with the latter observation, we found no association between *ACE* genotype and QF V_m or PCSA. Whatever the discrepancy at baseline, our work and other studies on the QF (Charbonneau, Hanson 2008) and elbow flexor (Pescatello, Kostek 2006; Thomis, Huygens 2004) muscle groups showed that muscle hypertrophy in response to RT was independent of *ACE* genotype. Collectively, these findings suggest that the influence of the *ACE* I/D polymorphism on human skeletal muscle size and training-induced hypertrophy is minimal. It was therefore unsurprising that *ACE* genotype was not associated with maximum isometric patellar tendon force, which corresponds with other measures of isometric strength and *ACE* genotype (McCauley, Mastana 2009; Pescatello, Kostek 2006; Thomis, Huygens 2004).

However, the training-induced increase in isometric strength has been found to be more pronounced in carriers of either the I- (Pescatello, Kostek 2006) or the D-allele (Folland, Leach 2000). We and others (Thomis, Huygens 2004; Williams, Day 2005), however, have found no *ACE* genotype association with this particular training response, even though we accounted for voluntary muscle activation, antagonist co-activation and moment arm length to measure the maximum force resolved at the tendon.

Controversy also surrounds the *ACTN3* R577X SNP regarding human muscle strength, power and size. In accord with smaller muscle fibre CSA in α-actinin-3 deficient mice than in wild-type mice (Chan et al. 2008), we found that RR homozygotes had larger V_m than their XX counterparts. V_m is a strong determinant of W_{max} (O'Brien et al. 2009; Pearson et al. 2006) and, while we found that both V_m and W_{max} were related to *ACTN3* genotype, the relationship between *ACTN3* genotype and W_{max} was no longer significant once we controlled for V_m. Therefore, the association between V_m and *ACTN3* genotype probably underlies the greater W_{max} observed in our untrained R-allele carriers compared to XX homozygotes. In addition, type II muscle fibres are larger and more powerful than type I fibres (Bottinelli, Canepari 1996; Gilliver, Degens 2009; Widrick, Stelzer 2002) and the muscles of our R-allele carriers might have had a larger proportion of type IIx fibres than XX homozygotes (Vincent, De Bock 2007), which would have affected both V_m and W_{max}. The lack of α-actinin-3 in type II fibres of XX homozygotes is thought to affect muscle function during high-velocity shortening contractions (MacArthur & North 2004; Yang, MacArthur 2003), which is supported by the lower 1-RM and W_{max} (both of which have a shortening component) in our XX

homozygotes and no association between *ACTN3* genotype and maximum isometric patellar tendon force or QF muscle specific force. Therefore, although *ACTN3* genotype-dependent differences in muscle fibre-type composition and the lack of α-actinin-3 in type II fibres of XX homozygotes should not be discounted as possible explanations, our data indicate that associations between *ACTN3* genotype and muscle isoinertial strength and power are primarily via the SNP's association with V_m.

In addition to the individual influence, we investigated the combined effect of the *ACE* I/D and *ACTN3* R577X polymorphisms on muscle phenotypes before and after RT. We found that those people with the 'optimal' genotype combination, i.e. the *ACE* DD or ID *plus ACTN3* RR or RX genotypes, had a greater 1-RM and W_{max} in the untrained state compared to those people with the less favourable profile. Thus, the influence of the *ACE* I/D polymorphism on maximum strength/power in untrained young healthy men is only significant when considered in combination with the *ACTN3* R577X SNP. Other studies have found no strength/power advantage of possessing the 'optimal' combined profile in young healthy men (Rodriguez-Romo et al. 2010) or older adults (Bustamante-Ara et al. 2010; Garatachea et al. 2012), although these investigations included different strength/power phenotypes to those assessed in this study.

In conclusion, *ACTN3* R-allele carriers demonstrated larger muscle volume, greater power and isoinertial strength than XX homozygotes in the untrained state but the responses to RT were unrelated to *ACTN3* genotype. Furthermore, while the *ACE* I/D polymorphism was not individually associated with muscle phenotype or training

response, when combined with the *ACTN3* R577X SNP, the 'optimal' genotypes were associated with greater isoinertial strength and maximum power.

Perspectives

The importance of genetics in determining sporting performance has gained considerable interest over the last decade, with the *ACE* I/D and *ACTN3* R577X polymorphisms being identified as strong candidates for predisposing elite strength/power athlete status (Nazarov, Woods 2001; Woods, Hickman 2001; Yang, MacArthur 2003). Although the mechanisms and hypotheses behind these associations are clear, the findings in untrained muscle phenotypes, and the responses to RT, are eqivacol (Charbonneau, Hanson 2008; Clarkson, Devaney 2005; Delmonico, Kostek 2007; McCauley, Mastana 2009; Thomis, Huygens 2004). The discrepancies in literature could be due to the way these complex phenotypes have been previously defined. Therefore, by assessing maximum muscle force resolved at the tendon, maximum power, muscle volume and specific force with state-of-the-art techniques, this study sought to shed new light on the potential genotype-phenotype associations by providing measures of muscle size and strength/power that have not previously been investigated in *ACE* or *ACTN3* genotype studies. This is the first study to demonstrate multiple associations between *ACTN3* genotype and muscle volume, maximum isoinertial strength and maximum power, as well as the combined influence of the *ACE* I/D and *ACTN3* R577X polymorphisms on the inter-individual variability in maximum isoinertial strength and maximum power.

Conflict of interest

The authors declare no conflict of interest.

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Tables

Table 1. The structures of the three different primers and two probes contained in the *ACE* I/D genotyping assay mix. VIC and FAM probes were conjugated with the 5' ends of the I- and D-allele-specific oligonucleotides, respectively. Minor groove binder (MGB) groups were attached to the 3' ends of the oligonucleotides.

Primer *ACE*111 (5'-3')	**Primer *ACE*112 (5'-3')**	**Primer *ACE*113 (5'-3')**	**I-allele specific probe (VIC-*ACE*100)**	**D-allele specific probe (FAM-*ACE*100)**
CCCATCCTTTC-TCCCATTTCTC	AGCTGGAATAA-AATTGGCGAAAC	CCTCCCAAAG-TGCTGGGATTA	VIC-5'-AGGCGTGA-TACAGTCA-3'-MGB	FAM-5'-TGCTGCCTA-TACAGTCA-3'-MGB

Table 2. Baseline values and training-induced changes in muscle strength, size and power in individuals according to angiotensin-I converting enzyme (*ACE*) I/D genotype.

	***ACE* genotype**			
Variable	**II**	**ID**	**DD**	**ID + DD**
	(*n* = 6)	**(*n* = 26)**	**(*n* = 19)**	**(*n* = 45)**
Pre 1 RM (kg)	47.0 ± 7.6	55.4 ± 11.3	54.7 ± 11.2	55.1 ± 11.1
Δ 1 RM (%)	103 ± 26	65 ± 27	61 ± 31	63.2 ± 28.0
Pre F_t (N)	5359 ± 983	5883 ± 1114	5669 ± 997	5793 ± 1060
Δ F_t (%)	16.8 ± 11.8	23.5 ± 10.8	21.1 ± 11.2	22.5 ± 10.9
Pre SF ($N \cdot cm^{-2}$)	24.6 ± 4.8	26.1 ± 5.4	24.8 ± 5.1	25.6 ± 5.3
Δ SF (%)	13.5 ± 12.7	17.3 ± 10.1	16.0 ± 12.6	16.8 ± 11.2
Pre V_m (cm^3)	2034 ± 279	2114 ± 279	2068 ± 221	2095 ± 254
Δ V_m (%)	5.8 ± 3.5	6.1 ± 3.6	5.2 ± 3.1	5.7 ± 3.4
Pre PCSA (cm^2)	229 ± 33	239 ± 42	242 ± 42	241 ± 41
Δ PCSA (%)	3.9 ± 3.6	6.9 ± 5.0	5.0 ± 3.7	6.1 ± 4.6
Pre W_{max} (W)	1322 ± 227	1437 ± 210	1432 ± 185	1435 ± 198
Δ W_{max} (%)	16.4 ± 5.9	2.9 ± 12.3	3.5 ± 10.9	3.1 ± 11.6

I, insertion allele; *D*, deletion allele; *Pre*, before training; Δ, relative change after training; *1-RM*, single repetition maximum; F_t, maximum isometric patellar tendon force; *SF*, quadriceps femoris muscle specific force; V_m, quadriceps femoris muscle volume; *PCSA*, quadriceps femoris muscle physiological cross-sectional area; W_{max}, maximum power output measured in a subsample (*II n* = 4; *ID n* = 22; *DD n* = 14; *DD + ID n* = 36).

Table 3. Baseline values and training-induced changes in muscle strength, size and power in individuals according to α-actinin-3 (*ACTN3*) R577X genotype.

	***ACTN3* genotype**			
Variable	**RR**	**RX**	**XX**	**RR + RX**
	(*n* = 20)	**(*n* = 24)**	**(*n* = 7)**	**(*n* = 44)**
Pre 1-RM (kg)	55.3 ± 9.6	56.1 ± 12.5	45.7 ± 4.5	55.8 ± 11.2***
Δ 1-RM (%)	70.7 ± 28.2	63.6 ± 31.9	71.0 ± 32.7	66.8 ± 30.1
Pre F_t (N)	5960 ± 1026	5674 ± 976	5351 ± 1370	5804 ± 998
Δ F_t (%)	17.3 ± 10.9	24.5 ± 10.5	25.7 ± 10.6	21.2 ± 11.1
Pre SF ($N \cdot cm^{-2}$)	25.3 ± 6.0	26.1 ± 3.8	23.7 ± 6.8	25.7 ± 4.9
Δ SF (%)	11.7 ± 12.1	19.0 ± 9.6	21.0 ± 10.5	15.7 ± 11.3
Pre V_m (cm^3)	2197 ± 244**	2053 ± 246	1895 ± 185	2118 ± 253*
Δ V_m (%)	5.5 ± 3.9	6.4 ± 3.1	4.3 ± 2.6	5.9 ± 3.5
Pre PCSA (cm^2)	253 ± 47	229 ± 37	238 ± 40	240 ± 43
Δ PCSA (%)	6.1 ± 4.0	5.7 ± 5.3	5.6 ± 3.2	5.9 ± 4.7
Pre W_{max} (W)	1478 ± 195	1424 ± 198	1251 ± 158	1449 ± 196***
Δ W_{max} (%)	4.1 ± 10.7	6.8 ± 11.8	-3.5 ± 14.3	5.6 ± 11.2

RR, wild-type homozygote; *RX*, heterozygote; *XX*, mutant homozygote; *Pre*, before training; Δ, relative change after training; *1-RM*, single repetition maximum; F_t, maximum isometric patellar tendon force; *SF*, quadriceps femoris muscle specific force; V_m, quadriceps femoris muscle volume; *PCSA*, quadriceps femoris muscle physiological cross-sectional area; W_{max}, maximum power output measured in a subsample (*RR* n = 16; *RX* n = 19; *XX* n = 5; *RR* + *RX* n = 35); *** $P < 0.010$, ** $P < 0.0167$ and * $P < 0.025$ significantly different from XX genotype.

Table 4. Baseline values and training-induced changes in muscle strength, size and power in individuals grouped according to the 'optimal' strength/power polygenic profile (*ACE* DD or ID + *ACTN3* RR or RX) vs. the 'sub-optimal' profile (possessing either one or both of *ACE* II and ACTN3 *XX*).

Variable	**Optimal profile (*n* = 39)**	**Sub-optimal profile (*n* = 12)**
Pre 1-RM (kg)	56.7 ± 11.1***	46.4 ± 6.0
Δ 1-RM (%)	63.0 ± 28.1	81.9 ± 33.5
Pre F_t (N)	5906 ± 1002	5207 ± 1074
Δ F_t (%)	21.8 ± 10.9	21.8 ± 12.1
Pre SF ($N \cdot cm^{-2}$)	26.0 ± 4.9	23.6 ± 5.7
Δ SF (%)	15.9 ± 11.0	17.9 ± 12.1
Pre V_m (cm^3)	2131 ± 247	1947 ± 240
Δ V_m (%)	5.9 ± 3.5	5.2 ± 3.1
Pre PCSA (cm^2)	241 ± 44	232 ± 27
Δ PCSA (%)	6.1 ± 4.7	4.7 ± 3.5
Pre W_{max} (W)	1465 ± 190**	1283 ± 182
Δ W_{max} (%)	4.2 ± 11.0	5.3 ± 15.0

Pre, before training; Δ, relative change after training; *1-RM*, single repetition maximum; F_t, maximum isometric patellar tendon force; *SF*, quadriceps femoris muscle specific force; V_m, quadriceps femoris muscle volume; *PCSA*, quadriceps femoris muscle physiological cross-sectional area; W_{max}, maximum power output measured in a subsample (Total $n = 40$; Optimal profile $n = 31$; Sub-optimal profile $n = 9$); *** $P = 0.010$ and ** $P < 0.0167$ significantly different from XX genotype.