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INVITED REVIEW

More than a 'speed gene': *ACTN3* R577X genotype, trainability, muscle damage, and the risk for injuries

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Abstract

A common null polymorphism (rs1815739; R577X) in the gene that codes for α-actinin-3 (*ACTN3*) has been related to different aspects of exercise performance. Individuals who are homozygous for the X allele are unable to express the α-actinin-3 protein in the muscle as opposed to those with the RX or RR genotype. α-actinin-3 deficiency in the muscle does not result in any disease. However, the different *ACTN3* genotypes can modify the functioning of skeletal muscle during exercise through structural, metabolic or signaling changes, as shown in both humans and in the mouse model. Specifically, the *ACTN3* RR genotype might favor the ability to generate powerful and forceful muscle contractions. Leading to an overall advantage of the RR genotype for enhanced performance in some speed and power-oriented sports. In addition, RR genotype might also favor the ability to withstand exercise-induced muscle damage, while the beneficial influence of the XX genotype on aerobic exercise performance needs to be validated in human studies. More information is required to unveil the association of *ACTN3* genotype with trainability and injury risk during acute or chronic exercise.

Keywords Genomics · Common human polymorphism · α-Actinin-3 deficiency · Athletic performance · Muscle performance

Abbreviations

ACE	Angiotensin converting enzyme
CK	Creatine kinase
KO	Knockout
mTOR	Mammalian target of rapamycin
SERCA1	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1
WT	Wild type

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Introduction

There are two muscle sarcomeric isoforms of α-actinin; α-actinin-2, and α-actinin-3, which are encoded by *ACTN2* and *ACTN3* genes, respectively (Beggs et al. 1992). The α-actinin-2 and α-actinin-3 proteins form major components of the contractile apparatus at the Z-line and are structured similarly (Fig. 1). However, α- actinin-2 is ubiquitously expressed in all muscle fiber types, while α-actinin-3 expression is found only in the fast type II fibers (Mills et al. 2001). This indicates that α-actinin-2 and 3 might have different physiological roles in the muscle (Lee et al. 2016). The protein α-actinin-2 plays a central role within the sarcomere for all types of locomotor activities and displacements (Ribeiro Ede et al. 2014) while the α-actinin-3 role might be more related to the generation of rapid muscle force and thus, for the production fast and explosive movements (MacArthur et al. 2007). Further the role of α-actinin-3 has been attributed to modulate the response to training, the recovery after exercise-induced muscle damage and the exercise-associated risk of injury (Pickering and Kiely 2017).

North et al. (1999) identified a common stop-codon polymorphism (rs1815739; R577X) in the *ACTN3* gene. Individuals who are homozygous for the X allele are unable to

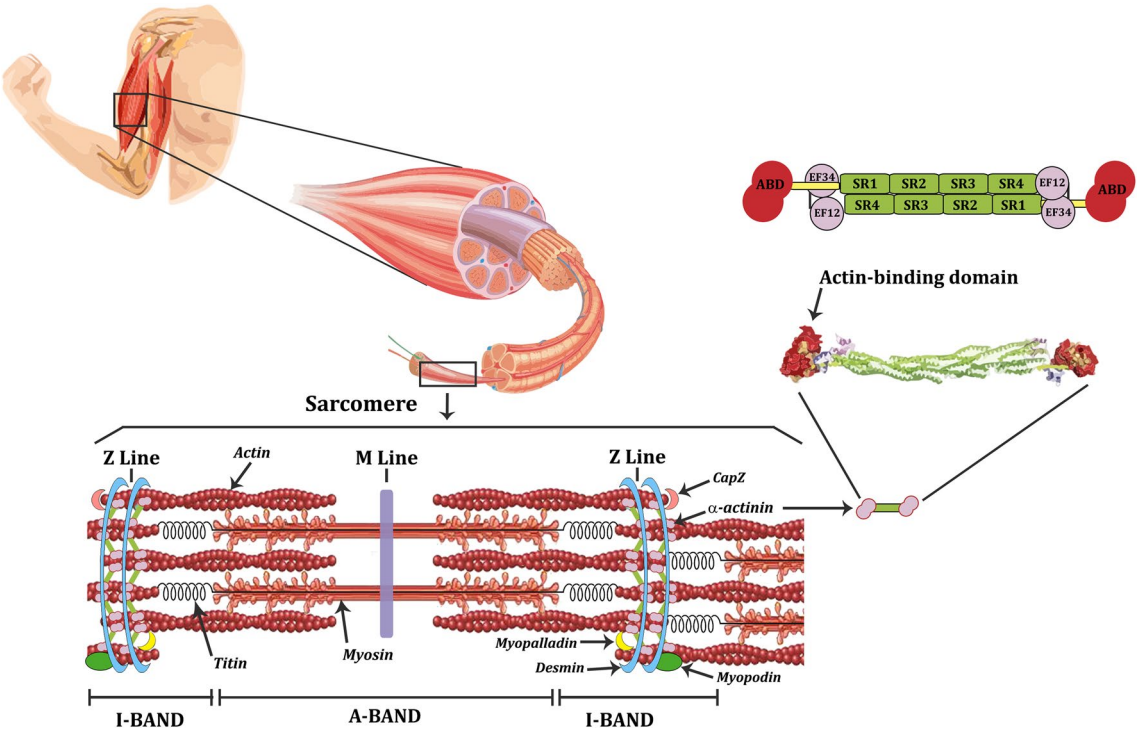

Fig. 1 Localisation of α-actinin in skeletal muscle. The sarcomeric α-actinins are essential for the contractile apparatus at the Z-line because they bind and cross-link the ends of F-actin filaments from adjacent sarcomeres. While the expression of α- actinin-2 is ubiquitous in all types of muscle fibers, α-actinin-3 is restricted to fast type II fibers, suggesting a different physiological role of each isoform for muscle contraction. α-actinins are antiparallel homodimers of more than 200 kDa, comprising an actin-binding domain (ABD), a central domain of four spectrin-like repeats (SR1-4), and a C-terminal calmodulin-like domain with two pairs of EF hand motifs (EF). Adapted from (Ribeiro Ede et al. 2014)

express α-actinin-3 in type II muscle fibers as opposed to those with the RX or RR genotype. Interestingly, individuals with the *ACTN3* XX genotype compensate the deficiency of α-actinin-3 with a higher expression of α-actinin-2 (Seto et al. 2011). This in turn might confer different properties to the muscle fiber altering muscle function at rest or during exercise (Eynon et al. 2011; Santiago et al. 2010). Thus, the physiological effects found in XX homozygotes are explicitly related to lack of α-actinin-3 instead of to a reduced amount of α-actinins within the muscle. Although α-actinin-2 and α-actinin-3 isoforms are almost identical in structure, subtle differences in the interaction with other proteins might have a crucial effect on both the Z-line and the entire sarcomere (Lee et al. 2016; Berman and North 2010). Around one-fifth (20%) of the world population has the XX genotype (MacArthur et al. 2007). Although α-actinin-3 deficiency is not translated into any muscle disease, the current evidence suggests that it might affect muscle physiology in athletes (Alfred et al. 2011), healthy individuals, (Broos et al. 2015) and in some clinical populations (Pickering and Kiely 2018).

Literature suggests that α-actinin-3 deficiency might play a beneficial role that would explain the perpetuation of the X allele through natural selection in human evolution. It has been postulated that the survival of the X allele has been influenced by ambient temperature (Lee et al. 2016) because its frequency in human populations increases with the distance from central latitudes (Amorim et al. 2015; Friedlander et al. 2013). This was confirmed by different researches that have found that the frequency distribution of the *ACTN3* XX genotype averages ~ 25% in Asians, 18% in Caucasians, 11% in Ethiopians, and 3% in US African Americans and only 1% in Kenyans (Yang et al. 2007; Scott et al. 2010; Pickering and Kiely 2017). The relatively high frequency of the XX genotype in human populations living in cold environments might be related to improved acclimatization and thermogenesis, due to increased metabolic heat generation during muscle activities (Head et al. 2015). In addition, the X allele offers enhanced metabolic efficiency (MacArthur et al. 2007, 2008) and therefore it might have persisted as a metabolically 'thrifty' allele (MacArthur and North 2004) that could have favored hunting in environments with scarce food resources (Amorim et al. 2015).

In this review, we will discuss the recent insights into the role of α-actinin-3 in muscle, based on studies in humans and the *Actn3* knockout (KO) mouse model. We will then

focus on the consequences of α-actinin-3 deficiency on human exercise performance, exercise-induced muscle damage, injury epidemiology and response to training.

Consequences of α-actinin-3 deficiency on sprint/power-oriented performance

The consequences of the *ACTN3* genotype on human exercise performance were first investigated in elite athletes. Initially, it was found that the *ACTN3* 577XX genotype was under represented in sprint athletes, when compared to a control population of healthy untrained individuals (Yang et al. 2003). In fact, none of the Olympic power/sprint athletes included in this first investigation by Yang et al. (2003) were α-actinin-3 deficient (XX), suggesting that this genotype was unfavorable for fast and powerful muscle contractions, at least in elite sports. This was replicated in several elite athlete cohorts where there is a higher frequency of the R allele in sprint and power disciplines (Eynon et al. 2009, 2013; Alfred et al. 2011; Kikuchi et al. 2014; Roth et al. 2008; Ginszt et al. 2018; Niemi and Majamaa 2005) and demonstrated in subsequent meta-analyses (Weyerstrass et al. 2018; Ma et al. 2013; see Table 1 for a summary). Further, recent literature suggests that the presence of α-actinin-3 might be especially advantageous for sprint, and power-based sports but not for strength-based sports disciplines (Ben-Zaken et al. 2016; Kim et al. 2014a). In addition, the role of α-actinin-3 for the generation of high-intensity muscle contractions has been confirmed in research with non-athletes. Untrained RR individuals have a higher baseline strength than their XX counterparts (Walsh et al. 2008; Clarkson et al. 2005a; Erskine et al. 2014) although this is contentious as other studies found no such differences between genotypes (Hanson et al. 2010; Norman et al. 2009). While muscle fiber composition is not affected by α-actinin-3 deficiency (Norman et al. 2009, 2014), the cross-sectional area of type II muscle fibers might be larger in RR than in XX individuals (Broos et al. 2016). Nonetheless, α-actinin-3 deficiency does not totally preclude the possibility of achieving high performance in power-like sports, because other cohorts of elite power/sprint athletes have reported a normal frequency of XX individuals (Ruiz et al. 2011, 2013; Sessa et al. 2011; Wang et al. 2013).

It has been proposed that the higher capacity of RR individuals to perform in speed/power sports might be also coupled with a better response to strength and power-oriented training (Pickering and Kiely 2017). For example, Delmonico et al. (2007) found greater increases in knee extensor peak power after 10 weeks of unilateral strength training in RR men and women compared to their XX counterparts. Norman et al. (2014) reported a higher exercise-induced increase in the phosphorylation of the mammalian target

Table 1 Summary of the physiological/performance consequences of α-actinin-3 deficiency in humans

	Sprint/power	Endurance	Muscle damage	Trainability	Risk of injury
Overview	↓ Sprint/power performance ↓ Muscle strength	Mixed results for endurance performance and fatigue resistance	↑ Muscle damage after eccentric exercise or weight-bearing endurance exercise	Mixed results for strength and endurance trainability	↑ Risk of ligament injury and mixed results for risk of muscle injury or muscle flexibility
Proposed mechanism	↓ Capacity to generate muscle force and power specially in muscle contractions that requires the recruitment of type 2 muscle fibers	↑ Metabolic efficiency ↑ Aerobic metabolism	↓ Capacity to resist muscle strain during acute eccentric or repeated concentric contractions	↓ Exercise-induced increase mTOR and p70S6k ↑ Calcineurin activity	↓ Capacity to resist muscle strain that could lead to reduced joint stability ↑ Ligament tension
Consequence for exercise and sport	↓ Frequency of XX individuals although this effect is minor in strength-based disciplines	↑ Frequency of XX individuals initially found but this has been disputed in more recent investigations	↑ Levels of serum markers of muscle damage ↑ Muscle pain after damaging exercise	No measurable consequences have been identified in sport	↑ Frequency of XX individuals among patients with ankle joint injuries compared to their injury-free peers

mTOR mammalian target of rapamycin

of rapamycin (mTOR) and p70S6k proteins in R allele carriers compared to the XX allele carriers' in human muscle fibers, suggesting an ameliorated muscle protein synthesis in α-actinin-3 deficient individuals. The *Actn3* KO mouse, firstly generated by MacArthur et al. (2007), mimics the α-actinin-3 deficient phenotype in humans. The *Actn3* knockout mice have identical morphological characteristics to wild type (WT) mice and they compensate the lack of α-actinin-3 with α-actinin-2 (Lee et al. 2016). In this mouse model, it has been found there is a higher calcineurin activity in *Actn3* KO mice (Seto et al. 2013) that would suggest a unfavorable physiological adaptability of α-actinin-3-deficient individuals to strength and power training stimuli ((Seto et al. 2013; Garton et al. 2014; Chin et al. 1998); Table 2). Indeed, calcineurin is a cytoplasmic calcium-regulated phosphatase implicated in fiber type transformations (Dunn et al. 1999), where activation in skeletal muscle selectively up-regulates promoters of specific slow-fiber genes (Chin et al. 1998). In this context, the muscle tissue of α-actinin-3-deficient individuals theoretically might be more prone to adapt to endurance training stimuli rather than to strength or power-oriented programs (Seto et al. 2013; Garton et al. 2014).

While these investigations provide mechanistic support for an increased training response to strength/power-oriented programs in individuals who are able to express α-actinin-3 (i.e., those with RR or RX genotypes) this might also be modulated by other genes. A report on the combined association of *ACTN3* and angiotensin converting enzyme (*ACE*) insertion (I)/deletion (D) genotypes in older women found that non α-actinin-3 deficient genotype (*ACTN3* RR) combined with the *ACE* DD genotype might favor training gains in muscle strength, power and functionality (i.e., during the sit-stand test) after a 12-week speed/power training protocol (Pereira et al. 2013a, b). The effectiveness of personalized resistance training based on genetics requires further investigation as it has only proven effective in one investigation, which included a cumulative genotype score based on *ACTN3* R77X and 14 other genetic polymorphisms (Jones et al. 2016). Finally, other investigations have not found higher strength gains in RR individuals when compared to XX counterparts (Erskine et al. 2014; Clarkson et al. 2005a). Thus, the evidence available does not suffice yet to support that RR individuals are more prone to obtain benefits from strength or power-based exercise programs than XX individuals.

Consequences of α-actinin-3 deficiency on endurance-oriented performance

Recent literature has shown that the absence of α-actinin-3 within the skeletal muscle might be advantageous in certain and specific situations, explaining the survival of the *ACTN3* 577X homozygosity through natural selection. In mouse model studies it has been found that there is a shift towards a more efficient aerobic muscle metabolism coupled with an improved recovery from fatigue in *Actn3* KO mice *vs* WT littermates (MacArthur et al. 2007, 2008; Chan et al. 2008). *Actn3* KO mice present with a higher activity of key oxidative enzymes, especially in fast muscle fibers, such as NADH-tetrazolium reductase and succinate dehydrogenase (MacArthur et al. 2007). This indicates an enhanced capacity for fat/carbohydrate oxidation during repeated and moderate-intensity muscle contractions (Table 2). However, in humans, the potential advantage of the X allele or the XX genotype for endurance sports performance is less clear, with some investigations reporting no increased frequency of the XX genotype in endurance athletes (Grealy et al. 2013; Guilherme et al. 2018; Papadimitriou et al. 2018; Ma et al. 2013; Lucia et al. 2006; Saunders et al. 2007; Yang et al. 2007) or even an under-representation of this genotype (Ahmetov et al. 2010; Kikuchi et al. 2016; Li et al. 2017) respect to control/untrained populations. Thus, it can be assumed that perhaps lack of α-actinin-3 does not offer a

Table 2 Summary of the physiological consequences of α-actinin-3 deficiency identified with the knockout mouse model for the α-actinin-3 gene (*Actn3*)

	Metabolic	Signaling	Structural	Calcium-handling
Overview	Shift towards more aerobic metabolism	↑ Adaptive response to endurance stimuli	Altered contractile properties	Altered calcium kinetics
Mechanism	↑ Oxidative enzymes and ↓ glycolytic enzymes	↑ Calcineurin activity	↑ Expression of Z-line proteins	↑ Calcium release and absorption
Physiological impact	↑ Endurance capacity and resistance to fatigue	↑ Endurance trainability	↓ Production of force	↑ Production of metabolic heat
Further considerations	It is the result of changes in various enzymes	It is the result of the preferential binding of calsarcin 2 to α-actinin-2	It is the result of the preferential binding of Z-line proteins to α-actinin-2	It is the result of higher levels of SERCA1

SERCA1 sarcoplasmic/endoplasmic reticulum calcium ATPase 1

major advantage for endurance performance, at least in athletic populations (Table 1).

Regarding training adaptations, XX might be more of a 'responder' (i.e., able to improve fitness outcomes) to endurance training than those with the RR genotype (Jones et al. 2016; Pickering and Kiely 2017). *Actn3* KO mice showed an improved adaptive response to 4 weeks of endurance training compared to WT mice (Seto et al. 2013). Interestingly, the muscle of WT mice did not display a shift in fiber type in response to endurance training whereas, *Actn3* KO mice had a decrease in the cross-sectional area of 2B fibers (which is the fastest muscle fiber type in mice) and an increase in 2X fibers, suggesting a "slowing" of the metabolic and physiological properties of fast fibers in this α-actinin-3 deficient mice (Seto et al. 2013). Further physiological changes within the muscle fiber produced by the lack of α-actinin-3 is higher calcineurin activity, which has been found in both *Actn3* KO mice and humans with the XX genotype (Seto et al. 2013). In this context, the muscle tissue of α-actinin-3-deficient individuals theoretically might be more prone to adapt to endurance training stimuli rather than to strength or power-oriented programs (Seto et al. 2013; Garton et al. 2014). Although Silva et al. (2015) found that RR individuals presented a higher adaptive response to endurance training than those with the XX genotype (Silva et al. 2015), Magi et al. (2016) found no influence of *ACTN3* genotype on the peak oxygen consumption responses to 5 years of endurance training in young cross-country skiers. The contradictory results might be due, at least partly, to differences between studies in the training protocols implemented or in the baseline fitness levels of the participants. Future investigations in the field should be carried out in both detrained and highly endurance trained individuals, with proper standardizations in the protocols used for training and controlling for factors that could affect trainability, such as the use of concurrent training sessions or of nutritional supplements and ergogenic aids.

The role of α-actinin-3 to reduce exercise-induced muscle damage

Exercise-induced muscle damage is a physiological process that typically occurs after unaccustomed exercise, particularly if the exercise involves a large amount of eccentric contractions (Clarkson and Hubal 2002). This phenomenon is associated with muscle soreness and is thought to start with mechanical disruption of the affected fibers (e.g., as manifested by Z-line streaming), which in turn leads to an inflammatory response. Surrogate markers such as increased levels of pro-inflammatory cytokines, and leakage of intramuscle proteins in the blood, such as creatine kinase (CK), are used to assess exercise-induced muscle damage (Yamin et al. 2010). The protective role of α-actinin-3 against damage in type II muscle fibers has been shown in several research protocols that included acute eccentric or concentric muscle actions. Individuals with the XX genotype presented with higher serum CK levels and muscle pain values than RR individuals after a protocol of eccentric knee extensions (Vincent et al. 2010). Similarly, XX soccer players showed higher serum CK concentrations than their R allele counterparts after a session of plyometric exercise (Pimenta et al. 2012). The athletes carrying the X allele presented higher reductions in jump height, and higher values of serum CK and self-reported muscle pain than RR athletes after a marathon (Del Coso et al. 2017a) or a half-ironman triathlon (Del Coso et al. 2016). XX individuals also presented with higher serum concentrations of serum myoglobin and CK than R allele carriers after an ultra-endurance adventure race (Belli et al. 2017). This role of α-actinin-3 for defending against damaging muscle activities during endurance/ultra-endurance exercise is somewhat unexpected when considering that slow-twitch fibers are preferentially recruited during these exercise tasks (Asp et al. 1999; North 2008). Perhaps, α-actinin-3 plays a role during the eccentric phase of endurance exercise activities that confers a higher capacity to the muscle, as a whole, to resist muscle damage despite the restricted expression of this protein to fast-twitch fibers.

Other investigations did not find an association between *ACTN3* R577X genotypes and muscle damage induced by elbow flexion eccentric exercises (Clarkson et al. 2005b). Interestingly, the "repeated-bout effect", that is, performing one bout of eccentric exercise to induce an adaptation such that the muscle is less vulnerable to muscle damage in a subsequent bout of the same type of exercise (Starbuck and Eston 2012) might be more marked in XX than in RR individuals suggesting that XX might be able to undertake more frequent training sessions (Venckunas et al. 2012). This finding was reported using drop jumps as the only exercise model to induce muscle damage, and therefore, requires further corroboration with other forms of exercise. A recent study found that, rather than the *ACTN3* R577X variant only, it was the cumulative influence of several genetic polymorphisms (including *ACTN3* R577X) that was associated with the magnitude of muscle damage after a marathon (Del Coso et al. 2017b). This latter investigation agrees with a previous analysis in which the *ACTN3* R577X genotype, in combination with other genes, was related to an increased likelihood of suffering a clinical case of exertional rhabdomyolysis (Deuster et al. 2013). Thus, the presence of α-actinin-3 could offer a structural benefit within the skeletal muscle fiber that might reduce the damage produced in the sarcomere during exercise, but with other hereditable factors involved in the phenotype of resistance against muscle fiber damage. In this regard, the upregulated production of α-actinin-2 in muscle fibers found in XX individuals (Seto et al. 2011) does

not suffice to prevent a higher likelihood of muscle damage and its accompanying symptoms in α-actinin-3 deficient individuals.

α-Actinin-3 deficiency and muscle injury

The influence of the *ACTN3* R577X genotype on the levels of exercise-induced muscle damage, with the latter being a physiological phenomenon, might also suggest that α-actinin-3 deficiency can be associated with a higher incidence or severity of exercise-related muscle injuries (i.e., a pathological phenomenon that might sometimes be linked to initial muscle damage, muscle contractures and strains, etc). It has been reported that XX soccer players (first league division, Italy) had almost a three- and twofold higher probability of suffering muscle injuries in general and severe muscle injuries, respectively, than their RR counterparts (Massidda et al. 2017). Yet, another study found that R allele carriers had an increased likelihood of suffering non-contact muscle injury during different sports-activities when compared to X allele carriers (Iwao-Koizumi et al. 2015). Interestingly, the authors hypothesized that the presence of α-actinin-3 would be associated with a higher magnitude of muscle strength in R allele carriers that would have produced a higher muscle strain during exercise, thereby explaining their results. In this regard, R allele carriers had increased passive hamstring stiffness compared to non-carriers, although this mechanical property did not increase the risk of strain injury (Miyamoto et al. 2018). In athletes of combat sports (judo, taekwondo, boxing), subjects with the XX genotype had a similar kinematic efficacy in the lower limbs than R allele carriers, as assessed with knee, angle and pelvis moments during a sprint with a change of direction and a vertical jump (Jung et al. 2016). Thus, the evidences that relate deficiency of α-actinin-3 with a higher risk for muscle injury during exercise are still inconsistent (Table 2).

α-Actinin-3 deficiency and other types of injuries

Although the absence of α-actinin-3 in skeletal muscle fibers has not been linked with significant changes in connective or ligament tissues, dancers with the XX genotype show a higher incidence of ankle injuries than R allele carriers (Kim et al. 2014b). The XX genotype has also been associated with a higher incidence of non-contact acute ankle sprains (Qi et al. 2016; Shang et al. 2015), although this association has not been replicated by others (Kim et al. 2017a). If accurate, the higher likelihood of injury in α-actinin-3 deficient individuals might be related to a dysfunction in the capacity of the muscle to hold the joint during the action, rather than to a dysfunction of the ligament tissue (Pickering and Kiely 2017). Another factor that is intrinsically related to the risk of joint injuries during exercise is the range of motion in active joints and muscle flexibility. In this context, Zempo et al. (2016) found that RR individuals had lower trunk flexibility than X allele carriers, as measured by the sit-and-reach test. This was replicated by Kikuchi et al. (2017) in a similar investigation with untrained individuals. However, a lower trunk flexibility has been found in XX ballerinas when compared to R allele carriers (Kim et al. 2014b). In regards to other joints, a reduced range of motion in the elbow has been found in RR homozygotes (Kikuchi et al. 2018). The discrepancies in the outcomes of these investigations indicate that a clear effect of the *ACTN3* R577X genotype on muscle flexibility and range of motion is yet to be elucidated.

In addition to its presence in fast glycolytic skeletal muscle fibers, α-actinin-3 is expressed in osteoblasts. *Actn3* KO mice presented lower bone mineral density and bone formation rates per unit of bone surface when compared to WT littermates, suggesting that the lack of α-actinin-3 is associated with disruptions in mineralisation and resorption (Yang et al. 2011). α-actinin-3 deficient humans also presented with lower levels of bone mineral density (Yang et al. 2011; Min et al. 2016), as well as higher values of serum bone remodeling markers than R allele carriers at rest (Levinger et al. 2017). This information suggests that XX genotype may contribute to a higher likelihood of bone injury during exercise, but to the date, there is no evidence for an effect of the *ACTN3* genotype on the risk or severity of bone injuries during exercise activities.

There is need for more research to clearly associate α-actinin-3 deficiency with injury risk in athletic and non-athletic populations. The use of genome-wide association studies might be effective in helping to fill the gaps of why some individuals are more susceptible to injury than others. This has already been found useful to explain higher risk of rotator cuff injury (Roos et al. 2017), Achilles tendinopathy and anterior cruciate ligament rupture (Kim et al. 2017b) and ankle injuries (Kim et al. 2017a).

Summary and conclusions

ACTN3 R577X genotype influences human performance in several manners related to the structural, metabolic and signaling effects by the absence or presence of α-actinin-3 within the skeletal muscle (Fig. 2). Table 3 includes an evidence-based analysis of the association between *ACTN3* genotype and different muscle phenotypes in human and animal experiments. The RR genotype, which results in the full expression α-actinin-3 in fast-twitch fibers, favors the ability to generate powerful and forceful muscle contractions, leading to an overall advantage of this genotype for performance

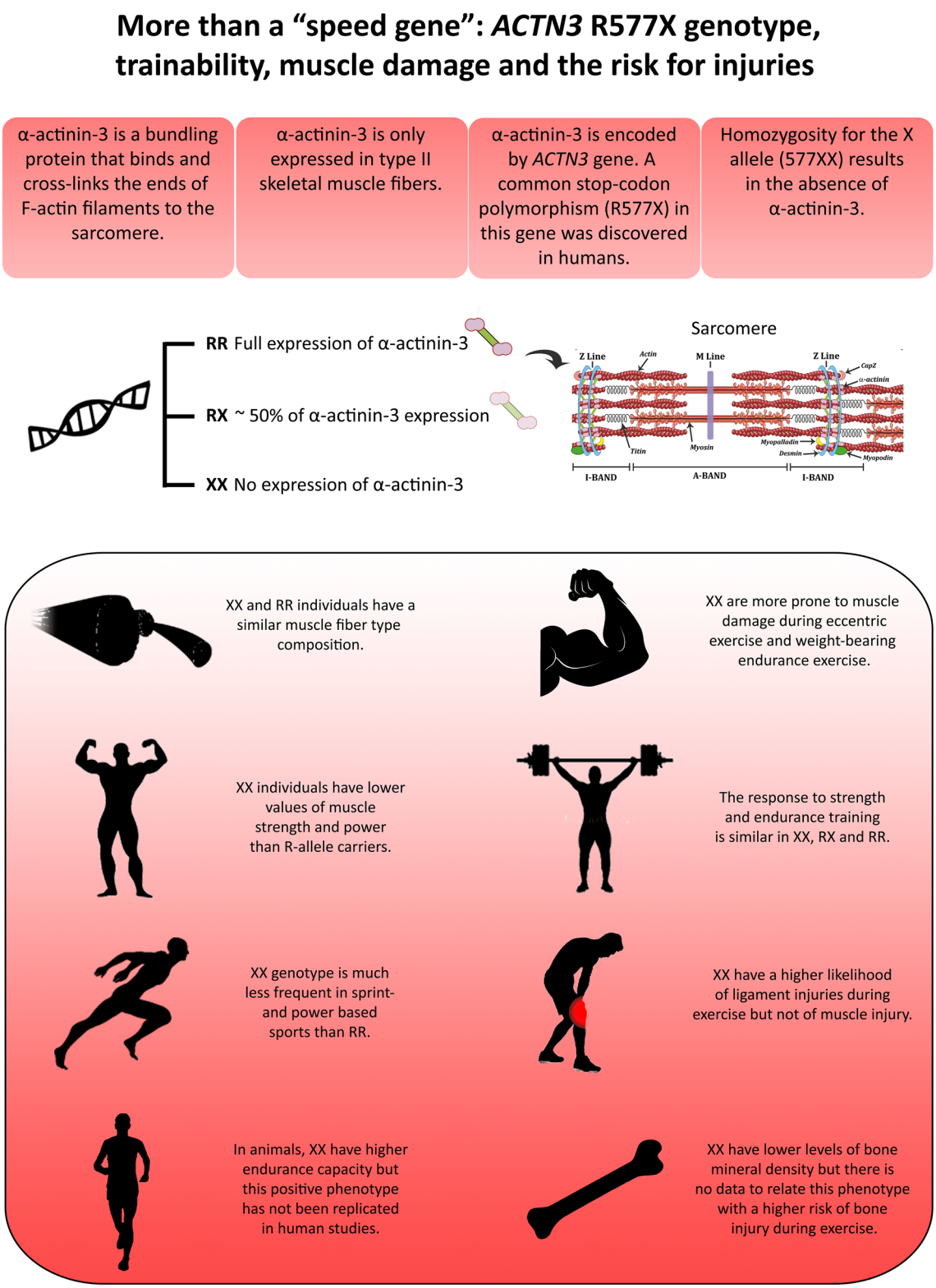

Fig. 2 Most common phenotypes related to α-actinin-3 deficiency due to homozygosity for the X allele in the ACTN3 R577X polymorphism

Table 3 Level of evidence from human and mouse model research for the effects of the α-actinin-3 deficiency on different muscle phenotype traits. Adapted from (Burns et al. 2011)

Muscle trait	Human	Mouse	Applications for exercise	References for human studies	References for mouse studies
↓ Sprint/power-based performance	I	I	Genotyping can be used to determine the likelihood of success in a sprint/power-based sport	Alfred et al. (2011), Yang et al. (2003), Weyerstrass et al. (2018), Ma et al. (2013), Eynon et al. (2013) and Kikuchi et al. (2014)	MacArthur et al. (2008), Quinlan et al. (2010), Lee et al. (2016) and North (2008)
↑ Training response to endurance training	V	II	Too early to use personalize endurance training based on *ACTN3* genotyping	Silva et al. (2015) and Magi et al. (2016)	Seto et al. (2013) and Chan et al. (2008)
↑ Endurance performance	III	II	Genotyping does not seem useful for detection of endurance talents	Yang et al. (2003), Silva et al. (2015), Pasqua et al. (2016) and Eynon et al. (2012)	MacArthur et al. (2007), Chan et al. (2008), Seto et al. (2013) and North (2008)
↓ Training response to strength training	IV	II	Too early to personalize strength training based on *ACTN3* genotyping	Norman et al. (2014) and Delmonico et al. (2007)	Garton et al. (2014), Seto et al. (2013) and Lee et al. (2016)
↑ Risk of muscle damage	II	IV	Specific training might be used to ameliorate muscle damage in XX individuals	Vincent et al. (2010), Del Coso et al. (2017a), and Del Coso et al. (2016)	Seto et al. (2011)
↑ Risk of muscle/ligament injury	IV	–	Prevention plans to reduce ligament injuries in XX individuals	Massidda et al. (2017), Kim et al. (2014b), Qi et al. (2016) and Shang et al. (2015)	–
↑ Risk of bone injury	IV	IV	Too early to develop prevention plants to avoid bone injuries in XX individuals	Yang et al. (2011), Min et al. (2016) and Levinger et al. (2017)	Yang et al. (2011)

Level I: systematic and narrative reviews, meta-analyses and high-quality prospective cohort studies with adequate power and with consistent results regarding the association of *ACTN3* genotype and the specific muscle trait. Level II: lesser high-quality prospective cohort studies, retrospective/comparative studies or systematic reviews and meta-analysis with inconsistent results regarding the *ACTN3* genotype and the specific muscle trait. Level III: case–control and retrospective studies with inconsistent results regarding the association of *ACTN3* genotype and the specific muscle trait. Level IV: Absence of association between the *ACTN3* genotype and the specific muscle trait or inconsistent results derived from cases series or poorly referenced investigations with no sensitivity analyses of phenotypes. Level V: expert opinion

ACTN3 α-actinin-3 gene

in some speed and power sports. Although more research is needed, this genotype might also favor the ability to withstand exercise-induced muscle damage. On the other hand, theoretically a beneficial influence of the XX genotype on aerobic exercise performance remains to be corroborated in human studies. More information is required to unveil the association of *ACTN3* genotype with injury risk during acute or chronic exercise.

Most of the information included in this review refers to research on *ACTN3* genotype frequency and their association with phenotypes related to elite athletic status. Hence, it is still too early to determine whether the information that is currently available on the *ACTN3* genotype-phenotype associations can be directly used for genetic testing in the general/amateur population. Studies on the impact of α-actinin-3 deficiency in amateur athlete populations with more ecological research protocols should be the focus of future lines of investigation.

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Compliance with ethical standards

Conflict of interest The authors of this investigation declare that there is no conflict of interest.

References

Ahmetov II, Druzhevskaya AM, Astratenkova IV, Popov DV, Vinogradova OL, Rogozkin VA (2010) The ACTN3 R577X polymorphism in Russian endurance athletes. Br J Sports Med 44(9):649–652. https://doi.org/10.1136/bjsm.2008.051540

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 life course physical capability: meta-analysis of the published literature and findings from nine studies. Hum Mutat 32(9):1008–1018. https://doi.org/10.1002/humu.21526

Amorim CE, Acuna-Alonzo V, Salzano FM, Bortolini MC, Hunemeier T (2015) Differing evolutionary histories of the ACTN3*R577X polymorphism among the major human geographic groups. PLoS One 10(2):e0115449. https://doi.org/10.1371/journal.pone.0115449

Asp S, Daugaard JR, Rohde T, Adamo K, Graham T (1999) Muscle glycogen accumulation after a marathon: roles of fiber type and pro- and macroglycogen. J Appl Physiol (1985) 86(2):474–478. https://doi.org/10.1152/jappl.1999.86.2.474

Beggs AH, Byers TJ, Knoll JH, Boyce FM, Bruns GA, Kunkel LM (1992) Cloning and characterization of two human skeletal muscle alpha-actinin genes located on chromosomes 1 and 11. J Biol Chem 267(13):9281–9288

Belli T, Crisp AH, Verlengia R (2017) Greater muscle damage in athletes with ACTN3 R577X (RS1815739) gene polymorphism after an ultra-endurance race: a pilot study. Biol Sport 34(2):105–110. https://doi.org/10.5114/biolsport.2017.64583

Ben-Zaken S, Eliakim A, Nemet D, Meckel Y (2016) Genetic variability among power athletes: The stronger vs. the faster. J Strength Cond Res. https://doi.org/10.1519/jsc.0000000000001356

Berman Y, North KN (2010) A gene for speed: the emerging role of alpha-actinin-3 in muscle metabolism. Physiology (Bethesda) 25(4):250–259. https://doi.org/10.1152/physiol.00008.2010

Broos S, Van Leemputte M, Deldicque L, Thomis MA (2015) History-dependent force, angular velocity and muscular endurance in ACTN3 genotypes. Eur J Appl Physiol 115(8):1637–1643. https://doi.org/10.1007/s00421-015-3144-6

Broos S, Malisoux L, Theisen D, van Thienen R, Ramaekers M, Jamart C, Deldicque L, Thomis MA, Francaux M (2016) Evidence for ACTN3 as a speed gene in isolated human muscle fibers. PLoS One 11(3):e0150594. https://doi.org/10.1371/journal.pone.0150594

Burns PB, Rohrich RJ, Chung KC (2011) The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 128(1):305–310

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(4):C897–C904. https://doi.org/10.1152/ajpcell.00179.2008

Chin ER, Olson EN, Richardson JA, Yang Q, Humphries C, Shelton JM, Wu H, Zhu W, Bassel-Duby R, Williams RS (1998) A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. Genes Dev 12(16):2499–2509

Clarkson PM, Hubal MJ (2002) Exercise-induced muscle damage in humans. Am J Phys Med Rehabil 81(11 Suppl):S52–S69. https://doi.org/10.1097/01.phm.0000029772.45258.43

Clarkson PM, Devaney JM, Gordish-Dressman H, Thompson PD, Hubal MJ, Urso M, Price TB, Angelopoulos TJ, Gordon PM, Moyna NM, Pescatello LS, Visich PS, Zoeller RF, Seip RL, Hoffman EP (2005a) ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. J Appl Physiol (1985) 99(1):154–163. https://doi.org/10.1152/japplphysiol.01139.2004

Clarkson PM, Hoffman EP, Zambraski E, Gordish-Dressman H, Kearns A, Hubal M, Harmon B, Devaney JM (2005b) ACTN3 and MLCK genotype associations with exertional muscle damage. J Appl Physiol (1985) 99(2):564–569. https://doi.org/10.1152/japplphysiol.00130.2005

Del Coso J, Salinero JJ, Lara B, Gallo-Salazar C, Areces F, Puente C, Herrero D (2016) ACTN3 X-allele carriers had greater levels of muscle damage during a half-ironman. Eur J Appl Physiol. https://doi.org/10.1007/s00421-016-3507-7

Del Coso J, Valero M, Salinero JJ, Lara B, Diaz G, Gallo-Salazar C, Ruiz-Vicente D, Areces F, Puente C, Carril JC, Cacabelos R (2017a) ACTN3 genotype influences exercise-induced muscle damage during a marathon competition. Eur J Appl Physiol 117(3):409–416. https://doi.org/10.1007/s00421-017-3542-z

Del Coso J, Valero M, Salinero JJ, Lara B, Gallo-Salazar C, Areces F (2017b) Optimum polygenic profile to resist exertional rhabdomyolysis during a marathon. PLoS One 12(3):e0172965. https://doi.org/10.1371/journal.pone.0172965

Delmonico MJ, Kostek MC, Doldo NA, Hand BD, Walsh S, Conway JM, Carignan CR, Roth SM, Hurley BF (2007) 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 62(2):206–212

Deuster PA, Contreras-Sesvold CL, O'Connor FG, Campbell WW, Kenney K, Capacchione JF, Landau ME, Muldoon SM, Rushing EJ, Heled Y (2013) Genetic polymorphisms associated with exertional rhabdomyolysis. Eur J Appl Physiol 113(8):1997–2004. https://doi.org/10.1007/s00421-013-2622-y

Dunn SE, Burns JL, Michel RN (1999) Calcineurin is required for skeletal muscle hypertrophy. J Biol Chem 274(31):21908–21912

Erskine RM, Williams AG, Jones DA, Stewart CE, Degens H (2014) The individual and combined influence of ACE and ACTN3 genotypes on muscle phenotypes before and after strength training. Scand J Med Sci Sports 24(4):642–648. https://doi.org/10.1111/sms.12055

Eynon N, Duarte JA, Oliveira J, Sagiv M, Yamin C, Meckel Y, Goldhammer E (2009) ACTN3 R577X polymorphism and Israeli top-level athletes. Int J Sports Med 30(9):695–698. https://doi.org/10.1055/s-0029-1220731

Eynon N, Ruiz JR, Oliveira J, Duarte JA, Birk R, Lucia A (2011) Genes and elite athletes: a roadmap for future research. J Physiol 589(Pt 13):3063–3070. https://doi.org/10.1113/jphysiol.2011.207035

Eynon N, Ruiz JR, Femia P, Pushkarev VP, Cieszczyk P, Maciejewska-Karlowska A, Sawczuk M, Dyatlov DA, Lekontsev EV, Kulikov LM, Birk R, Bishop DJ, Lucia A (2012) The ACTN3 R577X polymorphism across three groups of elite male European athletes. PLoS One 7(8):e43132

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(9):803–817. https://doi.org/10.1007/s40279-013-0059-4

Friedlander SM, Herrmann AL, Lowry DP, Mepham ER, Lek M, North KN, Organ CL (2013) ACTN3 allele frequency in humans covaries with global latitudinal gradient. PLoS One 8(1):e52282. https://doi.org/10.1371/journal.pone.0052282

Garton FC, Seto JT, Quinlan KG, Yang N, Houweling PJ, North KN (2014) alpha-Actinin-3 deficiency alters muscle adaptation in response to denervation and immobilization. Hum Mol Genet 23(7):1879–1893. https://doi.org/10.1093/hmg/ddt580

Ginszt M, Michalak-Wojnowska M, Gawda P, Wojcierowska-Litwin M, Korszen-Pilecka I, Kusztelak M, Muda R, Filip AA, Majcher P (2018) ACTN3 genotype in professional sport climbers. J Strength Cond Res. https://doi.org/10.1519/jsc.0000000000002457

Grealy R, Smith CL, Chen T, Hiller D, Haseler LJ, Griffiths LR (2013) The genetics of endurance: frequency of the ACTN3 R577X variant in Ironman World Championship athletes. J Sci Med Sport 16(4):365–371. https://doi.org/10.1016/j.jsams.2012.08.013

Guilherme J, Bertuzzi R, Lima-Silva AE, Pereira ADC, Lancha Junior AH (2018) Analysis of sports-relevant polymorphisms in a large Brazilian cohort of top-level athletes. Ann Hum Genet. https://doi.org/10.1111/ahg.12248

Hanson ED, Ludlow AT, Sheaff AK, Park J, Roth SM (2010) ACTN3 genotype does not influence muscle power. Int J Sports Med 31(11):834–838. https://doi.org/10.1055/s-0030-1263116

Head SI, Chan S, Houweling PJ, Quinlan KG, Murphy R, Wagner S, Friedrich O, North KN (2015) Altered Ca^{2+} kinetics associated with alpha-actinin-3 deficiency may explain positive selection for ACTN3 null allele in human evolution. PLoS Genet 11(2):e1004862. https://doi.org/10.1371/journal.pgen.1004862

Iwao-Koizumi K, Ota T, Hayashida M, Yonetani Y, Nakata K et al (2015) The ACTN3 gene is a potential biomarker for the risk of non-contact sports injury in female athletes. J Mol Biomark Diagn S6:002. https://doi.org/10.4172/2155-9929.S6-002

Jones N, Kiely J, Suraci B, Collins DJ, de Lorenzo D, Pickering C, Grimaldi KA (2016) A genetic-based algorithm for personalized resistance training. Biol Sport 33(2):117–126. https://doi.org/10.5604/20831862.1198210

Jung H, Lee N, Park S (2016) Interaction of ACTN3 gene polymorphism and muscle imbalance effects on kinematic efficiency in combat sports athletes. J Exerc Nutr Biochem 20(2):1–7. https://doi.org/10.20463/jenb.2016.06.20.2.1

Kikuchi N, Nakazato K, Min SK, Ueda D, Igawa S (2014) The ACTN3 R577X polymorphism is associated with muscle power in male Japanese athletes. J Strength Cond Res 28(7):1783–1789. https://doi.org/10.1519/jsc.0000000000000338

Kikuchi N, Miyamoto-Mikami E, Murakami H, Nakamura T, Min SK, Mizuno M, Naito H, Miyachi M, Nakazato K, Fuku N (2016) ACTN3 R577X genotype and athletic performance in a large cohort of Japanese athletes. Eur J Sport Sci 16(6):694–701. https://doi.org/10.1080/17461391.2015.1071879

Kikuchi N, Zempo H, Fuku N, Murakami H, Sakamaki-Sunaga M, Okamoto T, Nakazato K, Miyachi M (2017) Association between ACTN3 R577X polymorphism and trunk flexibility in 2 different cohorts. Int J Sports Med 38(5):402–406. https://doi.org/10.1055/s-0042-118649

Kikuchi N, Tsuchiya Y, Nakazato K, Ishii N, Ochi E (2018) Effects of the ACTN3 R577X genotype on the muscular strength and range of motion before and after eccentric contractions of the elbow flexors. Int J Sports Med 39(2):148–153. https://doi.org/10.1055/s-0043-120762

Kim H, Song KH, Kim CH (2014a) The ACTN3 R577X variant in sprint and strength performance. J Exerc Nutr Biochem 18(4):347–353. https://doi.org/10.5717/jenb.2014.18.4.347

Kim JH, Jung ES, Kim CH, Youn H, Kim HR (2014b) Genetic associations of body composition, flexibility and injury risk with ACE, ACTN3 and COL5A1 polymorphisms in Korean ballerinas. J Exerc Nutr Biochem 18(2):205–214. https://doi.org/10.5717/jenb.2014.18.2.205

Kim SK, Kleimeyer JP, Ahmed MA, Avins AL, Fredericson M, Dragoo JL, Ioannidis JPA (2017a) Two genetic loci associated with ankle injury. PLoS One 12(9):e0185355. https://doi.org/10.1371/journal.pone.0185355

Kim SK, Roos TR, Roos AK, Kleimeyer JP, Ahmed MA, Goodlin GT, Fredericson M, Ioannidis JP, Avins AL, Dragoo JL (2017b) Genome-wide association screens for Achilles tendon and ACL tears and tendinopathy. PLoS One 12(3):e0170422. https://doi.org/10.1371/journal.pone.0170422

Lee FX, Houweling PJ, North KN, Quinlan KG (2016) How does alpha-actinin-3 deficiency alter muscle function? Mechanistic insights into ACTN3, the 'gene for speed'. Biochim Biophys Acta 1863(4):686–693. https://doi.org/10.1016/j.bbamcr.2016.01.013

Levinger I, Yan X, Bishop D, Houweling PJ, Papadimitriou I, Munson F, Byrnes E, Vicari D, Brennan-Speranza TC, Eynon N (2017) The influence of alpha-actinin-3 deficiency on bone remodelling markers in young men. Bone 98:26–30. https://doi.org/10.1016/j.bone.2017.02.010

Li YC, Wang LQ, Yi LY, Liu JH, Hu Y, Lu YF, Wang M (2017) ACTN3 R577X genotype and performance of elite middle-long distance swimmers in China. Biol Sport 34(1):39–43. https://doi.org/10.5114/biolsport.2017.63731

Lucia A, Gomez-Gallego F, Santiago C, Bandres F, Earnest C, Rabadan M, Alonso JM, Hoyos J, Cordova A, Villa G, Foster C (2006) ACTN3 genotype in professional endurance cyclists. Int J Sports Med 27(11):880–884. https://doi.org/10.1055/s-2006-923862

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(1):e54685. https://doi.org/10.1371/journal.pone.0054685

MacArthur DG, North KN (2004) A gene for speed? The evolution and function of alpha-actinin-3. Bioessays 26(7):786–795. https://doi.org/10.1002/bies.20061

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(10):1261–1265. https://doi.org/10.1038/ng2122

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(8):1076–1086. https://doi.org/10.1093/hmg/ddm380

Magi A, Unt E, Prans E, Raus L, Eha J, Veraksits A, Kingo K, Koks S (2016) The association analysis between ACE and ACTN3 genes polymorphisms and endurance capacity in young cross-country skiers: longitudinal study. J Sports Sci Med 15(2):287–294

Massidda M, Voisin S, Culigioni C, Piras F, Cugia P, Yan X, Eynon N, Calo CM (2017) ACTN3 R577X polymorphism is associated with the incidence and severity of injuries in professional football players. Clin J Sport Med. https://doi.org/10.1097/jsm.0000000000000487

Mills M, Yang N, Weinberger R, Vander Woude DL, Beggs AH, Easteal S, North K (2001) Differential expression of the actin-binding proteins, alpha-actinin-2 and -3, in different species: implications for the evolution of functional redundancy. Hum Mol Genet 10(13):1335–1346

Min SK, Lim ST, Kim CS (2016) Association of ACTN3 polymorphisms with BMD, and physical fitness of elderly women. J Phys Ther Sci 28(10):2731–2736. https://doi.org/10.1589/jpts.28.2731

Miyamoto N, Miyamoto-Mikami E, Hirata K, Kimura N, Fuku N (2018) Association analysis of the ACTN3 R577X polymorphism with passive muscle stiffness and muscle strain injury. Scand J Med Sci Sports 28(3):1209–1214. https://doi.org/10.1111/sms.12994

Niemi AK, Majamaa K (2005) Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes. Eur J Hum Genet 13(8):965–969. https://doi.org/10.1038/sj.ejhg.5201438

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 (1985) 106(3):959–965. https://doi.org/10.1152/japplphysiol.91435.2008

Norman B, Esbjornsson M, Rundqvist H, Osterlund T, Glenmark B, Jansson E (2014) ACTN3 genotype and modulation of skeletal muscle response to exercise in human subjects. J Appl Physiol (1985) 116(9):1197–1203. https://doi.org/10.1152/japplphysiol.00557.2013

North K (2008) Why is alpha-actinin-3 deficiency so common in the general population? The evolution of athletic performance. Twin Res Hum Genet 11(4):384–394. https://doi.org/10.1375/twin.11.4.384

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(4):353–354. https://doi.org/10.1038/7675

Papadimitriou ID, Lockey SJ, Voisin S, Herbert AJ, Garton F, Houweling PJ, Cieszczyk P, Maciejewska-Skrendo A, Sawczuk M, Massidda M, Calo CM, Astratenkova IV, Kouvatsi A, Druzhevskaya AM, Jacques M, Ahmetov II, Stebbings GK, Heffernan S, Day SH, Erskine R, Pedlar C, Kipps C, North KN, Williams AG, Eynon N (2018) No association between ACTN3 R577X and ACE I/D polymorphisms and endurance running times in 698 Caucasian athletes. BMC Genom 19(1):13. https://doi.org/10.1186/s12864-017-4412-0

Pasqua LA, Bueno S, Artioli GG, Lancha AH Jr, Matsuda M, Marquezini MV, Lima-Silva AE, Saldiva PH, Bertuzzi R (2016) Influence of ACTN3 R577X polymorphism on ventilatory thresholds related to endurance performance. J Sports Sci 34(2):163–170

Pereira A, Costa AM, Izquierdo M, Silva AJ, Bastos E, Marques MC (2013a) ACE I/D and ACTN3 R/X polymorphisms as potential factors in modulating exercise-related phenotypes in older women in response to a muscle power training stimuli. Age (Dordr) 35(5):1949–1959. https://doi.org/10.1007/s11357-012-9461-3

Pereira A, Costa AM, Leitao JC, Monteiro AM, Izquierdo M, Silva AJ, Bastos E, Marques MC (2013b) The influence of ACE ID and ACTN3 R577X polymorphisms on lower-extremity function in older women in response to high-speed power training. BMC Geriatr 13:131. https://doi.org/10.1186/1471-2318-13-131

Pickering C, Kiely J (2017) ACTN3: More than Just a Gene for Speed. Front Physiol 8:1080. https://doi.org/10.3389/fphys.2017.01080

Pickering C, Kiely J (2018) ACTN3, Morbidity, and Healthy Aging. Front Genet 9:15. https://doi.org/10.3389/fgene.2018.00015

Pimenta EM, Coelho DB, Cruz IR, Morandi RF, Veneroso CE, de Azambuja Pussieldi G, Carvalho MR, Silami-Garcia E, De Paz Fernandez JA (2012) The ACTN3 genotype in soccer players in response to acute eccentric training. Eur J Appl Physiol 112(4):1495–1503. https://doi.org/10.1007/s00421-011-2109-7

Qi B, Liu JQ, Liu GL (2016) Genetic association between ACTN3 polymorphism and risk of non-acute ankle sprain. Genet Mol Res 15(4). https://doi.org/10.4238/gmr15048962

Quinlan KG, Seto JT, Turner N, Vandebrouck A, Floetenmeyer M, Macarthur DG, Raftery JM, Lek M, Yang N, Parton RG, Cooney GJ, North KN (2010) Alpha-actinin-3 deficiency results in reduced glycogen phosphorylase activity and altered calcium handling in skeletal muscle. Hum Mol Genet 19(7):1335–1346

Ribeiro Ede A Jr, Pinotsis N, Ghisleni A, Salmazo A, Konarev PV, Kostan J, Sjoblom B, Schreiner C, Polyansky AA, Gkougkoulia EA, Holt MR, Aachmann FL, Zagrovic B, Bordignon E, Pirker KF, Svergun DI, Gautel M, Djinovic-Carugo K (2014) The structure and regulation of human muscle alpha-actinin. Cell 159(6):1447–1460. https://doi.org/10.1016/j.cell.2014.10.056

Roos TR, Roos AK, Avins AL, Ahmed MA, Kleimeyer JP, Fredericson M, Ioannidis JPA, Dragoo JL, Kim SK (2017) Genome-wide association study identifies a locus associated with rotator cuff injury. PLoS One 12(12):e0189317. https://doi.org/10.1371/journal.pone.0189317

Roth SM, Walsh S, Liu D, Metter EJ, Ferrucci L, Hurley BF (2008) The ACTN3 R577X nonsense allele is under-represented in elite-level strength athletes. Eur J Hum Genet 16(3):391–394. https://doi.org/10.1038/sj.ejhg.5201964

Ruiz JR, Fernandez del Valle M, Verde Z, Diez-Vega I, Santiago C, Yvert T, Rodriguez-Romo G, Gomez-Gallego F, Molina JJ, Lucia A (2011) ACTN3 R577X polymorphism does not influence explosive leg muscle power in elite volleyball players. Scand J Med Sci Sports 21(6):e34–e41. https://doi.org/10.1111/j.1600-0838.2010.01134.x

Ruiz JR, Santiago C, Yvert T, Muniesa C, Diaz-Urena G, Bekendam N, Fiuza-Luces C, Gomez-Gallego F, Femia P, Lucia A (2013) ACTN3 genotype in Spanish elite swimmers: no "heterozygous advantage". Scand J Med Sci Sports 23(3):e162–e167. https://doi.org/10.1111/sms.12045

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(5):771–778. https://doi.org/10.1111/j.1600-0838.2009.01017.x

Saunders CJ, September AV, Xenophontos SL, Cariolou MA, Anastassiades LC, Noakes TD, Collins M (2007) No association of the ACTN3 gene R577X polymorphism with endurance performance in Ironman Triathlons. Ann Hum Genet 71(Pt 6):777–781. https://doi.org/10.1111/j.1469-1809.2006.00385.x

Scott RA, Irving R, Irwin L, Morrison E, Charlton V, Austin K, Tladi D, Deason M, Headley SA, Kolkhorst FW, Yang N, North K, Pitsiladis YP (2010) ACTN3 and ACE genotypes in elite Jamaican

and US sprinters. Med Sci Sports Exerc 42(1):107–112. https://doi.org/10.1249/MSS.0b013e3181ae2bc0

Sessa F, Chetta M, Petito A, Franzetti M, Bafunno V, Pisanelli D, Sarno M, Iuso S, Margaglione M (2011) Gene polymorphisms and sport attitude in Italian athletes. Genet Test Mol Biomark 15(4):285–290. https://doi.org/10.1089/gtmb.2010.0179

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(15):2914–2927. https://doi.org/10.1093/hmg/ddr196

Seto JT, Quinlan KG, Lek M, Zheng XF, Garton F, MacArthur DG, Hogarth MW, Houweling PJ, Gregorevic P, Turner N, Cooney GJ, Yang N, North KN (2013) ACTN3 genotype influences muscle performance through the regulation of calcineurin signaling. J Clin Investig 123(10):4255–4263. https://doi.org/10.1172/jci67691

Shang X, Li Z, Cao X, Xie C, Gu M, Chen P, Yang X, Cai J (2015) The association between the ACTN3 R577X polymorphism and noncontact acute ankle sprains. J Sports Sci 33(17):1775–1779. https://doi.org/10.1080/02640414.2015.1012098

Silva MS, Bolani W, Alves CR, Biagi DG, Lemos JR Jr, da Silva JL, de Oliveira PA, Alves GB, de Oliveira EM, Negrao CE, Krieger JE, Dias RG, Pereira AC (2015) Elimination of influences of the ACTN3 R577X variant on oxygen uptake by endurance training in healthy individuals. Int J Sports Physiol Perform 10(5):636–641. https://doi.org/10.1123/ijspp.2014-0205

Starbuck C, Eston RG (2012) Exercise-induced muscle damage and the repeated bout effect: evidence for cross transfer. Eur J Appl Physiol 112(3):1005–1013. https://doi.org/10.1007/s00421-011-2053-6

Venckunas T, Skurvydas A, Brazaitis M, Kamandulis S, Snieckus A, Moran CN (2012) Human alpha-actinin-3 genotype association with exercise-induced muscle damage and the repeated-bout effect. Appl Physiol Nutr Metab 37(6):1038–1046. https://doi.org/10.1139/h2012-087

Vincent B, Windelinckx A, Nielens H, Ramaekers M, Van Leemputte M, Hespel P, Thomis MA (2010) Protective role of alpha-actinin-3 in the response to an acute eccentric exercise bout. J Appl Physiol (1985) 109(2):564–573. https://doi.org/10.1152/japplphysiol.01007.2009

Walsh S, Liu D, Metter EJ, Ferrucci L, Roth SM (2008) ACTN3 genotype is associated with muscle phenotypes in women across the adult age span. J Appl Physiol (1985) 105(5):1486–1491. https://doi.org/10.1152/japplphysiol.90856.2008

Wang G, Mikami E, Chiu LL, Deason ADEP, Fuku M, Miyachi N, Kaneoka M, Murakami K, Tanaka H, Hsieh M, Hsieh LL, Caporossi SS, Pigozzi D, Hilley F, Lee A, Galloway R, Gulbin SD, Rogozkin J, Ahmetov VA, Yang II, North N, Ploutarhos KN, Montgomery S, Bailey HE, Pitsiladis ME YP (2013) Association analysis of ACE and ACTN3 in elite Caucasian and East Asian swimmers. Med Sci Sports Exerc 45(5):892–900. https://doi.org/10.1249/MSS.0b013e31827c501f

Weyerstrass J, Stewart K, Wesselius A, Zeegers M (2018) Nine genetic polymorphisms associated with power athlete status—a meta-analysis. J Sci Med Sport 21(2):213–220. https://doi.org/10.1016/j.jsams.2017.06.012

Yamin C, Oliveira J, Meckel Y, Eynon N, Sagiv M, Ayalon M, Alves AJ, Duarte JA (2010) CK-MM gene polymorphism does not influence the blood CK activity levels after exhaustive eccentric exercise. Int J Sports Med 31(3):213–217. https://doi.org/10.1055/s-0029-1243256

Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, Easteal S, North K (2003) ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet 73(3):627–631. https://doi.org/10.1086/377590

Yang N, MacArthur DG, Wolde B, Onywera VO, Boit MK, Lau SY, Wilson RH, Scott RA, Pitsiladis YP, North K (2007) The ACTN3 R577X polymorphism in East and West African athletes. Med Sci Sports Exerc 39(11):1985–1988. https://doi.org/10.1249/mss.0b013e31814844c9

Yang N, Schindeler A, McDonald MM, Seto JT, Houweling PJ, Lek M, Hogarth M, Morse AR, Raftery JM, Balasuriya D, MacArthur DG, Berman Y, Quinlan KG, Eisman JA, Nguyen TV, Center JR, Prince RL, Wilson SG, Zhu K, Little DG, North KN (2011) α-Actinin-3 deficiency is associated with reduced bone mass in human and mouse. Bone 49(4):790–798. https://doi.org/10.1016/j.bone.2011.07.009

Zempo H, Fuku N, Murakami H, Miyachi M (2016) The relationship between alpha-actinin-3 gene R577X polymorphism and muscle flexibility. Juntendo Med J 62(Suppl. 1):118–118