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ACTN3 Genotype Is Associated with Human Elite Athletic Performance

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Abstract

There is increasing evidence for strong genetic influences on athletic performance and for an evolutionary "trade-off" between performance traits for speed and endurance activities. We have recently demonstrated that the skeletal-muscle actin-binding protein α-actinin-3 is absent in 18% of healthy white individuals because of homozygosity for a common stop-codon polymorphism in the *ACTN3* gene, R577X. α-Actinin-3 is specifically expressed in fast-twitch myofibers responsible for generating force at high velocity. The absence of a disease phenotype secondary to α-actinin-3 deficiency is likely due to compensation by the homologous protein, α-actinin-2. However, the high degree of evolutionary conservation of *ACTN3* suggests function(s) independent of *ACTN2*. Here, we demonstrate highly significant associations between *ACTN3* genotype and athletic performance. Both male and female elite sprint athletes have significantly higher frequencies of the 577R allele than do controls. This suggests that the presence of α-actinin-3 has a beneficial effect on the function of skeletal muscle in generating forceful contractions at high velocity, and provides an evolutionary advantage because of increased sprint performance. There is also a genotype effect in female sprint and endurance athletes, with higher than expected numbers of 577RX heterozygotes among sprint athletes and lower than expected numbers among endurance athletes. The lack of a similar effect in males suggests that the *ACTN3* genotype affects athletic performance differently in males and females. The differential effects in sprint and endurance athletes suggests that the R577X polymorphism may have been maintained in the human population by balancing natural selection.

- Other Sections▼

The α-actinins are a family of actin-binding proteins related to dystrophin. In humans, there are two genes encoding skeletal-muscle α-actinins: *ACTN2* (MIM 102573), which is expressed in all fibers, and *ACTN3* (MIM 102574), which is restricted to fast (type 2) fibers. The sarcomeric α-actinins are major components of the Z line, where they crosslink actin thin filaments; they likely perform a static function in maintaining the ordered myofibrillar array, as well as a regulatory function in coordinating myofiber contraction (Blanchard et al. [1989]; Mills et al. [2001]). We have recently demonstrated that α-actinin-3 deficiency is common in the general population and is due to homozygosity for a premature stop codon in *ACTN3* (R577X) (North et al. [1999]). It is likely that α-actinin-2 is able to "compensate" for the absence of α-actinin-3 in type 2 fibers, although there is no upregulation of α-actinin-2 levels in response to α-actinin-3 deficiency (authors' unpublished observations). However, there is strong evidence to suggest that *ACTN3* has been maintained in the genome because of function(s) independent of *ACTN2: ACTN3* sequence has remained highly conserved, in evolutionary terms, since its divergence from *ACTN2* >300 million years ago; α-actinin-2 and α-actinin-3 are differentially expressed, spatially and temporally, during embryonic development; and *ACTN2* expression does not completely overlap *ACTN3* in mouse postnatal skeletal muscle (Mills et al. [2001]). In addition, the frequency of the α-actinin-3–deficient genotype (577XX) varies from 25% in Asian populations to <1% in an African Bantu population; the frequency in Europeans is ~18%. This raises the possibility that *ACTN3* genotype confers differential fitness in humans, under certain environmental conditions. The force-generating capacity of type 2 muscle fibers at high velocity, the speed and tempo of movements, and the capacity of the individual to adapt to exercise training are all strongly genetically influenced (Rankinen et al. [2002]). Thus, we hypothesized that *ACTN3* genotype may be one of the factors that influence normal variation in muscle function. Since any effect on muscle function will be most readily observable at the extremes of human performance, we collaborated with the Australian Institute of Sport to study *ACTN3* genotype frequencies in elite athletes.

We genotyped 436 unrelated white controls from three different sources (150 blood donors, 71 healthy children participating in an unrelated study, and 215 healthy adults participating in a talent-identification program with the Australian Institute of Sport), through use of the genotyping methodology described by Mills et al. ([2001]). Sex was known for 292 female controls and 134 male controls. We also genotyped 429 elite white athletes from 14 different sports. Athletes were defined as "elite" if they had represented Australia in their sport at the international level; 50 of the athletes had competed in Olympic Games. This study was approved by the institutional review boards of the Children's Hospital at Westmead, the University of Sydney, and the Australian Institute of Sport. Given the localization of α-actinin-3 in fast skeletal-muscle fibers, we hypothesized that deficiency of α-actinin-3 would reduce performance in sprint/power events and would therefore be less frequent in elite sprint athletes. To test this hypothesis, we analyzed genotypes of a subset of 107 elite athletes (72 male and 35 female) in our cohort, classified a priori as specialist sprint/power athletes by one of the authors (J.P.G.) at the Australian Institute of Sport, blinded to genotyping results. This group comprised 46 track athletes competing in events of ⩽800 m, 42 swimmers competing in events ⩽200 m, 9 judo athletes, 7 short-distance track cyclists, and 3 speed skaters. For comparison, we analyzed a subset of 194 subjects (122 male and 72 female) classified independently as specialist endurance athletes, including 77 long-distance cyclists, 77 rowers, 18 swimmers competing over distances of ⩾400 m, 15 track athletes competing in events of ⩾5,000 m, and 7 cross-country skiers. Thirty-two sprint athletes (25 male and 7 female) and 18 endurance athletes (12 male and 6 female) had competed at the Olympic level. Because of the stringency of the classification criteria, 128 of our elite athletes could not be unambiguously assigned into either the sprint/power or endurance groups and were excluded from subsequent analyses.

To test for homogeneity of *ACTN3* allele and genotype frequencies between athlete and control groups, we used the log-linear modeling approach described by Huttley and Wilson ([2000]), implemented in the statistical programming language R (version 1.6.2), through use of the package hwde (contributed by J. Maindonald; available from The R Project for Statistical Computing Web site). χ^2 values were estimated using genotype numbers for comparisons between athletes and controls.

The genotypic profiles of the three control groups (150 blood donors, 71 healthy children, and 215 healthy adults) did not differ significantly from one another (χ^2=0.19; P=.996) nor from a previously genotyped group of 107 white Europeans (Mills et al. [2001]), suggesting that the genotype frequencies in our control cohort are representative of the broader white population. *ACTN3* genotype frequencies did not vary significantly between male and female control subjects, and, overall, there was no significant deviation from Hardy-Weinberg (H-W) equilibrium.

ACTN3 genotyping data from the control, sprint/power, and endurance groups are summarized in table 1 and figure 1. There were no significant allele or genotype frequency differences between the elite athlete group as a whole and the controls. However, when the athletes were divided into sprint/power and endurance groups and compared with controls, there was strong evidence of allele frequency variation ($\chi^2_{[df=5]}$=23; P<.001). There were significant allele frequency differences between sprint athletes and controls for both males ($\chi^2_{[df=1]}$=14.8; P<.001) and females ($\chi^2_{[df=1]}$=7.2; P<.01). Sprint athletes had a lower frequency of the XX (α-actinin-3 null) genotype (6% vs. 18%), and no female elite sprint athletes or sprint Olympians were XX. The sprint athlete group also had a higher frequency of the RR genotype (50% vs. 30%) and a lower frequency of the heterozygous RX genotype (45% vs. 52%), compared with controls. Elite endurance athletes had a slightly higher frequency of the XX genotype (24%) than did controls (18%). Importantly, allele frequencies in sprint and endurance athletes deviated in opposite directions and differed significantly from each other in both males ($\chi^2_{[df=1]}$=13.3; P<.001) and females ($\chi^2_{[df=1]}$=5.8; P<.05). The differences between the two groups effectively "canceled each other out," explaining the lack of association when the entire elite athlete cohort was compared with the control group.

Table 1

Number and Frequency (%) of *ACTN3* Genotypes and Frequency (%) of *ACTN3* Alleles in Controls and Elite Sprint/Power and Endurance Athletes

	No. (%) with Genotype			Allele Frequency (%)	
Group (n)	RR	RX	XX	R	X
Male:					
Controls (134)	40 (30)	73 (54)	21 (16)	57	43
Sprint (72)	38 (53)	28 (39)	6 (8)	72	28
Endurance (122)	34 (28)	63 (52)	25 (20)	54	46
Female:					
Controls (292)	88 (30)	147 (50)	57 (20)	55	45
Sprint (35)	15 (43)	20 (57)	0 (0)	71	29
Endurance (72)	26 (36)	25 (35)	21 (29)	53	47
Total:					
Controls (436)	130 (30)	226 (52)	80 (18)	56	44
[illegible] (107)	53 (50)	48 (45)	6 (6)	72	28

Table 1

Number and Frequency (%) of *ACTN3* Genotypes and Frequency (%) of *ACTN3* Alleles in Controls and Elite Sprint/Power and Endurance Athletes

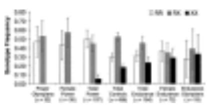

Figure 1

ACTN3 genotype frequency in controls, elite sprint/power athletes, and endurance athletes. Compared with healthy white controls, there is a marked reduction in the frequency of the *ACTN3* 577XX genotype (associated with α-actinin-3 deficiency) (more ...)

Overall, there was also evidence of genotype variation that is not explained by allele frequency differences ($\chi^2_{[df=5]}$=16.7; P<.01). This suggested variation in H-W disequilibrium coefficients among groups, despite there being no evidence for departure from H-W equilibrium overall. The effect was restricted to female sprint ($\chi^2_{[df=1]}$=7.4; P<.01) and endurance ($\chi^2_{[df=1]}$=6.0; P<.05) athletes, with more heterozygous female sprint athletes than expected at H-W equilibrium (20 vs. 15) and fewer than expected heterozygous female endurance athletes (25 vs. 36). The allele-frequency–independent genotype differences between female sprint and endurance athletes were highly significant ($\chi^2_{[df=1]}$=13.8; P<.001). No effect was seen in males, suggesting that the effect of *ACTN3* genotype on performance differs between males and females.

Our findings suggest that the *ACTN3* 577R allele provides an advantage for power and sprint activities. No female elite sprint athletes in our sample were α-actinin-3 deficient (compared with 8% of males). In males, the androgen hormone response to training is likely to make a significant contribution to improvements in performance, so that the relative effect of α-actinin-3 on muscle power may be reduced. Interestingly, all male Olympian power athletes in our cohort had at least one copy of the functional R allele of *ACTN3* (associated with the presence of α-actinin-3 in skeletal muscle), suggesting that "every variable counts" at the highest levels of sporting competition. Although at least 73 genetic loci have been associated with fitness and performance phenotypes (Rankinen et al. [2002]), *ACTN3* is the first structural skeletal-muscle gene for which such an association has been demonstrated.

The functional basis for this advantage is likely related to the fact that α-actinin-3 is the predominant fast fiber isoform in both mouse and human (Mills et al. [2001]) and may confer a greater capacity for the absorption or transmission of force at the Z line during rapid contraction. Approximately 45% of the variation in fiber type proportions is accounted for by genetic factors (Simoneau and Bouchard [1995]). Sarcomeric α-actinins bind to the gluconeogenic enzyme fructose-1,6-bisphosphatase (Gizak et al. [2003]), to the glycogen phosphorylase amorphin (Chowrashi et al. [2002]), and to the calsarcins (Frey et al. [2000]; Frey and Olson [2002]), which interact with calcineurin, a signaling factor that plays a role in the specification of muscle fiber type (Serrano et al. [2001]). Thus, α-actinin-3 may promote the formation of fast-twitch fibers or alter glucose metabolism in response to training. In addition, α-actinin-3 may be evolutionarily optimized for the minimization of damage caused by eccentric muscle contraction. The Z line in fast, glycolytic fibers is the structure most vulnerable to exercise-induced injury resulting in morphological damage and degradation of associated proteins, including the α-actinins (Friden and Lieber [2001]). We are currently exploring the mechanism by which the presence or absence of α-actinin-3 alters muscle function—and, hence, athletic performance—through the generation and analysis of an *Actn3* knockout mouse model.

From an evolutionary point of view, the challenge is to explain the high frequency of the 577XX *ACTN3* genotype, given the apparent power-performance advantage of the 577RR genotype. One possibility is that the power-performance effect of the 577RR genotype is only manifest in the extreme circumstances of athletic competition, outside the range of normal human activity, and is consequently of minimal evolutionary significance. In this model, the 577X allele could have been selectively neutral during human evolution and become established in the human population by random genetic drift. However, this explanation is difficult to reconcile with the high level of evolutionary conservation that we have previously demonstrated for *ACTN3* (North et al. [1999]; Mills et al. [2001]).

It is also possible that the X allele is selectively neutral but has reached its current frequency because of positive selection on a beneficial polymorphism at a nearby locus (i.e., "genetic hitchhiking") (Kaplan et al. [1989]). This hypothetical variant would need to be in strong linkage disequilibrium with 577X to result in the strong association observed in our study; however, it would be unlikely to reside within the *ACTN3* gene itself, since the 577X polymorphism results in deficiency of the α-actinin-3 protein. The distance over which "useful" linkage disequilibrium extends varies considerably between loci (Reich et al. [2001]); however, a distance of 10 kb has been proposed as a rough average value on the basis of population modeling (Ardlie et al. [2002]). The only identified gene other than *ACTN3* in the 20-kb region centered on the R577X polymorphism is the *CTSF* gene (MIM 603539), which encodes the papain-like cysteine protease cathepsin F (Wang et al. [1998]). The dbSNP Home Page identifies nine polymorphic sites within the *CTSF* gene, none of which alter the amino acid sequence of the encoded protein. Furthermore, the only characterized function of cathepsin F is related to antigen processing in macrophages (Shi et al. [2000]), making it an unconvincing candidate for influencing athletic performance. Although we cannot completely rule out that variations in *CTSF* or in other, more distant genes have influenced our results, it is more likely that the R577X polymorphism is directly responsible for the observed association with elite athletic performance.

The evolutionary model most consistent with our results is one in which 577XX genotype has been acted on by positive natural selection. Our data demonstrate a trend toward a higher frequency of the XX genotype in endurance athletes, although the association reached statistical significance only in females; the frequency of the 577RX genotype was also lower in female elite endurance athletes than in female controls (35% vs. 50%). However, the effect may be stronger than is indicated by these results, since a specific allelic association may be difficult to detect in a heterogeneous cohort of mixed athletic disciplines. If the 577XX genotype enhances endurance performance as the 577R allele appears to enhance sprint ability, then the 577R and 577X alleles may be maintained in the population because they both confer selective advantages under different environmental conditions and are thus kept at high population frequencies by balancing selection. We are currently studying the frequency of alleles and the pattern of genetic polymorphisms flanking the R577X locus in different human populations, to determine the origin of the X allele and to identify the form and magnitude of any selective pressures that have acted on the R577X locus.

Distinct beneficial effects on sprint and endurance athletic performance by different genotypes at a single locus have also been observed in studies of the gene encoding angiotensin-converting enzyme (*ACE*). The *ACE* gene has two alleles, termed "I" and "D"; the I allele is associated with lower ACE activity in both serum and tissue (Rieder et al. [1999]). An increased frequency of the *ACE* I allele has been observed in elite endurance athletes (Gayagay et al. [1998]; Montgomery et al. [1998]; Myerson et al. [1999]; Nazarov et al. [2001]). Conversely, an increased frequency of the *ACE* D allele has been associated with elite sprint performance (Myerson et al. [1999]; Nazarov et al. [2001]; Woods et al. [2001]). The absence of a correlation between the *ACE* I/D polymorphism and performance in other studies of elite athletes (Taylor et al. [1999]; Rankinen et al. [2000]) may be explained by the failure of these studies to adequately restrict their subjects to well-defined categories according to area of specialist performance, so that the allelic association is "canceled out" (Nazarov et al. [2001]).

It is likely that there is a "trade-off" between sprint and endurance traits that imposes important constraints on the evolution of physical performance in humans and other vertebrates (Garland et al. [1990]). This hypothesis is supported by recent data from world-class decathletes, which demonstrated that performance in the 100-m sprint, shot put, long jump, and 110-m hurdles (which rely on explosive power and fast fatigue-susceptible muscle fibers) is negatively correlated with performance in the 1,500-m race (which requires endurance and fatigue-resistant slow fiber activity) (Van Damme et al. [2002]). This suggests that an individual is inherently predisposed toward specialist performance in one area (sprint/power vs. endurance). In humans, this appears to have been achieved, in part, through the maintenance of genetic variation by balancing natural selection. The result is that there are genetic differences among individuals, such as we have demonstrated for the *ACTN3* locus, that may be useful predictors of athletic performance at the elite level.

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- 19:00 27 August 2003 by **Andy Coghlan**

A specific gene linked to athletic performance has been discovered by Australian sports scientists. The announcement comes as elite athletes vie for glory at the World Athletics Championships in Paris, and reopens the debate about whether top athletes can be screened and nurtured from birth.

The gene comes in two variants. People with one variant are predisposed to become sprinters. Those with the second are more likely to excel in endurance events. This is the second gene to be shown to confer athletic ability. The first, *angiotensin-converting enzyme*, or *ACE*, makes an enzyme which influences how efficiently our muscles burn oxygen, and the rate at which some muscles grow (**New Scientist** print edition, 23 May 1998).

The gene discovered by the Australian team is called *alpha-actinin-3*, or ACTN3. One version, the R allele, makes actinin, a protein found only in fast muscle fibres. These fibres help to produce the explosive bursts of speed and power that sprinters need. The other allele, called X, does not produce actinin-3.

The researchers studied the genetic profiles of over 300 athletes, 50 of whom had represented Australia at Olympic or international level at various sports. They found that 95 per cent of elite sprinters possessed at least one copy of the R allele while 50 per cent had two copies, one inherited from each parent (*American Journal of Human Genetics*, vol 73, p 627).

But just 76 per cent of endurance athletes possessed an R allele, with only 31 per cent inheriting both (see graphic). Out of over 400 controls taken from the general population, 82 per cent had one R allele and 30 per cent had two Rs.

Sprint Olympians

Some people inherit two X alleles, and so do not make actinin at all. Just 5 per cent of sprinters had two copies of the X allele, compared with 18 per cent of the controls. "No female elite sprinters or sprint Olympians were XX," says team leader Kathryn North of the Institute of Neuromuscular Research at the Children's Hospital at Westmead, Sydney.

However, when it came to endurance runners, a larger than average proportion, 24 per cent, had inherited the XX combination and so were unable to make actinin-3. "I hypothesise that absence of *alpha-actinin-3* means that an individual's muscles are more 'slow' in character, and better suited for endurance activities," says North.

The exact role of actinin-3 is unclear. "It may confer a greater capacity for the absorption or transmission of force during rapid, forceful contraction," North says. Her team are conducting lab and animal studies to find out.

North's team, which includes researchers from the Australian Institute of Sport, claims that ACTN3 is particularly significant because actinin forms a part of the musculature, whereas *ACE* only codes for an enzyme. "Although at least 73 genetic [regions] have been associated with fitness and performance, ACTN3 is the first structural skeletal muscle gene for which such an association has been found," she says.

Talent scouts

However, this interpretation is disputed by Montgomery, whose team at University College London discovered *ACE* and now says it has unpublished evidence pointing to a third gene that predisposes for enhanced physical performance.

ACE also has a direct impact on musculature, Montgomery says, because it influences whether "fast" or "slow" muscle fibres are laid down. And like ACTN3, *ACE* comes in two main inherited forms: the I form that favours endurance and the D form that favours sprinting.

Montgomery dismisses the notion that talent scouts could genetically screen for future elite athletes. "It's very unlikely there will be one gene that is a major indicator of performance." He says many factors influence sporting success, including body size, fibre type, metabolic efficiency, lung volume, psychological make-up and sheer application. "It's easier to go out with scouts and choose kids who are performing well."

Members of North's team accept there is something in this. "Being an elite athlete is not entirely dependent on ACTN3. It is still highly contentious whether we can use genetic markers to predict performance at all.

Positive discrimination

The research has not been done," says Jason Gulbin, who coordinates scouting activities for Australia's Institute of Sport. "But if we find a genetic profile has a useful predictive function, then I prefer to consider how this might be used to positively discriminate".

Multi-talented athletes only have a short time in which to decide which sporting areas will suit them best, so knowing their genetic make-up could help them make informed decisions about which discipline to focus on.

He rejects the idea that genetics would make sport even more elitist. "Let's not kid ourselves: elite sport is discriminatory. But not everyone can be a pilot either; certain skills are required to undertake specific tasks".

Rodney Walker, chairman of UK Sport, which oversees sporting development in Britain, is more cautious. "Screening would only ever give an indication, albeit a potentially valuable one, as to a child's athletic promise," he says. And it should be society as a whole rather than sport that judges whether using genetic screening is appropriate or desirable.

About Muscle Performance

Athletic performance can be influenced by a number of factors, some of which are genetic. Genes determine between 20-80% of the variation in traits like oxygen intake, cardiac performance, and muscle fiber composition. To date, more than 150 genes have been linked to different aspects of physical performance. One of the clearest associations is seen with a gene called ACTN3 that is normally turned on in a type of muscle fiber used for power-based sports. A single SNP can turn this gene off. While this genetic change does not cause any health effects, it may contribute to whether you are a sprinter or a marathoner.

Learn more about the biology of Muscle Performance...
Major discoveries in Muscle Performance...

1 of 4. Fast-twitch muscle fibers are specialized for the powerful bursts of force needed in power sports like sprinting or weightlifting.

Example Genetic Data

Who	Genotype	What It Means

Who	Genotype	What It Means
Greg Mendel (Dad)	CC	Two working copies of alpha-actinin-3 in fast-twitch muscle fiber. **Many** world-class sprinters and some endurance athletes have this genotype.
	CT	One working copy of alpha-actinin-3 in fast-twitch muscle fiber. **Many** world-class sprinters and some endurance athletes have this genotype.
	TT	No working copies of alpha-actinin-3 in fast-twitch muscle fiber. **Few** world-class sprinters have this genotype, but many world-class endurance athletes do.

Genes vs. Environment

Athletic performance has different estimates of heritability, depending on what aspect one examines. For example, differences in the relative proportion of fast-twitch and slow-twitch muscle fiber are thought to have a heritability of about 45%. Although it is not yet clear whether ACTN3 genotype affects this proportion, it has been shown that the SNP in ACTN3 that we report accounts for about 2.3% of the variation in sprinting performance. However, at the molecular level, whether you have 0, 1, or 2 working copies of alpha-actinin-3 is highly heritable. Lastly, muscle fiber only contributes a small part to your overall athletic performance. Other physical characteristics, such as lung capacity, and behaviors, such as regular exercise, also make important contributions to your prowess in sports.

Learn More About ACTN3

Marker: rs1815739

This gene produces a protein called alpha-actinin-3 that is only turned on in fast-twitch muscle fibers (the kind used for power events like sprinting or weightlifting). The protein forms part of the contractile machinery in muscle cells, where it is thought to play both structural and signalling roles.

The T version of the SNP in this gene prevents the full protein from being made. People with two copies of the T version thus have a total lack of alpha-actinin-3 in their fast-twitch muscle fibers. Those with the CT genotype have one functional copy of the gene and can still make the protein.

Surprisingly, a complete lack of the alpha-actinin-3 protein doesn't seem to cause any type of disease. This is probably because another closely related protein can step in for alpha-actinin-3 in people without a functional copy. The substitute protein likely does not perform its job as well as alpha-actinin-3, resulting in worse performance in power exercises.

Despite lack of a disease outcome, researchers wondered if the absence of alpha-actinin-3 might have an effect on athletic performance. Studies of elite athletes in Australia and Finland showed that power athletes—those whose performance depends on fast-twitch muscle fibers—were much more likely to have at least one working copy of the gene than non-athletes. In one study of Olympic power athletes (i.e., the best of the best), all had at least one working copy. Similar results were found in a study of Spanish professional soccer players.

But does alpha-actinin-3 make a difference for non-athletes? In fact, it does.

One study looked at a group of Greek teenagers who had been tested for a variety of fitness measures related to power and endurance sports. In this group, ACTN3 genotype had no effect on the girls, but boys with the TT genotype were significantly slower in a 40 m sprint. Interestingly, running was the only power event that the different versions of ACTN3 seemed to affect. For activities like throwing a basketball or jumping into the air, performance was unaffected by genotype.

Another study looked at arm strength in a group of people before and after 12 weeks of strength training. ACTN3 genotype appeared to have no effect in men, but women with the TT genotype had lower strength at the beginning of the study. After the training program women with the TT genotype—those without a working copy of alpha-actinin-3—had made greater gains than the women with at least one functioning copy. This was true in both European and Asian women.

Scientists aren't really sure why having alpha-actinin-3 would improve power performance. One theory is that the protein prevents damage in fast-twitch muscle fibers. The group who conducted the study of Greek teenagers thinks this explains why only running and not other power activities were affected by a lack of alpha-actinin-3. Running involves repeated use of the muscles, while jumping only uses muscles once: damage is not an issue.

The scientists who saw that women with the TT genotype were able to build up more strength than other women also think alpha-actinin-3 protects muscle fibers from damage. Muscle damage is what stimulates muscles to adapt and become stronger. Those with the TT genotype lack the protection against damage that alpha-actinin-3 normally provides, thus allowing a greater gain in strength.

Alpha-actinin-3 may also affect athletic performance by virtue of its effects on oxygen usage in muscle. Two studies (one in mice and one in humans) have shown that fast-twtich muscle fibers that lack functional copies of ACTN3 use more oxygen than those with at least one working copy. This type of metabolism might slow them down. Mice studies have also shown that these altered fibers are weaker and smaller than fibers containing alpha-actinin-3, but they are more efficient an resistant to fatigue—a situation that is better suited to endurance sports than sprinting.

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