

A common polymorphism in the skeletal muscle gene *ACTN3* influences athletic performance.

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Introduction

The four human *ACTN* genes encode the α -actinins, a family of actin-binding proteins related to dystrophin. α -Actinin-3 is a major structural component of the sarcomeric Z line in human fast-type skeletal muscle fibres. We have shown that the gene for α -actinin-3 (*ACTN3*) is polymorphic for a premature stop codon (R577X) resulting in complete α -actinin-3 deficiency in ~18% of normal Caucasians¹. This deficiency does not result in a disease phenotype, probably due to compensation by the closely related family member α -actinin 2. However, *ACTN3* is highly evolutionarily conserved, raising the possibility that it is not completely functionally redundant in humans². We thus hypothesised that *ACTN3* genotype affects muscle function at the extremes of performance.

Methods

We isolated genomic DNA from 152 Caucasian blood donors, 83 elite (national level) sprint athletes and 183 elite endurance athletes. Genotyping of these individuals was performed by amplifying a 291 bp region spanning exon 16 of the *ACTN3* gene using PCR, followed by digestion with *Dde* I and PAGE analysis of the resulting digest products. This technique allowed rapid identification of all three possible genotypes (Figure 1).

Results

Table 1 shows the frequencies of the three possible genotypes in the three groups. Analysis of the genotyping data revealed highly significant differences in *ACTN3* genotypic frequencies between elite sprint athletes and controls, with the frequency of the XX genotype (which results in an α -actinin-3 null phenotype) approximately threefold lower in sprint athletes compared to controls, and more than four-fold lower in sprinters compared to endurance athletes (Figure 2). The endurance group displayed a higher frequency of the XX genotype than controls, but this difference was not statistically significant with our current data set.

Table 1. *ACTN3* genotype frequencies in elite athletes and controls. Frequencies of the XX genotype (bold font) are illustrated in Figure 2.

<i>ACTN3</i> Genotype	Endurance (n=183)	Control (n=152)	Sprint (n=83)
RR	59 (0.32)	46 (0.30)	37 (0.45)
RX	77 (0.42)	78 (0.51)	41 (0.49)
XX	47 (0.26)	28 (0.18)	5 (0.06)

Discussion

These data suggest that the presence of α -actinin-3 protein has a positive effect on sprint performance, a finding consistent with the postulated structural and signalling functions of α -actinin-3 in fast skeletal muscle fibres. We are currently undertaking further studies, including the generation of a mouse model of *ACTN3* deficiency, to determine the precise physiological basis of this effect.

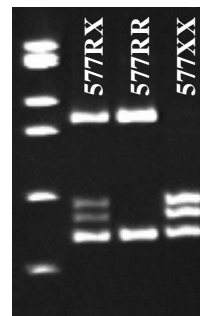


Figure 1. A simple PCR/restriction assay used to rapidly determine *ACTN3* genotype. Exon 16 of *ACTN3* was amplified from genomic DNA using PCR, then digested with the enzyme *Dde* I. The 577X allele contains an extra *Dde* I restriction site, allowing genotype to be identified by PAGE analysis of restriction products.

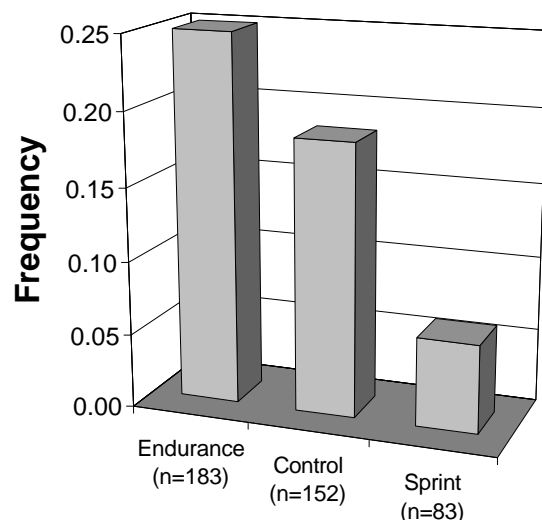


Figure 2. Frequency of the XX genotype in controls and elite sprint and endurance athletes. Significant differences in XX frequency were observed between controls and sprint athletes ($\chi^2 = 6.84$, d.f. = 1, $p = 0.009$) and between sprint and endurance athletes ($\chi^2 = 14.03$, d.f. = 1, $p = 0.0002$).

1. North, K.N., Yang, N., Wattanasirichaigoon, D., Mills, M., Tong, H.Q., Eastale, S. & Beggs, A.H. *Nature Genetics* **21**, 353-354 (1999).
2. Mills, M., Yang, N., Weinberger, R., Vander Woude, D.L., Beggs, A.H., Eastale, S. & North, K. *Human Molecular Genetics* **10**, 1335-1346 (2001).

A common sequence variant in the *ACTN3* gene results in deficiency of α -actinin-3 in skeletal muscle in ~18% of the normal population. We have found a significant association between the presence of α -actinin-3 and sprint performance at an elite level, suggesting a role for α -actinin-3 in the generation of force at high velocity.