A gene for speed: *ACTN3*, athletes, evolution and impact on human health

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The human *ACTN3* gene encodes the protein α-actinin-3, a component of the contractile apparatus in fast skeletal muscle fibres. In 1999, we identified a common polymorphism in *ACTN3* (R577X) that results in absence of α-actinin-3 in more than one billion people worldwide, despite the *ACTN3* gene being highly conserved during human evolution. In 2003, we demonstrated that *ACTN3* genotype influences elite athletic performance, and the association between *ACTN3* genotype and skeletal muscle performance has since been replicated in athletes and non-athlete cohorts. We have also studied the evolution of the R577X allele during human evolution and demonstrated that the null (X) allele has undergone strong, recent positive selection in Europeans and Asian populations. We have developed an *Actn3* knockout mouse model that replicates α-actinin-3 deficiency in humans and has already provided insight into the role of α-actinin-3 in the regulation of skeletal muscle metabolism, fibre size, muscle mass and contractile properties. In particular, mouse muscle lacking α-actinin-3 uses energy more efficiently, with the fast fibres displaying metabolic and contractile properties of slow oxidative fibres. While this favors endurance activities, the trade off is that the muscle cannot generate the rapid contractions needed to excel in sprinting. We propose that the shift towards more efficient aerobic muscle metabolism associated with α-actinin-3 deficiency also underlies the adaptive benefit of the 577X allele. We have now shown that α-actinin-3 plays a role in regulating the activity of glycogen phosphorylase. Our current studies are focussed on the effect of *ACTN3* genotype on response to exercise, the onset and severity of muscle disease phenotype, glucose homeostasis, and weight gain in response to changes in diet.