New insights into the influence of *ACTN3* on muscle performance

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The *ACTN3* R577X polymorphism remains the most widely studied and best replicated genetic variant shown to influence human muscle performance. α-Actinin-3 deficiency due to homozygosity for the common null allele (*ACTN3* 577XX) occurs in 1 in 5 people worldwide and is associated with reduced sprint and power performance and enhanced endurance performance in elite athletes and the general population. We were the first to identify its association with human elite athletic performance and we have since generated and extensively phenotyped the *Actn3* knockout mouse model, which recapitulates human α-actinin-3 deficiency, in order to understand the molecular mechanisms underlying the *ACTN3* R577X effect on human muscle performance. Using a systems biology approach, we found that absence of α-actinin-3 in skeletal muscle reduces glycogen breakdown, enhances calcineurin signalling and alters Ca^{2+} handling properties, resulting in a shift in metabolic and contractile properties of fast-twitch fibres towards those of slower oxidative fibres.

Given its influence on muscle mass and strength, we and others have also identified *ACTN3* R577X as a risk factor for falling in the elderly and a genetic modifier of muscle disorders such as Duchenne muscular dystrophy (DMD) – demonstrating that findings from athletes have direct relevance to human health. Additionally, the mechanisms we identified in healthy muscles also explain the *ACTN3* R577X modifier effect on disease progression of DMD. The approaches in our studies, refined over 19 years, provide a useful guideline for validating new genetic candidates and understanding their potential impact on health as well as elite athletic performance.