The evolution of *ACTN3*: Why has α-actinin-3 deficiency become so common and why do we care?

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α-Actinin-3 is a major component of the skeletal muscle Z-disk expressed specifically in fast glycolytic muscle fibres. α-Actinin-3 is typically considered to be a structural muscle protein which cross links actin and myosin, providing support during contraction. However, the α-actinins also interact with a wide array of metabolic, signalling and calcium handling proteins. A common genetic variant in *ACTN3* (R577X) has been identified. Homozygosity for the *ACTN3* null allele (577XX) is common and results in complete α-actinin-3 deficiency in ~1.5 billion individuals worldwide.

The *ACTN3* X-allele is ancient, dating back to over 1 million years old. We have identified strong, recent positive selection for the X-allele as modern humans migrated out of Africa into the colder climates of the Northern hemisphere (MacArthur *et al.*, 2007; Friedlander *et al.*, 2013). This increase in frequency corresponds to a greater global latitudinal gradient, lower mean annual temperature and reduced species richness/diversity. A higher prevalence of the X-allele has been observed in specific populations including Native Americans, Asians and Caucasians of European descent (Amorim *et al.*, 2015). The mechanism for the increase in X-allele frequency is currently unclear. We have developed an *ACTN3* knockout mouse to study this phenomenon further.

The *Actn3* KO mouse replicates many of the features seen in α-actinin-3 deficient humans; KO mice display reduced muscle mass, fast fibre size and grip strength, as well as enhanced endurance performance, and a shift in muscle metabolic towards a slower more oxidative muscle fibre type. Using this model we have begun to decipher the complex molecular mechanisms which result in altered muscle function. A combination of increased glycogen accumulation (*via* reduced glycogen phosphorylase activity), enhanced calcineurin signalling and elevated calcium release and reuptake (through increases in SERCA1 expression at the sarcoplasmic reticulum) are thought to result in a shift in muscle metabolism towards a more oxidative profile in the absence of α-actinin-3. We propose that this shift towards more energy-efficient skeletal muscle delivers an adaptive benefit against famine and cold exposure that, in-turn, would provide a selective advantage through improved survival.

Intriguingly, we have recently discovered that α-actinin-3 expression is also expressed in brown adipose tissue (BAT), which is known to play a key role in adaptive thermogenesis.

Both skeletal muscle and BAT share a common myogenic lineage (Timmons *et al.*, 2007). Until recently BAT was not considered to be present or functional in adults, however it is now thought to be activated with cold exposure, and plays an important role in energy metabolism and adaptive thermogenesis in both new-borns and adults (Lee *et al.*, 2014). Using our *Actn3* whole body KO mouse we are able to study the role of α-actinin-3 in both skeletal muscle and BAT.

The current focus of our research is to understand the effect of *ACTN3* genotype on glucose homeostasis, weight gain/loss, and adaptive thermogenesis in both skeletal muscle and BAT. Developing a better understand of the role α-actinin-3 plays in adaptive thermogenesis will help explain both the positive selection benefits and potentially highlight important mechanism responsible for alterations in weight gain/loss and type 2 diabetes (T2D).

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