

Metabolic consequences of α -actinin-3 deficiency – more than a structural muscle protein!

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Homozygosity for a common null polymorphism (R577X) in the gene ACTN3 results in absence of the fast muscle fibre protein α -actinin-3 in approximately 18% of the general population. ACTN3 genotype has been shown to influence elite and general athletic performance, muscle mass and strength (Yang *et al.*, 2003). Specifically α -actinin-3 deficient fast muscle fibres show a shift towards an oxidative phenotype. While this favors endurance, the trade-off is that the muscle cannot generate the rapid contractions needed to excel in power/sprint activities. Furthermore, preliminary data from five human cohorts has demonstrated that α -actinin-3 deficiency is associated with a reduced frequency of obesity, altered glucose and insulin homeostasis along with an increased risk of developing type-2 diabetes when obese.

An Actn3 knockout (KO) mouse model has been established to examine muscle performance and metabolism (MacArthur & North, 2007; MacArthur *et al.*, 2007,2008). This model has shown that α -actinin-3 plays a role in the post-translational regulation of glycogen phosphorylase, and α -actinin-3 deficiency leads to a significantly reduced capacity to use glycogen as an energy source (Quinlan *et al.*, 2010). We have now determined that the absence of α -actinin-3 also influences glucose metabolism and alters weight gain on a high fat diet (HFD). Specifically KO mice show improved glucose clearance at baseline and resistance to weight gain following HFD. We have now begun to identify the molecular pathways involved in this response – highlighting α -actinin-3 as an important genetic regulator of key metabolic signaling pathways AMPK and calcineurin.

α -Actinin-3 is commonly considered to be a structural muscle protein. Through this research we have shown a prominent effect in skeletal muscle energy metabolism. The existence of a common genetic variant that affects the structural and metabolic function of muscle has important implications for health – in particular regarding weight gain, obesity, type-2 diabetes and metabolic disease.

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