α-actinin-3 and sarcoplasmic reticulum function

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Over 1.5 billion people lack the skeletal muscle fast-twitch fibre protein α-actinin-3 due to homozygosity for a common null polymorphism (R577X) in the ACTN3 gene. The α-actinin-3 deficiency is detrimental to sprint performance in elite athletes and beneficial to endurance activities. The ACTN3 null variant has undergone strong positive selection during recent human evolution, appearing to provide a survival advantage where food resources are scarce and climate is cold. This adaptation hypothesis has recently been assessed through the analysis of global ACTN3 genotype and biodiversity data compared to geographical location. Friedlander *et al.* (2013) provide evidence that the ACTN3 577XX genotype has evolved in association with global latitudinal gradient, suggesting that environmental variables including climate (mean annual temperature) and diet, have influenced the evolution of the R577X polymorphism in recent humans. This cold-acclimatisation and thermogenesis in α-actinin-3-deficient muscle provides one possible explanation for the selective favouring of the ACTN3 577X null polymorphism in populations living in cold environments during recent evolution, one of the very rare cases in the human genome of positive selection for a single-gene null allele. Our group used the non-shivering "fast-twitch" Flexor digitorum brevis (FDB) toe muscle from the mouse to investigate possible mechanism/s responsible for providing this improved adaption to cold climates (Head *et al.*, 2015). We did this by looking at the kinetics of the Ca^{2+}-transients (twitch and tetanic), the Ca^{2+}-frequency-release curves and fatigue resistance of the tetanic Ca^{2+} in individual FDB muscle fibres. We also made the first direct determinations of the unloaded speed of shortening of a single twitch in Actn3 KO muscle using an ultra-high frame rate camera in order to correlate the actual speed of shortening with the rise time of the Ca^{2+} transient. Finally we assessed the expression of key proteins involved in Ca^{2+} regulation of the SR including, SERCA1, calsequestrin 1, CSQ1, SR luminal Ca^{2+} buffering protein, the Ca^{2+} release channel, ryanodine receptor (RyR1)and sarcalumenin as well as the cytosolic Ca^{2+} binding protein parvalbumin. Taken together, our data have shown that the absence of α-actinin-3 results in a shift in the fast-muscle fibre Ca^{2+} handling properties without altering the speed of contraction or the myosin heavy chain isoform. Such changes could be described as effectively pre-acclimatising the muscles of Actn3 KO mice to cold environments and endurance muscle performance. We hypothesize that these mechanisms are partially or wholly responsible for an increased survival rate of α-actinin-3 deficient (577XX) individuals, resulting in positive selection of the X-allele in the temperate northern hemisphere.

Friedlander SM, Herrmann AL, Lowry DP, Mepham ER, Lek M, North KN, Organ CL. (2013) ACTN3 allele frequency inhumans covaries with global latitudinal gradient. *PLoS ONE* **8:** e52282. doi: 10.1371/journal.pone.0052282

Head SI, Chan S, Houweling PJ, Quinlan KG, Murphy R, Wagner S, Friedrich 6, North KN. (2015) Altered Ca^{2+} Kinetics associated with α-actinin-3 deficiency may explain positive selection for ACTN3 null allele in human evolution. *PLoS Genet* **11**: e1004862. doi: 10.1371/journal.pgen.1004862