α-Actinin-3: a novel genetic modifier of Duchenne muscular dystrophy

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Homozygosity for a common null polymorphism (R577X) in the *ACTN3* gene results in deficiency of the fast muscle fibre protein, α-actinin-3, in ~18% of the world's population (North *et al.*, 1999). *ACTN3* genotype significantly influences muscle performance in elite athletes (Yang *et al.*, 2003) and in the general population (Clarkson *et al.*, 2005). On this basis we hypothesized that *ACTN3* genotype may contribute to the phenotypic variation in disease progression seen in DMD patients (Desguerre *et al.*, 2009).

Analysis of the CINRG natural history cohort reveals α-actinin-3 deficient DMD patients have significantly reduced muscle strength and longer 10m walk test times at baseline, indicating lower overall muscle function. In order to investigate this further, we crossed our *Actn3*$^{-/-}$ mouse line with the *mdx* model of DMD. Consistent with our findings in patients, isolated muscles from *Actn3*$^{-/-}$ *mdx* mice show reduced maximum specific force and are significantly more damaged by eccentric stretching.

However, aged *Actn3*$^{-/-}$ *mdx* mice show reduced accumulation of branched fibres and are protected from stretch-induced eccentric damage, suggesting that α-actinin-3 deficiency ameliorates the progression of dystrophic pathology. Preliminary longitudinal analysis of the CINRG natural history cohort suggests that α-actinin-3 deficiency is similarly protective against progression in DMD patients.

α-Actinin-3 deficiency is associated with increased calcineurin signaling which induces expression of the slow myogenic program and causes a shift towards slow, oxidative muscle metabolism. Over-expression of calcineurin can ameliorate pathology in *mdx* mice, suggesting that the metabolic shift associated with α-actinin-3 deficiency may underlie the protective effect observed in DMD.

Genetic modifiers have immediate importance in the stratification and analysis of results of therapeutic trials and have the potential to provide insight into the molecular pathogenesis of DMD. Our studies in *Actn3*$^{-/-}$ *mdx* mice suggest that α-actinin-3 deficiency is detrimental to muscle performance in DMD at baseline, but ameliorates the progression of dystrophic pathology over time.

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