Mutations in the α-tropomyosin-slow gene (TPM3) cause sarcomeric dysfunction in slow muscle fibres

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Tropomyosin (TM) is an important regulatory protein in the thin filament of the muscle sarcomere. Dominant mutations in TPM3, which encodes α-tropomyosin-slow (α-TM-slow), cause a congenital myopathy, characterized by static or slowly progressive muscle weakness. TPM3 mutations result in a selective decrease in slow muscle fibre size. Additional pathological features such as nemaline bodies may be present. The mechanism by which TPM3 mutations cause muscle weakness and the role of slow fibre hypotrophy in this process is poorly understood. In this study we used 10 archived frozen muscle biopsies from patients with six dominant TM mutations. We characterized tropomyosin isoform expression and used single, permeabilized muscle fibres to determine sarcomeric function.

All patients showed normal tropomyosin isoform expression and mutant tropomyosin accounted for between 30-50% of α-TM-slow. Contractile measurements on single permeabilized patient muscle fibres showed most mutations are associated with a selective decrease of force generation capacity at saturating calcium levels in slow muscle fibres. In addition, the slow fibres typically displayed changes in cross bridge cycling kinetics and reduced calcium sensitivity of muscle contraction. The severity of the abnormalities at the single fibre level correlated with clinical severity observed in the patients. Interestingly, fast muscle fibres did not appear to be affected.

Our study confirmed that mutant tropomyosin causes muscle weakness by altering cross-bridge cycling and calcium sensitivity of the thin filament specifically in slow muscle fibres. The fact that fast muscle fibres are unaffected but cannot compensate for slow fibre dysfunction emphasizes the distinct role of the two fibre types. We believe slow muscle fibre hypotrophy could be a direct effect of reduced calcium sensitivity resulting in reduced sarcomere activation at submaximal calcium levels. Recently, drugs have been developed that specifically target calcium sensitivity of muscle contraction. Our findings indicate that these drugs may improve slow fibre activation and may increase muscle strength in many patients with congenital myopathy caused by TM mutations.