Nemaline myopathy and distal arthrogryposis associated with an autosomal recessive TNNT3 splice variant.

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Abstract
A male neonate presented with severe weakness, hypotonia, contractures and congenital scoliosis. Skeletal muscle specimens showed marked atrophy and degeneration of fast fibres with striking nemaline rods and hypertrophy of slow fibres that were ultrastructurally normal. A neuromuscular gene panel identified a homozygous essential splice variant in TNNT3 (chr11:1956150G > A, NM_006757.3:c.681+1G > A). TNNT3 encodes skeletal troponin-Tfast and is associated with autosomal dominant distal arthrogryposis. TNNT3 has not previously been associated with nemaline myopathy, a rare congenital myopathy linked to defects in proteins associated with thin filament structure and regulation. cDNA studies confirmed pathogenic consequences of the splice variant, eliciting exon-skipping and intron retention events leading to a frameshift. Western blot showed deficiency of troponin-Tfast protein with secondary loss of troponin-Ifast. We establish a homozygous splice variant in TNNT3 as the likely cause of severe congenital nemaline myopathy with distal arthrogryposis (NM-DA), characterised by specific involvement of Type-2 fibres and deficiency of troponin-Tfast. This article is protected by copyright. All rights reserved.

KEYWORDS: Genetics; Nemaline myopathy; Neuromuscular disease; TNNT3; Troponin T-fast

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