Abstract

OBJECTIVE: Comprehensive clinical characterisation of congenital titinopathy to facilitate diagnosis and management of this important emerging disorder.

METHODS: Using massively parallel sequencing we identified 30 patients from 27 families with two pathogenic nonsense, frameshift and/or splice site TTN mutations in trans. We then undertook a detailed analysis of the clinical, histopathology and imaging features of these patients.

RESULTS: All patients had prenatal- or early-onset hypotonia and/or congenital contractures. None had ophthalmpoplegia. Scoliosis and respiratory insufficiency typically developed early and progressed rapidly, whereas limb weakness was often slowly progressive, and usually did not prevent independent walking. Cardiac involvement was present in 46% of patients. Relatives of two patients had dilated cardiomyopathy. Creatine kinase levels were normal to moderately elevated. Increased fibre size variation, internalised nuclei and cores were common histopathological abnormalities. Cap-like structures, whorled or ring fibres, and mitochondrial accumulations were also observed. Muscle MRI showed gluteal, hamstring and calf muscle involvement. Western blot analysis showed a near-normal sized titin protein in all samples. The presence of two mutations...
predicted to impact both N2BA and N2B cardiac isoforms appeared to be associated with greatest risk of cardiac involvement. One third of patients had one mutation predicted to impact exons present in fetal skeletal muscle, but not included within the mature skeletal muscle isoform transcript. This strongly suggests developmental isoforms are involved in the pathogenesis of this congenital/early-onset disorder.

**INTERPRETATION:** This detailed clinical reference dataset will greatly facilitate diagnostic confirmation and management of patients and has provided important insights into disease pathogenesis. This article is protected by copyright. All rights reserved.

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