A Novel Recessive TNNT1 Congenital Core-Rod Myopathy in French Canadians.

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Abstract

OBJECTIVE: Recessive null variants of the slow skeletal muscle troponin T1 (TNNT1) gene are a rare cause of nemaline myopathy that is fatal in infancy due to respiratory insufficiency. Muscle biopsy shows rods and fiber type disproportion. We report on four French Canadians with a novel form of recessive congenital TNNT1 core-rod myopathy.

METHODS: Patients underwent full clinical characterization, lower limb MRI, muscle biopsy and genetic testing. A zebrafish loss-of-function model using morpholinos was created to assess the pathogenicity of the identified variant. Wild type or mutated human TNNT1 mRNAs were co-injected with morpholinos to assess their abilities to rescue the morphant phenotype.

RESULTS: Three adults and one child shared a novel missense homozygous variant in the TNNT1 gene (c.287T>C; p.Leu96Pro). They developed from childhood very slowly progressive limb-girdle weakness with rigid spine and disabling contractures. They suffered from restrictive lung disease requiring non-invasive mechanical ventilation in three patients, as well as recurrent episodes of rhabdomyolysis triggered by infections, which were relieved by dantrolene in one patient. Older patients remained ambulatory into their sixties. MRI of the leg muscles showed fibro-fatty infiltration predominating in the posterior thigh and the deep posterior leg compartments. Muscle biopsies showed multi-minicores and lobulated fibers, rods in half the patients and no fiber type disproportion. Wild type TNNT1 mRNA rescued the zebrafish morphants but mutant transcripts
failed to do so.

**INTERPRETATION:** This study expands the phenotypic spectrum of TNNT1 myopathy and provides functional evidence for the pathogenicity of the newly identified missense mutation. This article is protected by copyright. All rights reserved.

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**KEYWORDS:** TNNT1; congenital myopathy; multi-minicores; nemaline rods; rhabdomyolysis

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