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Clinical phenotype and loss of the slow skeletal muscle troponin T in three new patients with recessive TNNT1 nemaline myopathy

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Abstract

Background: Congenital nemaline myopathies are rare pathologies characterised by muscle weakness and rod-shaped inclusions in the muscle fibres.

Methods: Using next-generation sequencing, we identified three patients with pathogenic variants in the *Troponin T type 1* (*TNNT1*) gene, coding for the troponin T (TNT) skeletal muscle isoform.

Results: The clinical phenotype was similar in all patients, associating hypotonia, orthopaedic deformities and progressive chronic respiratory failure, leading to early death. The anatomopathological phenotype was characterised by a disproportion in the muscle fibre size, endomysial fibrosis and nemaline rods. Molecular analyses of *TNNT1* revealed a homozygous deletion of exons 8 and 9 in patient 1; a heterozygous nonsense mutation in exon 9 and retention of part of intron 4 in muscle transcripts in patient 2; and a homozygous, very early nonsense mutation in patient 3.Western blot analyses confirmed the absence of the TNT protein resulting from these mutations.

Discussion: The clinical and anatomopathological presentations of our patients reinforce the homogeneous character of the phenotype associated with recessive *TNNT1* mutations. Previous studies revealed an impact of recessive variants on the tropomyosin-binding affinity of TNT. We report in our patients a complete loss of TNT protein due to open reading frame disruption or to post-translational degradation of TNT.

Keywords: diagnosis; neuromuscular diseases.

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