Format: Abstract

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The transcription coactivator ASC-1 is a regulator of skeletal myogenesis, and its deficiency causes a novel form of congenital muscle disease.

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Abstract

Despite recent progress in the genetic characterization of congenital muscle diseases, the genes responsible for a significant proportion of cases remain unknown. We analysed two branches of a large consanguineous family in which four patients presented with a severe new phenotype, clinically marked by neonatal-onset muscle weakness predominantly involving axial muscles, life-threatening respiratory failure, skin abnormalities and joint hyperlaxity without contractures. Muscle biopsies showed the unreported association of multi-minicores, caps and dystrophic lesions. Genome-wide linkage analysis followed by gene and exome sequencing in patients identified a homozygous nonsense mutation in TRIP4 encoding Activating Signal Cointegrator-1 (ASC-1), a poorly characterized transcription coactivator never associated with muscle or with human inherited disease. This mutation resulted in TRIP4 mRNA decay to around 10% of control levels and absence of detectable protein in patient cells. ASC-1 levels were higher in axial than in limb muscles in mouse, and increased during differentiation in C2C12 myogenic cells. Depletion of ASC-1 in cultured muscle cells from a patient and in Trip4 knocked-down C2C12 led to a significant reduction in myotube diameter ex vivo and in vitro, without changes in fusion index or markers of initial myogenic differentiation. This work reports the first TRIP4 mutation and defines a novel form of congenital muscle disease, expanding their histological, clinical and molecular spectrum. We establish the importance of ASC-1 in human skeletal muscle, identify transcriptional co-regulation as novel pathophysiological pathway, define ASC-1 as a regulator of late myogenic differentiation and suggest defects in myotube growth as a novel myopathic mechanism.

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