Homozygous SYNE1 mutation causes congenital onset of muscular weakness with distal arthrogryposis: a genotype-phenotype correlation.

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Abstract
The exceptionally large SYNE1 (spectrin repeat-containing nuclear envelope protein 1) gene encodes different nesprin-1 isoforms, which are differentially expressed in striated muscle and in cerebellar and cerebral neurons. Nesprin-1 isoforms can function in cytoskeletal, nuclear, and vesicle anchoring. SYNE1 variants have been associated with a spectrum of neurological and neuromuscular disease. Homozygosity mapping combined with exome sequencing identified a disease-causing nonsense mutation in the ultimate exon of full-length SYNE1 transcript in an 8-year-old boy with distal arthrogryposis and muscular hypotonia. mRNA analysis showed that the mutant transcript is expressed at wild-type levels. The variant truncates nesprin-1 isoforms for the C-terminal KASH (Klarsicht-ANC-Syne homology) domain. This is the third family with recessive arthrogryposis caused by homozygous distal-truncating SYNE1 variants. There is a SYNE1 genotype-phenotype correlation emerging, with more proximal homozygous SYNE1 variants causing recessive cerebellar ataxia of variable onset (SCAR8; ARCA-1).