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Knockin mouse model of the human CFL2 p.A35T mutation results in a unique splicing defect and severe myopathy phenotype.

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Abstract

Cofilin-2 is an actin-binding protein that is predominantly expressed in skeletal and cardiac muscles and belongs to the AC group of proteins which includes cofilin-1 and destrin. In humans, cofilin-2 (CFL2) mutations have been associated with congenital myopathies that include nemaline and myofibrillar myopathy. To understand the pathogenicity of the human CFL2 mutation, p.A35T, that first linked cofilin-2 with the human disease, we created a knock-in mouse model. The Cfl2A35T/A35T (KI) mouse were indistinguishable from their wild-type littermates at birth, but they rapidly worsened and died by postnatal day 9. The phenotypic, histopathologic and molecular findings mimicked the constitutive Cfl2-knockout (KO) mice described previously, including sarcomeric disruption and actin accumulations in skeletal muscles and negligible amounts of cofilin-2 protein. In addition, KI mice demonstrated a marked reduction in Cfl2 mRNA levels in various tissues including skeletal muscles. Further investigation revealed evidence of alternative splicing with the presence of two alternate transcripts of smaller size. These alternate transcripts were expressed at very low levels in the wild-type mice and were significantly upregulated in the mutant mice, indicating that pre-translational splicing defects may be a critical component of the disease mechanism associated with the mutation. Evidence of reduced expression of the full-length CFL2 transcript was also observed in the muscle biopsy sample of the patient with p.A35T mutation.

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