Reducing dynamin 2 (DNM2) rescues DNM2-related dominant centronuclear myopathy.

Buono S1,2,3,4,5, Ross JA6, Tasfaout H1,2,3,4, Levy Y6, Kretz C1,2,3,4, Tayefeh L7, Matson J7, Guo S7, Kessler P1,2,3,4, Monia BP7, Bitoun M8,9,10, Ochala J6, Laporte J11,2,3,4, Cowling BS

Author information

Abstract

Centronuclear myopathies (CNM) are a group of severe muscle diseases for which no effective therapy is currently available. We have previously shown that reduction of the large GTPase DNM2 in a mouse model of the X-linked form, due to loss of myotubularin phosphatase MTM1, prevents the development of the skeletal muscle pathophysiology. As DNM2 is mutated in autosomal dominant forms, here we tested whether DNM2 reduction can rescue DNM2-related CNM in a knock-in mouse harboring the p.R465W mutation (Dnm2RW/+) and displaying a mild CNM phenotype similar to patients with the same mutation. A single intramuscular injection of adeno-associated virus-shRNA targeting Dnm2 resulted in reduction in protein levels 5 wk post injection, with a corresponding improvement in muscle mass and fiber size distribution, as well as an improvement in histopathological CNM features. To establish a systemic treatment, weekly i.p. injections of antisense oligonucleotides targeting Dnm2 were administered to Dnm2RW/+ mice for 5 wk. While muscle mass, histopathology, and muscle ultrastructure were perturbed in Dnm2RW/+ mice compared with wild-type mice, these features were indistinguishable from wild-type mice after reducing DNM2. Therefore, DNM2 knockdown via two different strategies can efficiently correct the myopathy due to DNM2 mutations, and it provides a common therapeutic strategy for several forms of centronuclear myopathy. Furthermore, we provide an example of treating a dominant disease by targeting both alleles, suggesting that this strategy may be applied to other dominant diseases.

KEYWORDS: adeno-associated virus; antisense oligonucleotides; congenital myopathy; dynamin 2; myotubular myopathy

PMID: 30291191 DOI: 10.1073/pnas.1808170115
Conflict of interest statement

LinkOut - more resources