Dysfunctional sarcomere contractility contributes to muscle weakness in ACTA1-related nemaline myopathy (NEM3).

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Abstract

OBJECTIVE: Nemaline myopathy (NM) is one of the most common congenital non-dystrophic myopathies and is characterized by muscle weakness, often from birth. Mutations in ACTA1 are a frequent cause of NM (i.e. NEM3). ACTA1 encodes alpha-actin 1, the main constituent of the sarcomeric thin filament. The mechanisms by which mutations in ACTA1 contribute to muscle weakness in NEM3 are incompletely understood. We hypothesized that sarcomeric dysfunction contributes to muscle weakness in NEM3 patients.

METHODS: To test this hypothesis, we performed contractility measurements in individual muscle fibers and myofibrils obtained from muscle biopsies of fourteen NEM3 patients with different ACTA1 mutations. To identify the structural basis for impaired contractility, low angle x-ray diffraction and stimulated emission-depletion microscopy were applied.

RESULTS: Our findings reveal that muscle fibers of NEM3 patients display a reduced maximal force generating capacity, which is caused by dysfunctional sarcomere contractility in the majority of patients, as revealed by contractility measurements in myofibrils. Low angle x-ray diffraction and stimulated emission-depletion microscopy indicate that dysfunctional sarcomere contractility in NEM3 patients involves a lower number of myosin heads binding to actin during muscle activation. This lower number is not the result of reduced thin filament length. Interestingly, the calcium sensitivity of force is unaffected in some patients, but decreased in others.

INTERPRETATION: Thus, dysfunctional sarcomere contractility is an important contributor to muscle weakness in the majority of NEM3 patients, information which is crucial for patient stratification in future clinical trials. This article is protected by copyright. All rights reserved.

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