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Imaging-based evaluation of pathogenicity by novel DNM2 variants associated with centronuclear myopathy

Kenshiro Fujise [1], Mariko Okubo [2] [3], Tadashi Abe [1], Hiroshi Yamada [1], Kohji Takei [1], Ichizo Nishino [2], Tetsuya Takeda [1], Satoru Noguchi [2]

Affiliations
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Abstract

Centronuclear myopathy is a group of inherited congenital diseases showing clinically progressive muscle weakness associated with the presence of centralized myonuclei, diagnosed by genetic testing and muscle biopsy. The gene encoding dynamin 2, DNM2, has been identified as a causative gene for an autosomal dominant form of centronuclear myopathy. However, the information of a DNM2 variant alone is not always sufficient to gain a definitive diagnosis as the pathogenicity of many gene variants is currently unknown. In this study, we identified 5 novel DNM2 variants in our cohort. To establish the pathogenicity of these variants without using clinicopathological information, we used a simple in cellulo imaging-based assay for T-tubule-like structures to provide quantitative data that enable objective determination of pathogenicity by novel DNM2 variants. With this assay, we demonstrated that the phenotypes induced by mutant dynamin 2 in cellulo are well correlated with biochemical gain-of-function features of mutant dynamin 2 as well as the clinicopathological phenotypes of each patient. Our approach of combining an in cellulo assay with clinical information of the patients also explains the course of a disease progression by the pathogenesis of each variant in DNM2-associated centronuclear myopathy. This article is protected by copyright. All rights reserved.

Keywords: DNM2; T-tubules; centronuclear myopathy; in cellulo assay; membrane remodeling.