Compensatory effect of Dnm2 gain-of-function and loss-of-function mutations in centronuclear myopathy and Charcot-Marie-Tooth neuropathy

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Résumé

Dominant mutations in DNM2, encoding a GTPase implicated in membrane trafficking, result in two distinct neuromuscular diseases. Centronuclear myopathy (CNM) is characterized by muscle weakness and structural myofiber anomalies, and Charcot-Marie-Tooth neuropathy (CMT) is associated with sensory loss and neuron defects. CNM and CMT presumably involve an inverse pathomechanism with DNM2 gain-of-function in CNM and loss-of-function in CMT. However, the precise effect of the mutations is poorly understood, and no cure is approved for any of the diseases.

In order to investigate the potential compensatory effect of CNM and CMT mutations, we crossed Dnm2S619L/+ CNM with Dnm2K562E/+ CMT mice, and the Dnm2S619L/K562E offspring underwent behavioral, functional, morphological and biochemical investigations at 8 weeks. Dnm2S619L/K562E mice were larger than Dnm2S619L/+ and Dnm2K562E/+ littermates and manifested an increased general muscle force. Moreover, Dnm2S619L/K562E mice did not display the coordination defects observed in Dnm2K562E/+mice on the treadmill, and the in situ muscle force was significantly higher compared with Dnm2S619L/+ littermates. Compared with Dnm2S619L/+ and Dnm2K562E/+ mice, histological analyses of Dnm2S619L/K562E muscle sections showed an increase of myofiber diameter, and a normalization of myofiber architecture with a normal localization of nuclei and mitochondria and restored collagen thickness. Sciatic nerve analysis of both individual disease models revealed a decreased g-ratio, attributed to axonal hypotrophy, while Dnm2S619L/K562E nerve fibers presented a normalized g-ratio due to axonal hypertrophy and myelin thickening. Taken together, these results show an improvement of muscle function, structure, and peripheral nerves defects in Dnm2S619L/K562E mice, compared with Dnm2S619L/+ and Dnm2K562E/+ mice.

Overall, this study is the first to report a compensatory effect of two different mutations in

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the same gene, causing two different disorders. This study confirms the loss-of-function mechanism in DNM2-CMT, and suggests the increase of DNM2 activity as potential therapeutic strategy.

Mots-Clés: Myopathy, neuropathy, Charcot, Marie, Tooth, disease, dynamin, compensation