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Clinicopathological features of titinopathy from a Chinese neuromuscular center

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Abstract

Titin, one of the largest proteins in humans, is a major component of muscle sarcomeres. Pathogenic variants in the titin gene (TTN) have been reported to cause a range of skeletal muscle diseases, collectively known as titinopathy. Titinopathy is a heterogeneous group of disabling diseases characterized by muscle weakness. In our study, we aimed to establish the clinicopathological-genetic spectrum of titinopathy from a single neuromuscular center. Three patients were diagnosed as having definite titinopathy, and additional three patients were diagnosed as having possible titinopathy according to the diagnostic criteria. All the patients showed initial symptoms from age one to 40 years. Physical examination revealed that five patients had muscle weakness, and that one patient experienced behavioral changes. Muscle biopsy specimens obtained from all six patients demonstrated multiple myopathological changes, including increased fiber size variation, muscle fiber hypertrophy or atrophy, formation of centralized cell nuclei, necklace cytoplasmic bodies, and formation of rimmed vacuoles and cores. Genetic testing revealed 11 different TTN alterations, including missense (6/11), nonsense (2/11), frameshift (2/11), and splicing (1/11) mutations. Our study provides further evidence that TTN mutations are more likely to be responsible for an increasing proportion of various myopathies, such as hereditary myopathy with early respiratory failure (HMERF), core myopathy, and distal myopathy with rimmed vacuoles, than currently recognized mutations. Our findings expand the clinical, pathohistological and genetic spectrum of titinopathy.

Keywords: TTN gene; myopathy; neuromuscular disorder; pathology; titinopathy.

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