論 文 要 旨

Complex hereditary peripheral neuropathies caused by novel variants in mitochondrial-related nuclear genes

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Abstract

Mitochondrial disorders are a group of clinically and genetically heterogeneous multisystem disorders and peripheral neuropathy is frequently described in the context of mutations in mitochondrial-related nuclear genes. This study aimed to identify the causative mutations in mitochondrial-related nuclear genes in suspected hereditary peripheral neuropathy patients. We enrolled a large Japanese cohort of clinically suspected hereditary peripheral neuropathy patients who were mutation negative in the prescreening of the known Charcot–Marie–Tooth disease-causing genes. We performed whole-exome sequencing on 247 patients with autosomal recessive or sporadic inheritance for further analysis of 167 mitochondrial-related nuclear genes. We detected novel bi-allelic likely pathogenic/pathogenic variants in four patients, from four mitochondrial-related nuclear genes: pyruvate dehydrogenase beta-polypeptide (*PDHB*), mitochondrial poly(A) polymerase (*MTPAP*), hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, beta subunit (*HADHB*), and succinate-CoA ligase ADP-forming beta subunit (*SUCLA2*). All these patients showed sensory and motor axonal polyneuropathy, combined with central nervous system or multisystem involvements. The pathological analysis of skeletal muscles revealed mild neurogenic changes without significant mitochondrial abnormalities. Targeted screening of mitochondria-related nuclear genes should be considered for patients with complex hereditary axonal polyneuropathy, accompanied by central nervous system dysfunctions, or with unexplainable multisystem disorders.

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