論 文 要 旨

Mutations in *MME* Cause an Autosomal-Recessive Charcot–Marie–Tooth Disease Type 2

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Objective: The objective of this study was to identify new causes of Charcot–Marie–Tooth (CMT) disease in patients with autosomal-recessive (AR) CMT.

Methods: To efficiently identify novel causative genes for AR-CMT, we analyzed 303 unrelated Japanese patients with CMT using whole-exome sequencing and extracted recessive variants/genes shared among multiple patients. We performed mutation screening of the newly identified membrane metalloendopeptidase (*MME*) gene in 354 additional patients with CMT. We clinically, genetically, pathologically, and radiologically examined 10 patients with the *MME* mutation.

Results: We identified recessive mutations in *MME* in 10 patients. The *MME* gene encodes neprilysin (NEP), which is well known to be one of the most prominent beta-amyloid (Ab)-degrading enzymes. All patients had a similar phenotype consistent with late-onset axonal neuropathy. They showed muscle weakness, atrophy, and sensory disturbance in the lower extremities. All the *MME* mutations could be loss-of-function mutations, and we confirmed a lack/decrease of NEP protein expression in a peripheral nerve. No patients showed symptoms of dementia, and 1 patient showed no excess Ab in Pittsburgh compound-B positron emission tomography imaging.

Interpretation: Our results indicate that loss-of-function *MME* mutations are the most frequent cause of adult-onset AR-CMT2 in Japan, and we propose that this new disease should be termed AR-CMT2T. A loss-of-function *MME* mutation did not cause early-onset Alzheimer's disease. Identifying the *MME* mutation responsible for AR-CMT could improve the rate of molecular diagnosis and the understanding of the molecular mechanisms of CMT.