論文審査の要旨

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Hereditary Sensory and Autonomic Neuropathy Type IID Caused by an SCN9A Mutation
（*SCN9A* 遺伝子変異による新疾患遺伝性感覚・自律神経性ニューロパチーType IID の確立）

Hereditary sensory and autonomic neuropathy (HSAN) is a rare, clinically and genetically heterogeneous group of disorders, characterized by predominant sensory nerve dysfunction and varying degree of autonomic nervous dysfunction. Till date, 11 HSAN disease-causing genes have been reported. However, the research about clinical and genetic features of Japanese patients with HSAN was limited. On the basis of clinical, electrophysiological, and sural nerve pathological studies, the degree applicant collected 9 Japanese patients with suspected HSAN. Using a next-generation sequencing system (Illumina MiSeq), a panel of 16 (11 disease-causing and 5 disease-related) genes in these patients were sequenced.

After the genetic study, together with the clinical, electrophysiological, and pathological findings, the following results were presented:

1) In patient 1 and 2, a homozygous frameshift mutation, c.3993delGinsTT, was identified in exon 22 of *SCN9A*. This mutation was co-segregated in their pedigrees. Meanwhile, an elder sister of patient 1 was found harboring the same genotype.
2) All of the three patients suffered from definite insensitivity to pain and temperature and varying degree of autonomic dysfunctions, accompanied by hyposmia, hearing loss, hypogeusia, bone dysplasia, or fracture.
3) The nerve conduction study revealed sensory-predominant axonal multiple mononeuropathy in an asymmetric distribution, which was inconsistent with their clinical symptoms.
4) The sural nerve pathology exhibited varying severity among fasciculi, or between patients, while both small and large nerve fibers were involved.

SCN9A encodes the voltage-gated sodium channel ($Na_V1.7$), and is preferentially expressed within the dorsal root ganglion and sympathetic ganglion neurons and their small-diameter peripheral axons. Gain-of-function and loss-of-function mutations of *SCN9A* have been found to be associated with several phenotypes. However, the applicant successfully proved that the new phenotype of their patients is distinct from all the previously reported patients. For the first time, this study demonstrated that an *SCN9A* loss-of-function mutation could generate an HSAN phenotype, as HSAN type IID.

This study identified a new subtype of HSAN in the Japanese patients. As an academic dissertation, it is valuable and well-finished.