

論 文 要 旨

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

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【Introduction and Objective】

Hereditary sensory and autonomic neuropathy (HSAN) encompass a clinically and genetically heterogeneous group of disorders that are associated with sensory dysfunction (altered pain and temperature perception, etc.) and varying degrees of autonomic dysfunction (postural hypotension, sweating abnormalities, etc.). Till date, HSAN has been classified into six main groups on the basis of their mode of inheritance and clinical features, and eleven HSAN disease-causing genes have been demonstrated. The objective of this study is to identify the clinical features of Japanese patients with suspected HSAN on the basis of genetic diagnosis.

【Material and Methods】

On the basis of clinical, electrophysiological, and pathological findings of sural nerve biopsy, nine Japanese patients with sensory and autonomic nervous dysfunctions, but without multiple motor nerve involvement, were selected. Using a next-generation sequencing system (Illumina MiSeq), 357 coding exons and exon-intron junctions of eleven known HSAN disease-causing genes and five related genes (*SCN9A*, *CCT5*, *PRNP*, *FLVCRI*, and *RNF170*) were screened.

The protocol of this study was reviewed and approved by the Institutional Review Board of Kagoshima University. All patients and family members provided written, informed consents to participate in this study.

【Results】

Using the MiSeq sequencing system, all of the nine cases were genotyped successfully. A homozygous frameshift mutation, c.3993delGinsTT, was identified in exon 22 of *SCN9A* from two male patients (patient 1 and 2: 50 and 33 years old, respectively). The clinical phenotype was characterized by adolescent or congenital onset with loss of pain and temperature sensation, autonomic nervous dysfunctions, hearing loss, and hyposmia. This mutation co-segregated with the patients in their pedigrees, and was subsequently found in a sister of patient 1, who also

exhibited sensory and autonomic nervous system dysfunctions, with recurrent fractures being the most predominant feature. Nerve conduction studies revealed asymmetric sensory nerve involvement, especially in patient 1. Besides, sural nerve pathology showed loss of large myelinated fibers in patient 1, while patient 2 showed no evidence of abnormalities.

【Conclusion and Discussion】

In two Japanese families with autosomal recessive HSAN, we identified a novel homozygous mutation, c.3993delGinsTT, in *SCN9A*. This loss-of-function mutation is expected to shift the reading frame and generate a premature stop codon. For the first time, we demonstrated that an *SCN9A* mutation could generate an HSAN phenotype. We propose this discovery as a new disease entity, HSAN type IID.

SCN9A encodes the voltage-gated sodium channel (Nav1.7), and is preferentially expressed within the dorsal root ganglion and sympathetic ganglion neurons and their small-diameter peripheral axons. The Nav1.7 is crucial for the depolarizing phase of neuronal action potentials, and it seems to determine the excitability and repetitive firing properties of neurons. Gain-of-function *SCN9A* mutations result in several painful disorders due to hyperexcitable nociceptive neurons and states, such as inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and small nerve fiber neuropathy (SFN); loss-of-function *SCN9A* mutations produce no sodium current and generate channelopathy-associated insensitivity to pain (CIP), which is characterized by congenital insensitivity to pain perception and anosmia.

However, the autonomic dysfunction has been regarded as exclusionary criteria for the diagnosis of CIP. In addition, in our patients, the onset age and limited pain insensitivity (distal limb) are also distinct from the CIP. To sum up, the clinical features of present patients are different from all of the known *SCN9A*-related disorders.

On the other hand, in all the reported cases with *SCN9A* mutation, no definite abnormalities have been described using either nerve conduction study or sural nerve pathological examination. But in our index patients, specifically in patient 1, abnormalities were detected in both the nerve conduction study and sural nerve pathology, which suggested that the large myelinated fibers were affected. Moreover, a mismatch between the distribution of affected fibers and the severity of the loss-of-pain sensations was also uncovered. Taken together, all these findings may indicate that the dysfunction of the dorsal root ganglion is more predominant than that of the peripheral nerve.

The age of onset and predominant symptoms were significantly different in three patients. We are able to summarize that one loss-of-function *SCN9A* mutation can produce heterogeneous phenotype, and the genotype-phenotype association still requires further research.