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SHORT COMMUNICATION

Acute encephalopathy with a novel point mutation in the *SCN2A* gene

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Summary Mutations of the neuronal voltage-gated sodium channel alpha subunit type II (*SCN2A*) cause various epileptic syndromes, but have never been reported in association with acute encephalopathy. To validate the involvement of *SCN2A* mutations in acute encephalopathy, we screened 25 patients and found a novel missense mutation (Met1128Thr) in a patient with acute encephalitis with refractory, repetitive partial seizures (AERRPS). This finding suggests that *SCN2A* mutation is a predisposing factor for acute encephalopathy.

Introduction

Mutations of the neuronal voltage-gated sodium channel alpha subunit type II (*SCN2A*) gene cause various epileptic syndromes, including intractable childhood epilepsies (Kamiya et al., 2004; Ogiwara et al., 2009; Shi et al., 2009; Liao et al., 2010) and benign familial neonatal—infantile seizures (Sugawara et al., 2001; Heron et al., 2002). However, the association of this gene with acute encephalopathy has never been reported previously. We present here a patient with acute encephalopathy (AE) who met most of the diagnostic criteria for acute encephalitis with refractory, repetitive partial seizures (AERRPS) (Awaya and Fukuyama, 1986; Sakuma, 2009). This is the first case report of acute encephalopathy with an *SCN2A* mutation.

Subjects and methods

Patients

Subjects of this study included 25 Japanese patients who had been diagnosed with AE. Regarding the syndrome classification of AE, the clinical diagnosis was AERRPS in 8

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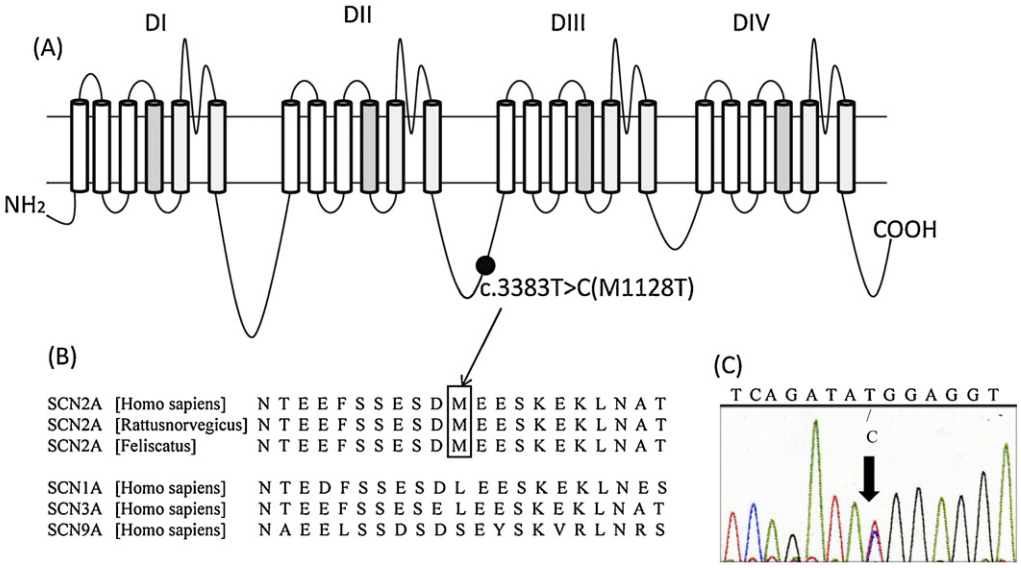

Figure 1 A novel missense mutation, c.3383T > C (Met1128Thr), affecting conserved amino acid in the *SCN2A* gene. Structure of human SCN2A with localization of the Met1128Thr mutation (closed circle) in the loop between domains II and III (A). Met1128 (boxed) and the surrounding amino acids are highly conserved in mammalians (B). Electropherogram of the patient's mutation (C).

patients, acute encephalopathy with biphasic seizures and reduced diffusion (AESD) (Takanashi et al., 2006) in 3, acute necrotizing encephalopathy (Mizuguchi et al., 1995) in 1, and unclassified AE in 13, based on the diagnostic criteria described previously (Mizuguchi et al., 2007; Kobayashi et al., 2010; Saitoh et al., 2012). Normal control subjects were obtained from the Human Science Research Resources Bank (Osaka, Japan). The genetic analysis was approved by the Ethics Review Committee of both Okayama University and the University of Tokyo.

Genetic analysis

Genomic DNA of the patient was prepared from peripheral blood cells. Twenty-six exons of the *SCN2A* gene were amplified with intronic primers. All PCR products were purified with a kit (QIAGEN, Venlo, Netherlands), reacted with the Big Dye Terminator FS ready reaction kit (Applied Biosystems, Foster City, CA, USA), and analyzed on an ABI PRISM310 sequencer (Applied Biosystems). Reference sequence of mRNA was based on information available from RefSeq (accession number: Human SCN2A NM021007).

Results and discussion

Among the 25 subjects, a male patient had a missense mutation c.3383T > C (Met1128Thr) in the *SCN2A* gene. This mutation has never been reported in the literature, and was not found in 100 normal controls. The amino acid residue 1128 is conserved among mammalians, and is assigned to the intracellular linker between domain II and domain III (Fig. 1). The cytoplasmic II—III region of voltage gated sodium channels Nav1.2 (Nav1.2) contains axonal initial segment (AIS) motif, which reportedly regulates electrical excitability during development and plasticity (Garrido et al., 2003). Since Met1128 is located in the AIS motif, the above mutation could affect Nav1.2 function. In this study, we were unable to analyze DNA of the patient's parents to determine whether this mutation is *de novo*. Neither could we analyze the patient's tissues other than peripheral blood to exclude the possibility of mosaicism.

This patient was born after a 41-week uneventful pregnancy with a weight of 3260 g. The family history was unremarkable. He developed normally during infancy and early childhood. At 6 years and 6 months of age, he had an initial generalized convulsive seizure after two days of prodromal fever and cold-like symptoms. He slept postictally with only a brief period of intermittent arousal, and then had three more convulsions. When the patient was admitted to a local hospital, he was delirious, but the physical examination was unremarkable. Laboratory data excluded the direct CNS infection. He remained comatose for 12 days with very frequent seizures, which were refractory to treatment and occurred up to 100 times per day. Interictal electroencephalogram (EEG) showed slow basic activity. Cranial computed tomography (CT) was initially normal, but later showed brain edema. Seizures were temporarily suppressed with gradual recovery of consciousness in about 30 days from the seizure onset. Seizures, however, recurred in about a month with alternating dominance involving either side of face and extremities, often in clusters, and remained uncontrollable. Intelligence gradually deteriorated with associated autistic behaviors. At 29 years of age, his intelligence was judged to be at around the two-year-old level. EEG showed slow background activity and rare multifocal spikes over the right temporal and bilateral frontopolar regions, and MRI disclosed mild cerebral atrophy without apparent involvement of the mesial temporal structures at 29 years of age.

The present case was the first case of AE associated with an *SCN2A* mutation. Our patient had AE at the age of 6 years, with characteristics: (1) a prolonged acute phase of about 30 days; (2) seizures frequently evolving into status