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DATA REPORT

A novel *KCNT1* mutation in a Japanese patient with epilepsy of infancy with migrating focal seizures

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Epilepsy of infancy with migrating focal seizures (EIFMS) is a rare, early-onset epileptic encephalopathy characterized by polymorphous focal seizures. *De novo* mutations of *KCNT1* have been identified in cases of this disorder. We encountered a sporadic patient with EIFMS, who suffered tonic convulsions at the age of 9 days. Using Sanger sequencing, we identified a *de novo* missense mutation of the same amino acid affected by a previously identified mutation, c.1420C>T (p.Arg474Cys).

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Epilepsy of infancy with migrating focal seizures (EIFMS), first described as migrating partial seizures of infancy (MMPSI) in 1995, is a rare, early-onset epileptic encephalopathy characterized by polymorphous focal seizures that commence within the first 6 months after birth.[1] This clinical condition is classified as early infantile epileptic encephalopathy 14 (MIM #614959) by the online database Mendelian inheritance in man (OMIM; http://www.omim.org/). Seizures are pharmacoresistant and ictal electroencephalogram (EEG) discharges show migrating ictal foci. In 2012, mutations of the potassium channel, subfamily T, member 1 gene (*KCNT1*; MIM #608167) located at 9q34.3 were identified in familial patients with severe autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE; MIM #615005) associated with intellectual/psychiatric problems.[2] Also, *de novo* mutations of *KCNT1* were reported in 6 out of 12 unrelated patients (50%) with EIFMS,[3] indicating the existence of clinical heterogeneity within *KCNT1* mutations. Those results suggested that familial mutations and *de novo* mutations of *KCNT1* correlate with ADNFLE and EIFMS, respectively. Different mutations of *KCNT1* were identified by subsequent analyses in EIFMS patients.[4] These findings suggested that *KCNT1* is the major disease-associated gene for the EIFMS phenotype.

KCNT1 encodes a sodium-activated potassium (KNa) channel that is highly expressed in the nervous system.[3] It is thought to regulate hyperpolarization following repetitive firing. The C-terminal cytoplasmic domain of KCNT1 interacts with a protein network, including the Fragile X mental retardation protein, thus stimulating the KCNT1 channel.[5] Barcia *et al.*[3] reported that mutations in the cytoplasmic C-terminal domain lead to constitutive activation of the KCNT1 channel. Our previous study reported two unrelated patients with EIFMS caused by a *de novo* missense mutation at the pore region of the KCNT1 channel.[4]

In the present study, we report on a 6-month-old Japanese male infant, the first child of nonconsanguineous healthy parents, born at 39 weeks of gestation using vacuum extraction because of diminished heart sounds. The child experienced an episode of apnea 4 days after delivery and tonic convulsions at day 9. Seizures evolved to frequent focal motor seizures that alternated from one side of the body to the other. Ictal EEGs showed asynchronous multifocal spikes derived from both brain hemispheres (Figure 1a). Seizures were intractable and easily led to status epilepticus, occurring in clusters. The child's psychomotor development was markedly delayed, he was confined to his bed and exhibited poor responses to his surroundings. Brain magnetic resonance imaging (MRI) conducted at 6 months of age showed delayed myelination and thin corpus callosum (Figure 1b). These findings have been supported by a cohort study of 14 patients with EIFMS, one-third of the patients exhibited delayed myelination with white matter hyperintensity revealed by a brain MRI[6] and 3 among the 6 patients with *KCNT1* mutations showed a thin corpus collosum.[3] On the basis of these clinical features, the child was diagnosed with EIFMS.

This study has been approved by Ethics Committee of Tokyo Women's Medical University. Upon obtaining written informed consent from the patient's family, mutation analysis using standard Sanger sequencing was performed for all exons of *KCNT1* and a heterozygous missense mutation (c.1420C>T, p.Arg474Cys) identified in exon 15 was the only variant found (Figure 2). Because both parents did not exhibit this mutation, it was determined to be *de novo* in origin. This alteration has not been previously reported and is not found in the single-nucleotide variation database (https://genome.ucsc.edu/). The affected amino acid is highly conserved among species (Figure 2). A *de novo* missense mutation at the same amino-acid, p.Arg474His, has been reported in a patient with EIFMS.[3] The clinical features of both patients with amino-acid changes at p.Arg474 are summarized in Table 1. Because both patients shared quite similar clinical characteristics, we concluded that p.Arg474Cys identified in this study could be pathogenic.

In conclusion, we identified a novel *de novo* missense mutation of *KCNT1* in a patient with sporadic EIFMS. This finding provides additional evidence to better understand *KCNT1* pathogenesis.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.524.

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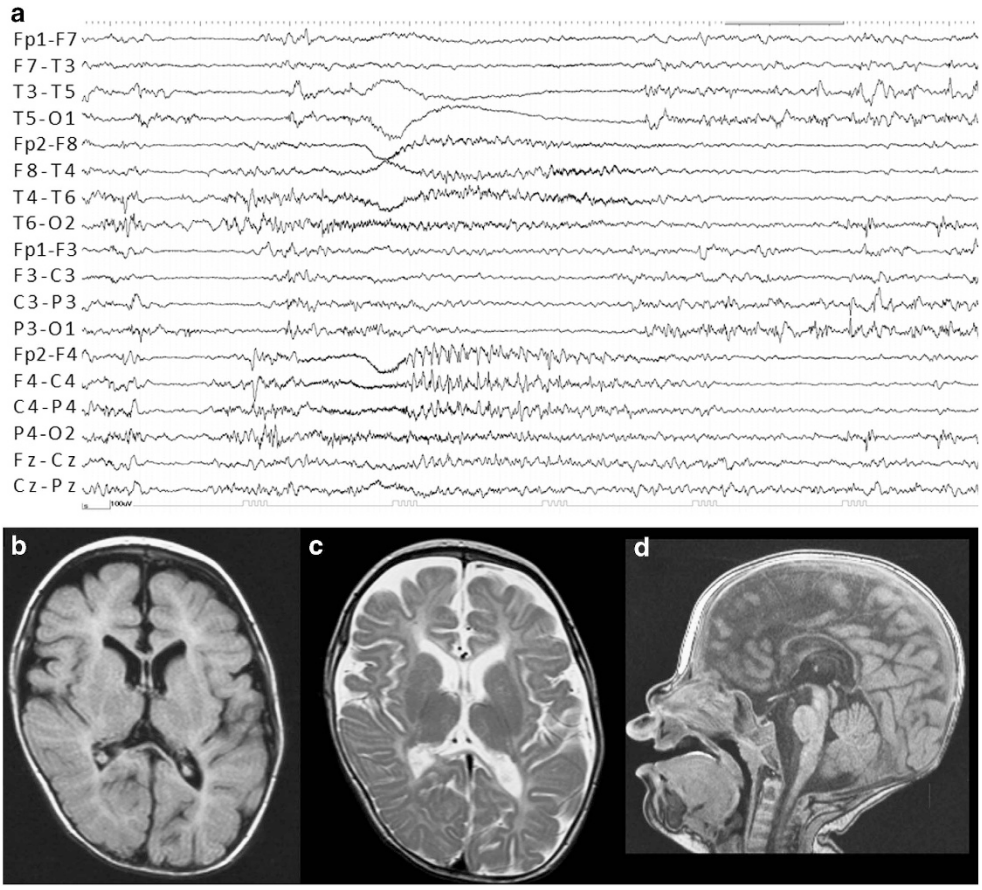

Figure 1. Patient clinical information. (**a**) Ictal electroencephalogram (EEG) examined at 6 months. A short EEG seizure discharge begins at the right frontal region. (**b**–**d**) Brain magnetic resonance imaging examined at 6 months. Extracerebral spaces can be seen in axial images, (**b** and **c**) possibly indicating brain atrophy. Both (**b**) T1- and (**c**) T2-weighted images show high intensity in the deep white matter, indicating delayed myelination. (**d**) The corpus callosum is thin in the T1-weighted sagittal image.

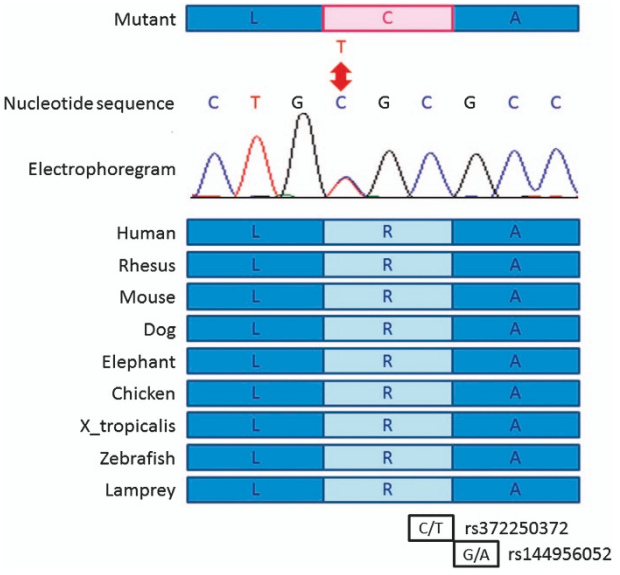

Figure 2. Electropherogram and corresponding genomic data. The electropherogram of the *KCNT1* exon 15 indicates a heterozygous missense mutation, c.1420C>T (p.Arg474Cys), in *KCNT1*. The affected residue is conserved across species. Although there are some single-nucleotide variants (SNVs) proximal to the identified mutation, the same SNVs are not found in the database.

Table 1. Comparison of the clincial features of the patients with missense mutation at p.Arf474

Patient's clinical features	*Patient 5 by Barcia et al. (2012)*	*Patient in this study*
Gender	M	M
Nucleotide alteration	c.1421G>A	c.1420C>T
Amino-acid change	p.Arg474His	p.Arg474Cys
Ethnic origin	France	Japan
Age at seizure onset	2 weeks	9 days
Seizure type at onset	Focal motor	Focal motor
Neurological evaluation at onset	Axial hypotonia	Axial hypotonia
Age at observation	6 months	6 months
Neurological evaluation	Lack of contact Axial hypotonia	Poor response to the surroundings Axial hypotonia
MRI findings (age)	Normal (at 1 month)	Myelination delay and this corpus callosum (at 6 months)

Abbreviations: M, male; MRI, magnetic resonance imaging.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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