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Short communication

A missense variant of *SMC1A* causes periodic pharmaco-resistant cluster seizures similar to *PCDH19*-related epilepsy

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ABSTRACT

SMC1A variants causing Cornelia de Lange syndrome (CdLS) produce another phenotype characterized by moderate to severe neurological impairment and severe early-onset epilepsy without morphological characteristics of CdLS. The patients are all female and have truncation mutations in *SMC1A*. The epilepsy also follows a characteristic clinical course with pharmaco-resistant cluster seizures since infancy, mimicking that of *PCDH19*-related epilepsy. We report here that a missense variant of the *SMC1A* gene affecting a daughter (proband) and her mother caused similar phenotypes of early-onset (2 years and 1 month of age) and late-onset (12 years of age) epilepsy, respectively. Both patients lacked the morphological characteristics of CdLS, and had severe and moderate intellectual disability, respectively. The cluster seizures were characteristic, occurring approximately every 2–4 weeks (interval; mean ± SD: 20.2 ± 8.3 days) at the peak of the clinical course, especially in the proband. Thus, *SMC1A*-related encephalopathy is caused not only by truncation mutations but also by missense variants of the *SMC1A* gene. The periodicity of cluster seizures mimicking that of *PCDH19*-related epilepsy may characterize *SMC1A*-related encephalopathy.

1. Introduction

Epilepsy is a complex neurological disorder affecting 0.5˜1% of the population (Engel, 2013). Although the etiology of epilepsy is diverse and heterogeneous, the genetic etiology has received growing attention because an increasing number of gene mutations potentially causing epilepsy have been identified for these 20 years. To date, 84 genes were considered epilepsy genes, producing specific epilepsies or epileptic syndromes (Wang et al., 2017). In the last few years, whole exome or genome sequence analyses using next-generation sequencing (NGS) techniques have accelerated the identification of new genes responsible not only for developmental and epileptic encephalopathies but also for rare malformation syndromes demonstrating epilepsy and other neurological and neurodevelopmental symptoms. The pathogenic variants of the *SMC1A* gene were first reported to cause Cornelia de Lange syndrome (CdLS), characterized by facial dysmorphism, limb anomalies, and growth and cognitive deficits (Deardorff et al., 2007; Liu et al., 2009; Mannini et al., 2010). Later, patients with the *SMC1A* truncation mutations, all female, were described to have a different clinical phenotype exhibiting moderate to severe neurological impairment and pharmaco-resistant epilepsy without morphological characteristics of CdLS (Goldstein et al., 2015; Jansen et al., 2016; Lebrun et al., 2015; Mannini et al., 2010). In most recent reports, cases of epilepsy in this group ran the characteristic clinical course with cluster seizures, mimicking that of *PCDH19*-related epilepsy (Marini et al., 2010; Symonds et al., 2017). Herein, we presented that a missense variant of the *SMC1A* gene affecting a daughter and her mother caused severe childhood-onset epilepsy with cluster seizures.

2. Case report

2.1. Patient 1

The proband was an 8-year-old girl born uneventfully at 38 weeks gestation from a mother with chronic epilepsy. There was no other notable family history. Her body weight, length and head circumference were 2634 g (−0.6 SD), 47.5 cm (−0.1 SD) and 34.0 cm (+0.7 SD), respectively. She exhibited developmental delay since 9 months of age. G-banding chromosomal analysis was normal. She independently walked at 1 year and 9 months of age, but spoke no

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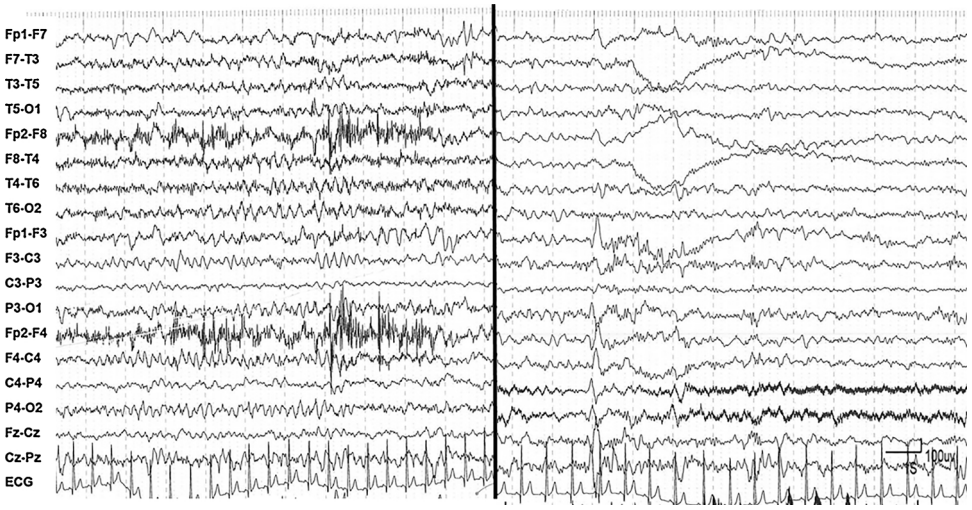

Fig. 1. Interictal EEG of Patient 1 at 8 years and 1 months of age.
Background activity during wakefulness consisted of diffuse 4-5-Hz theta activity. During sleep, there was symmetrical vertex sharp transients and spindle activity. There were no epileptiform EEG discharges in this long-term video-EEG examination.

meaningful words. She began having epileptic seizures at 2 years and 1 month of age, which occurred up to 10 times a day and lasted for a few days. The attacks were initially characterized by focal motor seizures developing either from the left or right arm with secondary generalization lasting for a few minutes. Between 2 years and 1 month and 6 years and 3 months of age, she was admitted to the local hospital 24 times for the treatment of cluster seizures occurring once a month despite multiple antiepileptic drug (AED) treatment. She was referred to our hospital at 6 years and 9 months because her family moved. She was short in stature (−2.2 SD) without microcephalus (−1.4 SD). There were no typical CdLS morphological features including her face and hands, but she had a flat nasal bridge, short neck and mildly bushy eyebrows. She demonstrated ataxic gait and was unable to speak meaningful words or comprehend words. No notable abnormality except for mild thinness of the corpus callosum was observed on brain MRI. The interictal EEG examinations repeated every 6 months exhibited diffuse slow background activity (4–5 Hz) during wakefulness and relatively organized sleep background activity without any epileptiform abnormality (Fig. 1). Although she had tried valproic acid (VPA), carbamazepine(CBZ), phenytoin(PHT), topiramate (TPM), zonisamide (ZNS), lamotrigine (LTG), clobazam (CLB), phenobarbital (PB) and levetiracetam (LEV), she had cluster seizures up to 8 times per day spontaneously for a few days approximately once every 2–4 weeks (interval; mean ± SD: 20.2 ± 8.3 days) periodically (Fig. 2). There were no provoking factors, such as high-fever, for the seizure clusters. Long-term video-EEG examination was performed at 8 years and 6 months of age, which captured two types of her habitual seizures (Fig. 3A). The first one was an autonomic seizure during sleep characterized by sudden onset awakening followed by respiratory difficulty and behavioral automatism for 1–2 minutes. This corresponded to the focal discharges arising from both frontal regions on the EEG. Another seizure type was an atonic drop seizure during wakefulness, which corresponded to the sudden occurrence of generalized seizure discharges with slight right-sided predominance lasting 10 s (Fig. 3B).

Since the first visit, potassium bromide (KBr) and high-dose PB were added to LEV and CLB, which gradually disrupted the periodicity of the cluster seizures and reduced the seizure frequency. However, a reduction of PB due to moderate sleepiness and ataxia caused an increase in the seizure frequency and cluster seizures occurred once every few days to a week.

2.2. Patient 2

This is the mother of the patient 1 who was 45 years of age at the examination. She was born uneventfully at 40 weeks of gestation, weighing 4300 g. She developed normally until 12 years of age, when she began to have cluster seizures, which had continued once a month at menstrual period. They were characterized by staring followed by hypermotor activity and resistant to antiepileptic drug treatment. In her early twenties, she was suspected to have some sort of spinocerebellar degeneration because of cerebellar atrophy by brain MRI. However, it was later denied due to absence of ataxia. The cluster seizures have gradually decreased in frequency and changed in a manifestation to staring or arrest of motion only since her late twenties. The EEG showed diffuse high-amplitude spike-and-waves at 32 years of age. Recently, she has had monthly to yearly seizures. There was no typical CdLS morphological features, such as hirsutism, connected eyebrows or syndactyly. She was moderately retarded and her cognitive level was equivalent to that of a 7-year-old.

3. Genetic analysis

Whole exome sequencing was performed as previously described (Nakashima et al., 2019) on Patient 1, which revealed a variant of the *SMC1A* gene (c.2683C > G:pArg895Gly). Sanger sequencing confirmed the variant only in the proband and her mother, but not in the other family members (maternal grandmother and maternal half-brother; family tree in the supplemental Fig. 1). Sanger sequencing showed no evidence of mosaicism of the variant in the mother. The blood sample of the father and maternal grand-father was not obtained because of divorce. The variant was not observed in gnomAD, a variant database comprising of 125,748 exome sequencing and 15,708 genome sequencing (Karczewski et al., 2019). The variant was in-silico predicted to deleterious by SIFT (Nucleic acids research 31, 3812-3814(2003).) probably damaging by PlyPhen2 Hvar (Nat Methods 7, 248–249 (2010).), and disease-causing by Mutation Taster (Nat Methods 11, 361–362 (2014).) The variant is at one of the two RecF/RecN/SMC N terminal domains, which form an intra-molecular coiled coil and essential for correct folding of SMC proteins (Matityahu and Onn, 2018). Missense variants in the two domains are under strong natural selection in gnomAD (https://decipher.sanger.ac.uk). This variant was judged to be likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al., 2015).

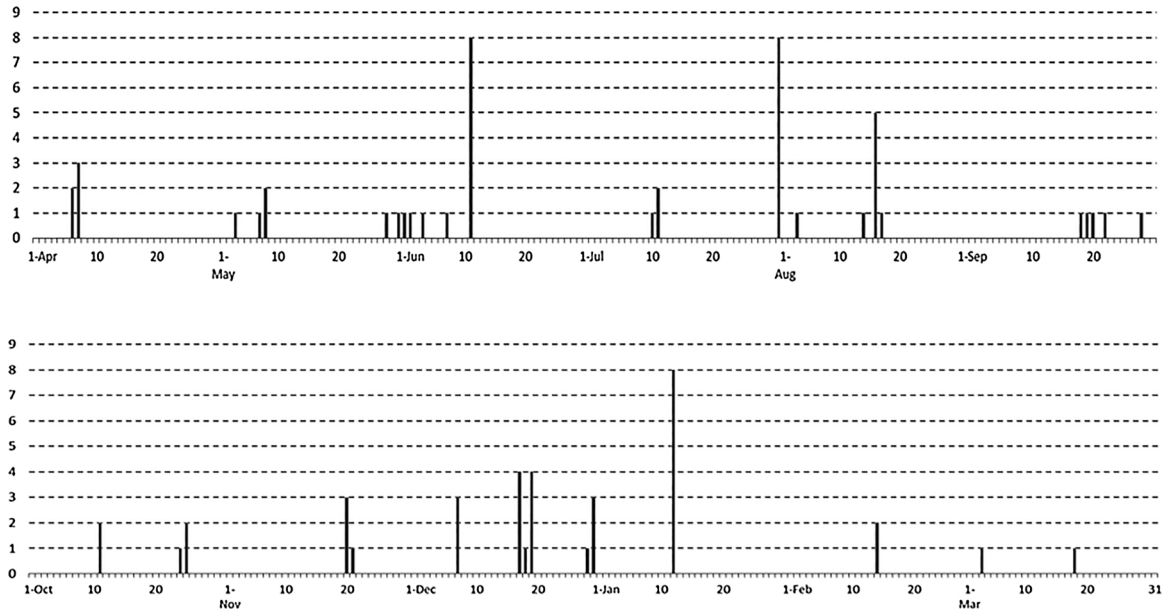

Fig. 2. Periodic appearance of cluster seizures.
The cluster seizures occurred up to 8 times per day for a few or couple of days in approximately 2–4-week intervals for the 1 st year from the first visit to our hospital (6 years and 9 months of age). An interval between one seizure cluster and another one was 20 days in average (range: 9˜33 days, mean ± SD: 20.2 ± 8.3 days, the cluster seizures were defined as a seizure frequency more than 2 times/day or once a day lasting more than 2 consecutive days in this calculation). The caregivers counted the number of seizures every day and informed us at each visit. Vertical and horizontal axes indicate the number of seizures per day and the date, respectively.

To analyze skewness of X inactivation in the patients 1 and 2, we performed human androgen receptor gene (HUMARA) assay as previously described (Saitsu et al., 2013). Patient 1 showed marked skewness of X inactivation for the maternally inherited mutant allele. The finding is consistent with a previous report (Parenti et al., 2014) of female cases of the *SMC1A* pathogenic variants and give additional evidence on the pathogenicity of our variant. Patient 2 had homozygous allele in HUMARA loci, and skewness of X inactivation was not inferred.

Informed consent was obtained from all participants in accordance with the Japanese regulatory requirements. The study was approved by the institutional review boards of the Yokohama City University School of Medicine and the Showa University School of Medicine.

4. Discussion

The characteristic features of epilepsy in these two patients comprised pharmaco-resistant focal and generalized seizures occurring in clusters. In the proband in particular, the periodicity of cluster seizures was approximately 2–4-week intervals (more precisely, the intervals of 20 days in average) regardless of antiepileptic drug treatment. This periodic occurrence of cluster seizures lasted for more than 6 years. Although KBr and high-dose PB recently disrupted this periodicity, the seizures continued to occur frequently.

A recent report suggested that heterozygous truncation mutations of the *SMC1A* gene cause severe early-onset epilepsy with cluster seizures in females (Symonds et al., 2017) . On the other hand, the present patients having a missense variant of the *SMC1A* gene shared similar clinical features. In addition, the proband had typical features characterized by severe developmental delay and early-onset pharmaco-resistant cluster seizures, whereas her mother having the same *SMC1A* variant had a milder phenotype with normal development before the onset of epilepsy and relatively late-onset epilepsy. The cluster seizures are one of the characteristic features of *PCDH19*-related epilepsy, which also shares other clinical features with *SMC1A*- related encephalopathy except for the absence of severe psychomotor retardation before the onset of epilepsy and positive provoking factors (fever and elevated temperature) for cluster seizures.

The *SMC1A* gene is located on the X chromosome and encodes one of four core subunits that compose the cohesin ring. The cohesin ring regulates the separation of sister chromatids during cell division, facilitates spindle attachment onto chromosomes and DNA repair by recombination, and also has been reported to be responsible for transcriptional regulation (Mehta et al., 2013). CdLS is one of several developmental conditions caused by mutations in the cohesin subunits. However, the female patients with *SMC1A*-related encephalopathy do not have the typical morphological characteristics of CdLS, like our patients (Huisman et al., 2017).

The reason why Patient 1 was more severely affected than Patient 2 was unknown. We excluded possibilities that the *SMC1A* variant was mosaic in Patient 2 or a higher proportion of the wild-type allele was inactivated in Patient 1 than Patient 2. *SMC1A* is known to partially escape inactivation in inactivated X chromosome and be expressed (Brown et al., 1995; Parenti et al., 2014). Therefore, a mutant *SMC1A* allele was expressed even in female patients with marked skewness of X inactivation for mutant alleles. Patient 1 might express more transcripts from the mutant *SMC1A* allele than Patient 2, and that might be the cause of different severity between Patient 1 and Patient 2.

Regarding epilepsy type, previous reports suggested the multifocal origin of epileptic seizures based on the combination of both focal and generalized seizures and multifocal epileptiform EEG abnormalities (Symonds et al., 2017). In our patient, the ictal video-EEG supported this suggestion because she had frontal-onset and generalized-onset seizures independently, although interictal EEG demonstrated only diffuse slowing of background activity without epileptic abnormality. Regarding the mode of seizure occurrence, three previous case reports described the details of the cluster seizures that occurred every 1–4 weeks (Goldstein et al., 2015; Jansen et al., 2016; Symonds et al., 2017). This periodicity of cluster seizures mimicking that of *PCDH19*-related epilepsy should characterize the epilepsy of *SMC1A*-related encephalopathy, although the interval between clusters may be shorter in the former than in the latter which was described as 2 weeks to monthly (Marini et al., 2010; Trivisano et al., 2018). The treatment strategy for this seizure clusters is challenging, as is that for *PCDH19*-related epilepsy, at present.

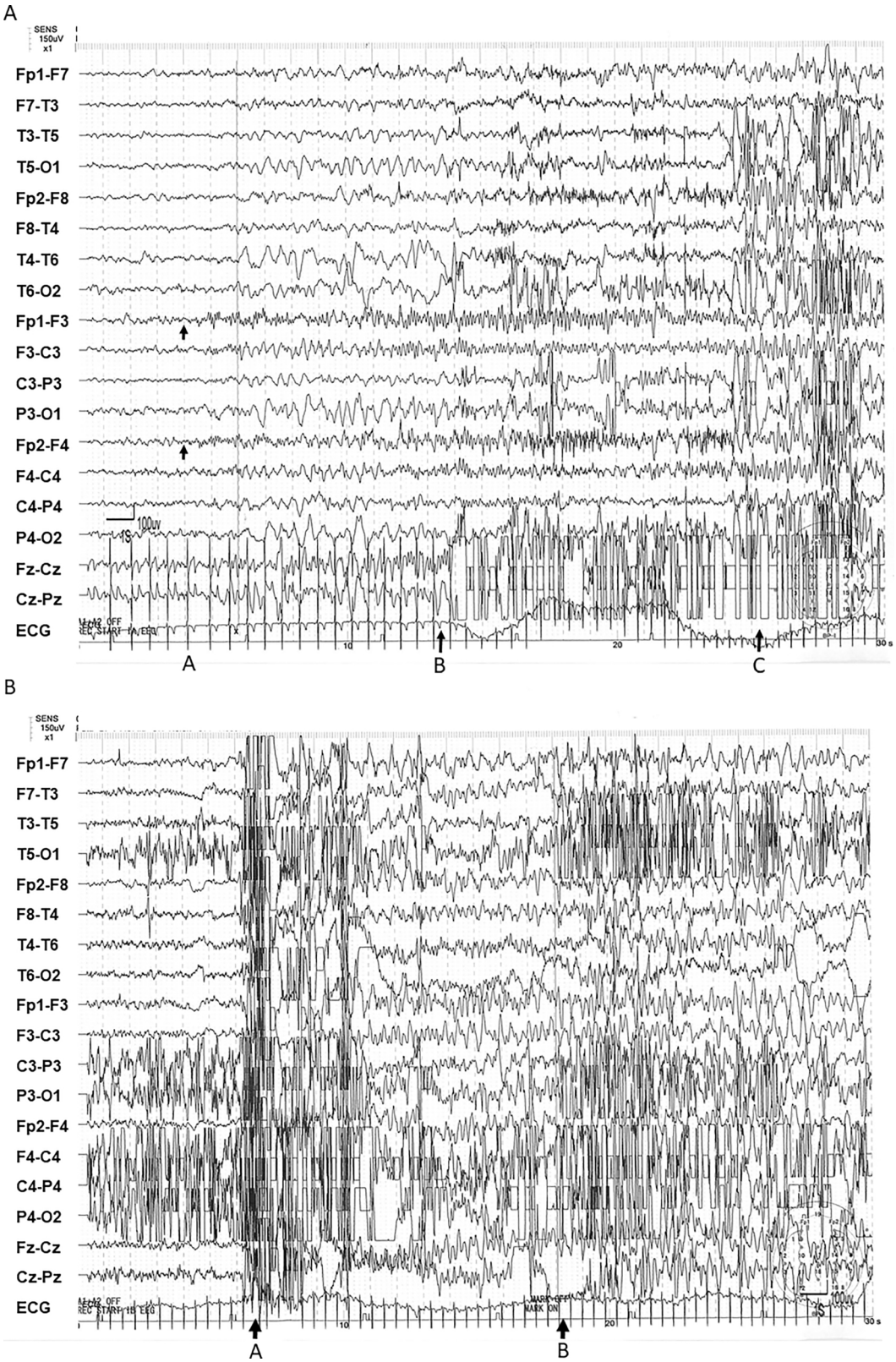

Fig. 3. Ictal EEG of Patient 1 at 8 years and 6 months of age.

A. Autonomic seizures

During sleep stage 2, ictal beta discharges developed from both frontal lobe regions (A) slowly building up in amplitude and slowing in frequency, but confined in both frontal regions until the end of the seizure. It lasted for 30 s. The patient was awakened (B) and began to have difficulty in breathing (C), followed by behavioral automatism.

B. Atonic drop seizures

She was standing on the bed and suddenly fell (A), and then started to recover (B). The EEG was initially obscured by artifacts, followed by low amplitude fast discharges arising from both hemispheres with right-sided predominance.

5. Conclusion

SMC1A-related encephalopathy is caused not only by truncation mutations but also by missense variants the *SMC1A* gene, and is characterized by periodic pharmaco-resistant cluster seizures.

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We certify that we have read the journal's position regarding issues pertaining to ethical publications, and confirm that this report is consistent with those guidelines. Disclosure of Conflict of Interest: There are no conflicts of interest related to this manuscript. We are grateful to the patients and their families for their participation in this study. We are also grateful to Dr. Taisuke Ohtsuki, Bethel hospital, who offered medical information of the patient.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.06.001.

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