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Brief Communication

A partial *ARID1B* deletion in a female child with intractable epilepsy

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Abstract

Although epilepsy is a known complication in Coffin-Siris syndrome, its clinical symptoms and effective treatment methods have not been thoroughly investigated so far. Here, we present the case of a female with a 594-kb interstitial deletion at 6q25.3, involving partially *ARID1B*, with developmental delay, short stature, and intractable epilepsy. At 4 years of age, she developed epilepsy with clonic seizures in the right half of her body. Treatment with carbamazepine, levetiracetam, or topiramate was ineffective. The frequency of epileptic seizures gradually worsened. At the peak of her seizures, she had focal onset clonic seizures 3-4 times a month, and neck atonic seizures lasting for several seconds more than 10 times a day. After administration of sodium valproate, her epileptic seizures decreased to 0-1 times a year. In conclusion, gathering genetic information in Coffin-Siris syndrome allows improvement of epilepsy treatment and outcomes in these patients.

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Introduction

Coffin–Siris syndrome (CSS; MIM 135900), first described by Coffin and Siris in 1970, is a congenital disorder characterized by intellectual disability, growth deficiency, microcephaly, coarse facial features, and hypoplastic or absent fifth fingernails and/or toenails [1]. Despite epilepsy being a known complication of CSS, so far its clinical symptoms and effective treatment methods have not been thoroughly investigated.

In this report, we describe an interstitial deletion at 6q25.3, involving the *ARID1B* gene, in a female child with developmental delay, short stature, and intractable epilepsy. The patient did not respond to various antiepileptic drugs including carbamazepine (CBZ), levetiracetam (LEV), and topiramate (TPM), but eventually responded to sodium valproate (VPA).

Case Presentation

A Japanese girl aged 8 years and 9 months was the second child of non-consanguineous, healthy parents who had no remarkable family history and three other healthy sons. She was born weighing 2530 g at 37 weeks of gestation. No notable abnormalities were observed during the perinatal period. She exhibited moderate developmental delay from birth: she began to walk at 2 years of age and spoke only at 3 years of age. At 3 years and 9 months of age, her parents brought her to our hospital to consult about her developmental delay. Multiple facial anomalies (thick eyebrows, long eyelashes, wide nose bridge and nose top, and thin upper lip), short stature, and hypoplastic fifth finger (Figure 1) were observed. At the age of 4 years and 4 months, she developed epilepsy with focal onset impaired awareness clonic seizures; however, brain MRI was normal. On electroencephalogram (EEG), focal spikes and sharp waves were found predominantly in both left and right central areas. CBZ was initiated and the dose was increased to 11.8 mg/kg/day, but clonic seizures (dominant in right half of the body, or left half, or systemic) recurred once a month. LEV administration up to 60 mg/kg/day, and TPM up to 8.1 mg/kg/day were also initiated, but these drugs had no effect on her seizures. During the period of highest seizure frequency at the age of 5 years and 7 months, she had focal onset clonic seizures 3-4 times a month, and neck atonic seizures lasting several seconds more than 10 times a day. By that time, EEG abnormalities were gradually worsened with increasing frequencies, spike amplitude, and sharp waves (Figure 2). VPA treatment was initiated at 5 years and 7 months of age and gradually increased to 330 mg/day (26 mg/kg/day). Simultaneously, TPM was tapered. Eventually, her epileptic seizures decreased to 0-1 times a year. From age 6 years onwards, epileptic seizures were

Figure 1. **A**: Characteristic facial findings (thick eyebrows, long eyelashes, wide nose bridge and nose top, and thin upper lip) were observed. **B**: Hypoplastic fifth finger.

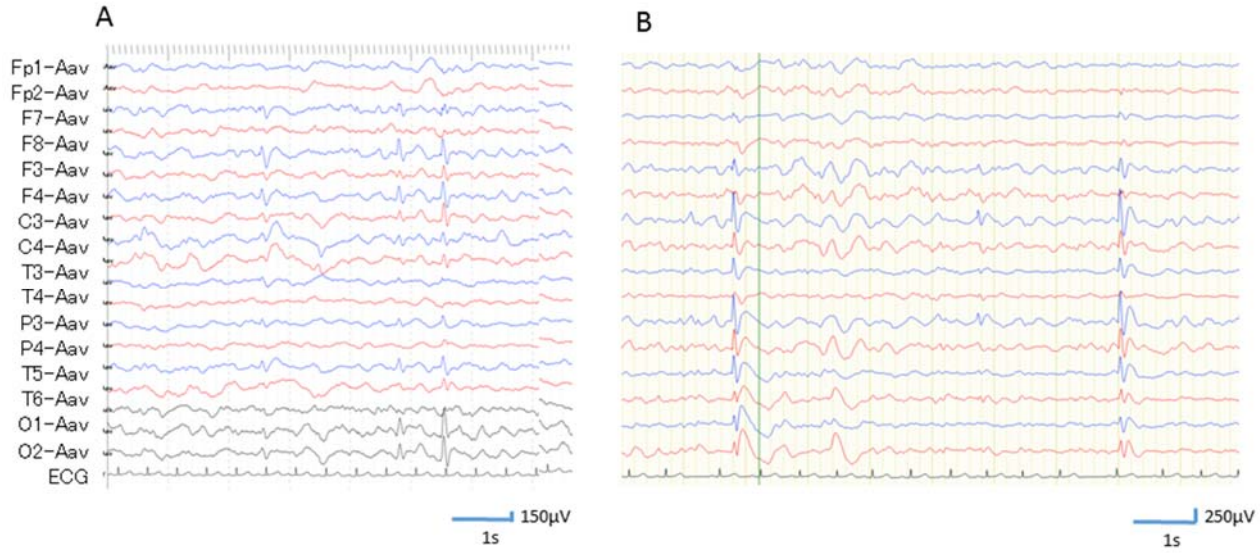

Figure 2. Interictal electroencephalograms during sleep. Focal spikes and sharp waves are observed frequently in both left and right central areas. **A**: 4 years and 9 months of age. The amplitude of focal spike is approximately 400 μV. **B**: 5 years and 7 months of age. The amplitude of focal spike is approximately 1 mV.

recorded only three times. However, there was no apparent improvement in EEG findings. Based on the developmental delay, characteristic facial findings, short stature, and intractable epilepsy in this patient, we suspected that she had a genetic disorder. At 7 years 3 months of age, we consulted with the Initiative on Rare and Undiagnosed Diseases to conduct a genetic investigation. Whole exome analysis was performed as described previously [2], which identified a 594 Kb heterozygous chromosomal deletion within 6q25.3 (Chr 6: 157150291 -157744610 [hg19]), involving *ARID1B* (NM_020732.3) from intron 1 to the last exon and entire *TMEM242* (NM_018452.6) (Figure 3A and B). Quantitative PCR confirmed this deletion in the patient, but not in her parents (Figure 3C). Therefore, this deletion should have occurred *de novo*. *ARID1B* is well known to be a causative gene for autosomal dominant CSS and intellectual disability. Consequently, she was diagnosed with CSS based on clinical signs and genetic test results. To date, the function of the *TMEM242* gene has not been elucidated, and no association with any disease has been reported. She showed gradual development and began to speak two-word sentences at 8 years 1 month of age. Other CSS complications were already under treatment. For instance, her height was 105.0 cm (-3.0 SD) at age 7 years 6 months. Therefore growth hormone was administered for short stature. Furthermore, she also started wearing prostheses for scoliosis (Cobb angle 32°).

Discussion

CSS has been reported to be caused by gene mutations affecting subunits of the BAF -complex (BRG1 and BRM-associated factor, also referred to as switch/sucrose non-fermenting [SWI/SNF]): *SMARCB1*, *SMARCA4, SMARCA2, SMARCE1, ARID1A,* and

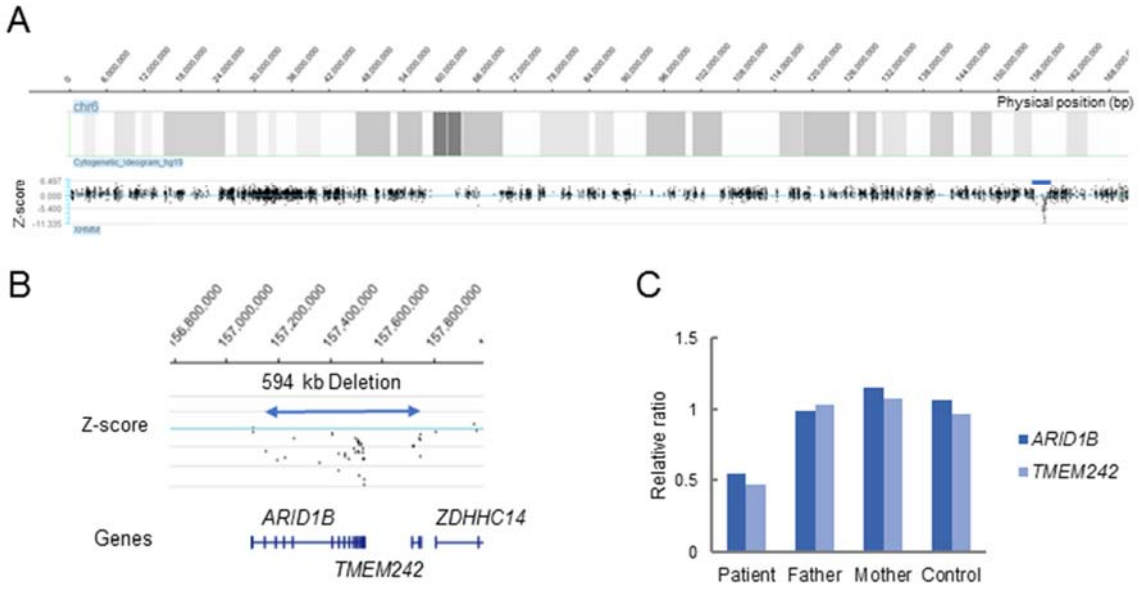

Figure 3. **A**: Copy number variant analysis by whole exome sequencing. Blue horizontal bar shows a deletion at 6q25.3. **B**: Enlarged view of the deleted region. Vertical lines in genes represent exons. **C**: Quantitative PCR confirmed a *de novo* deletion in the patient.

ARID1B [3]. The BAF complex is an ATP-dependent chromatin remodeler that regulates the spacing of nucleosomes, thereby controlling gene expression [4].

The overall mutation detection rate of the five BAF complex genes (*SMARCA4*, *SMARCB1*, *SMARCE1*, *ARID1A* and *ARID1B*) and *PHF6* in CSS ranged from 54.9 to 69.5% [5], with the majority of the mutations being found in *ARID1B* [4, 5]. Furthermore, large-scale exome sequencing studies invariably found that pathogenic variants in *ARID1B* are among the most frequently identified causes in unspecified intellectual disability cohorts (usually around 1%) [6]. Thus, *ARD1B* gene abnormality could possibly have an effect on the central nervous system through gene expression, although the mechanism remains unknown.

In a retrospective analysis of 143 patients with *ARID1B* abnormalities, van der Sluijs et al. reported seizures in 27.5% of the patients. Seizure onset occurred between the ages of 0-14 years with a median age of 4 years. However, response to antiepileptic drugs was favorable in all the treated patients [6]. Horino et al. reported a case of CSS in a girl with intractable epilepsy. Her seizure types were focal onset clonic seizures starting from the left side of the mouth during sleep and atonic seizures of the upper limbs and trunk with eye blinking in wakefulness [7]. Various antiepileptic drugs such as CBZ, zonisamide, clobazam, lamotrigine, LEV, VPA and phenobarbital were administered, but epileptic seizures could not be suppressed. In their case, the existence of intractable seizures such as clonic and atonic seizures resembled our case. From

these reports it is clear that despite the usually good response of epileptic seizures associated with *ARlD1B* gene abnormality to antiepileptic drugs, there are cases in which the response is poor, as in our case.

For our patient, VPA in addition to LEV was the most effective treatment to suppress seizures. VPA promotes the increase of gamma-aminobutyric acid level, dopamine level, and serotonin metabolism, contributing to the activation of an intracerebral suppression network. This activation mechanism probably contributed to seizure suppression in our patient. Nonetheless, to our knowledge, there is no data on the correlation between *ARID1B* gene and the intracerebral suppression network.

In conclusion, we report a case of a girl with CSS and intractable epilepsy arising from a 6q25.3 interstitial deletion involving parts of *ARID1B*. The patient did not respond to various antiepileptic drugs but eventually responded to VPA. Although a single case is not enough to discuss drug efficacies, it can help achieve better understanding of epilepsy in CSS and improve treatment protocols and patient outcomes.

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Ethical Statement

The study was performed according to a protocol reviewed and approved by the Ethics Committee of the Institutional Review Boards (IRBs) of the Tokushima University Hospital. The patient's parents gave consent to publish her clinical information, including her picture in this research article.

Conflict of Interest Disclosure

The authors have no conflicts of interest directly relevant to the content of this article.

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