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Case Report

Biallelic mutations in *SZT2* cause a discernible clinical entity with epilepsy, developmental delay, macrocephaly and a dysmorphic corpus callosum

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Abstract

Mutations in *SZT2* were first reported in 2013 as a cause of early-onset epileptic encephalopathy. Because only five reports have been published to date, the clinical features associated with *SZT2* remain unclear. We herein report an additional patient with biallelic mutations in *SZT2*. The proband, a four-year-old girl, showed developmental delay and seizures from two years of age. Her seizures were not intractable and readily controlled by valproate. She showed mildly dysmorphic facies with macrocephaly, high forehead, and hypertelorism, and also had pectus carinatum. An EEG showed epileptic discharges which rarely occurred. A brain MRI revealed a short and thick corpus callosum. Whole-exome sequencing detected compound heterozygous biallelic mutations (c.8596dup (p.Tyr2866Leufs*42) and c.2930-17_2930-3delinsCTCGTG) in *SZT2*, both of which were novel and predicted to be truncating. This case suggested a broad phenotypic spectrum arises from *SZT2* mutations, forming a continuum from epileptic encephalopathy and severe developmental delay to mild intellectual disability without epilepsy. The characteristic thick and short corpus callosum observed in 7/8 cases with epilepsy, including the proband, but not in three non-syndromic cases, appears to be specific, and thus useful for indicating the possibility of *SZT2* mutations. This feature has the potential to make loss of *SZT2* a clinically discernible disorder despite a wide clinical spectrum.

Keywords: Intellectual disability; Epileptic encephalopathy; Seizure; Whole-exome sequencing

1. Introduction

Seizure threshold 2 (*SZT2*), containing 71 exons located in chromosome 1p34.2, is transcribed in many tissues, with the predominant expression in the parietal and frontal cortices, hippocampus, cerebellum, and dor-

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sal root ganglia, and thus *SZT2* has been shown to play important roles in epileptogenesis and human brain development [1,2]. The first clinical report in 2013 revealed that biallelic mutations in *SZT2* caused early-onset epileptic encephalopathy and absent developmental milestones, as well as a dysmorphic corpus callosum on brain MRI [3]. The second report of *SZT2* mutations described three siblings having non-syndromic mild or moderate intellectual disability without seizures [4]. Because only five reports have been published to date, the clinical features associated with *SZT2* mutations remain unclear. All patients, including ours, were diagnosed by whole-exome sequencing, indicating the challenge of clinically diagnosing a patient with mutations in *SZT2* [3–7]. Herein we report another case of a patient with *SZT2* mutations and describe the characteristics of clinical features in comparison to previous reports.

2. Case report

The proband is a four-year-old girl admitted to our hospital with developmental delay at the age of two. She is the second of two children of healthy nonconsanguineous Japanese parents. No family members, including her elder brother, have neurological diseases including macrocephaly. She was born by Caesarean section at a gestational age of 29 weeks due to maternal pregnancy-induced hypertension. At birth her weight was 1060 g (−1.4 SD), length was 39 cm (+0.1 SD) and head circumference was 28 cm (+0.6 SD). The neonatal period was uneventful, but she showed developmental delay in holding up her head at seven months, sitting at two years, and walking unassisted at three years. Although she was not able to speak meaningful words at four years, she followed her parents' direction and used gestures or pointing. Seizures, characterized by the loss of consciousness followed by tonic-clonic generalization, began at two years and ten months. An initial EEG at the time of presentation showed background slowing, but no apparent epileptic discharges. A brain MRI revealed a characteristic shape of short and thick corpus callosum (Fig. 1A). At three years and four months of age, seizures increased to at most five times per month and valproate treatment was started, which readily controlled the seizures. The most recent EEG

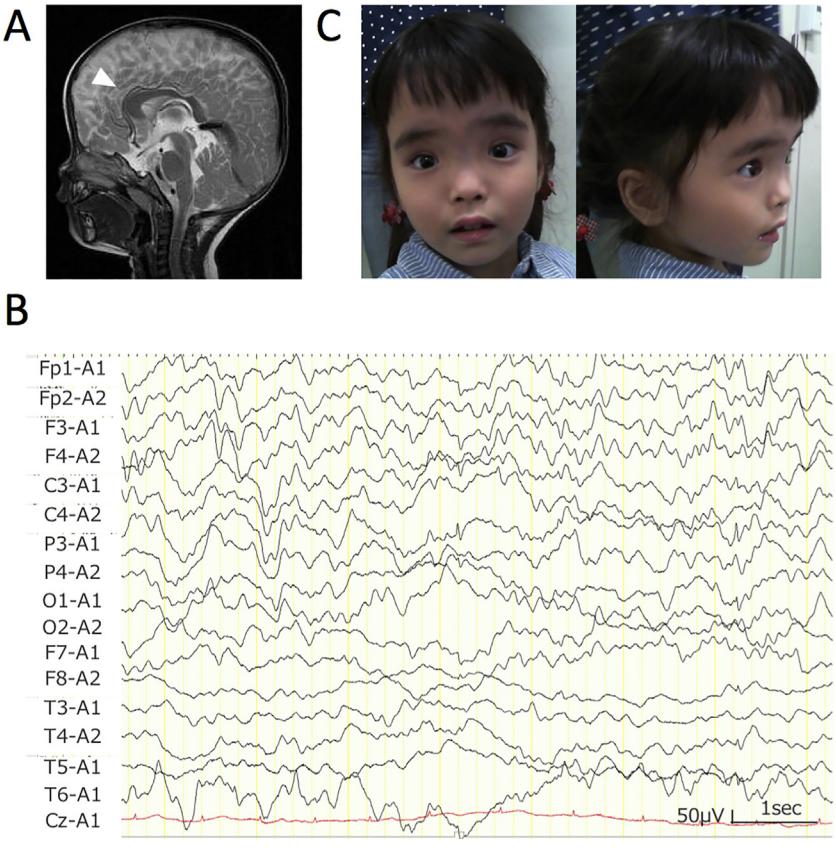

Fig. 1. (A) Brain MRI (T2 weighted image) of the patient. The arrowhead indicates thick and short corpus callosum. (B) EEG during sleep showed focal epileptic discharges in the left parietal region. (C) Facial features of high forehead and hypertelorism. Informed consent to use these photos was obtained from her parents.

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