CASE REPORT

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Perampanel markedly improved clinical seizures in a patient with a Rett-like phenotype and 960-kb deletion on chromosome 9q34.11 including the *STXBP1*

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Abstract

Intractable epilepsy was successfully controlled using perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid-type glutamate receptor antagonist, in a 27-year-old woman who presented with a Rett syndrome-like phenotype and novel 960-kb deletion involving syntaxin-binding protein 1 on chromosome 9q34.11. Perampanel may be an effective antiepileptic drug for intractable epilepsy associated with *STXBP1* mutations.

KEYWORDS
AMPA receptor, intractable epilepsy, perampanel, Rett-like disorder, *STXBP1* mutation, West syndrome

Syun Yoshida and Masano Amamoto contributed equally to this work.

1 | INTRODUCTION

Rett syndrome (RTT, MIM #312750) is an X-linked dominant neurodevelopmental disorder that primarily affects girls at a frequency of 1:10,000 live female births. RTT is mainly caused by mutations in methyl-CpG-binding protein 2 (*MECP2*) at Xq28.[1,2] Approximately 90%–95% of typical RTT cases harbor loss-of-function variants in X-linked *MECP2*.[1,2] However, pathogenic variants in other genes can also lead to RTT or Rett syndrome-like phenotype (RTT-P), including cyclin-dependent kinase-like 5 (*CDKL5*) and forkhead box G1 (*FOXG1*) genes.[3–5] Typically, females with RTT appear to develop normally until 6–18 months of age and regress thereafter. Clinical manifestations include microcephaly, loss of achieved motor and speech skills, intellectual disability, autistic behaviors, and characteristic hand stereotypies. Recently, mutations in the syntaxin-binding protein 1 (*STXBP1*) gene, whose variants cause Ohtahara and West syndromes, were also reported to cause typical RTT or RTT-P.[5–11] Herein, we demonstrate for the first time that perampanel (PER), an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptor antagonist, markedly improved intractable seizures in a Japanese female patient with RTT-P and a 960-kb deletion on chromosome 9q34.11 including the *STXBP1* gene.

2 | CASE REPORT

The female patient was referred to our hospital at the age of 22 years old, because of recurrent pneumonia and intractable epilepsy. The patient showed frequent generalized tonic-clonic seizures, which were diagnosed as generalized epilepsy, and developed intractable epilepsy based on the International League Against Epilepsy (ILAE) 2017 Classification.[12] The seizures were drug-resistant and treated with a combination of anticonvulsants at another hospital, which included 800 mg of valproic acid, 28 mg of clobazam, 600 mg of carbamazepine, and 800 mg of levetiracetam (LEV). The patient showed an increase in screaming behavior after LEV administration. In addition, she was suspected of having neurodevelopmental disorders, including Rett-like phenotype of unknown etiology, based on the recent diagnostic criteria for RTT (Figure 1). This patient met the diagnostic criteria for RTT-P, including two required conditions, four main criteria, two exclusion criteria, and 8 of 11 supportive criteria.[2]

This patient was one (R008) of the five patients with RTT-P caused by an *STXBP1* gene abnormality that we identified and reported previously.[5] Total genomic DNA was prepared from peripheral blood leukocytes according to standard procedures. The research protocol was approved by the Ethics Committees of Kurume University School of Medicine and Yokohama City University School of Medicine. Written informed consent for the collection of blood samples was obtained from the patient's parents. The patient and parents received a complete *MECP2* mutation analysis, including exon 1, and an evaluation of large DNA rearrangements by Southern blotting or multiplex ligation-dependent probe amplification. No pathogenic variants of *MECP2*, *CDKL5*, and *FOXG1* genes were found in the patient or parents. Whole exome sequencing of the patient together with the eXome Hidden Markov Model and Nord's method, identified a 960-kb deletion at 9q34.11 involving *STXBP1* and endoglin (*ENG*) in this patient (Figure 1C). The *STXBP1* and *ENG* deletions were confirmed by quantitative PCR, and analyses of her parents' DNA confirmed that the chromosomal deletion occurred *de novo*. *STXBP1* and *ENG* were registered in the Human Gene Mutation Database. *ENG* mutations are associated with hereditary hemorrhagic telangiectasia (HHT). Our patient did not present with clinical signs and symptoms of recurrent telangiectasia of the skin or mucous membranes. Furthermore, she did not display any organ vascular anomalies, and none of the family had a history of HHT. Importantly, individuals with 9q34.11 deletions encompassing *STXBP1* have been previously described, and these patients presented with epilepsy and intellectual disability.[13] These findings revealed that the *STXBP1* deletion is disease-causative. Detailed methods have been reported elsewhere.[5]

The patient's mother returned her to our hospital when she was 27 years old because of her drug-resistant epilepsy. An EEG detected spike and wave discharges in the bilateral regions (O1, O2 and T5, T6; arrows) of the patient's brain (Figure 2A). We administered 2 mg of PER on admission, which led to a significantly reduced frequency of seizures that have since been completely controlled using a daily dose of 8 mg of PER. At 30 years of age, the patient's sleep EEG showed no spike and wave discharges (Figure 2B). Seizure-free status was confirmed at 30 years of age (Figure 3).

The early medical history of this patient is as follows. The patient was born after 40 weeks of gestation to unrelated parents. None of the family members had neurological or neuromuscular diseases. Her birth weight was 2,376 g. The mother's pregnancy was uneventful, and there were no delivery complications. Thirteen days after birth, the patient developed generalized tonic convulsions that showed a temporary response to phenobarbital. However, she displayed generalized tonic seizures after treatment with 50 mg of phenobarbital and 2 mg of nitrazepam at 3 months of age. Her seizures were drug-resistant, and she developed a cluster of spasms at 5 months of age. Electroencephalography showed hypsarrhythmia, and
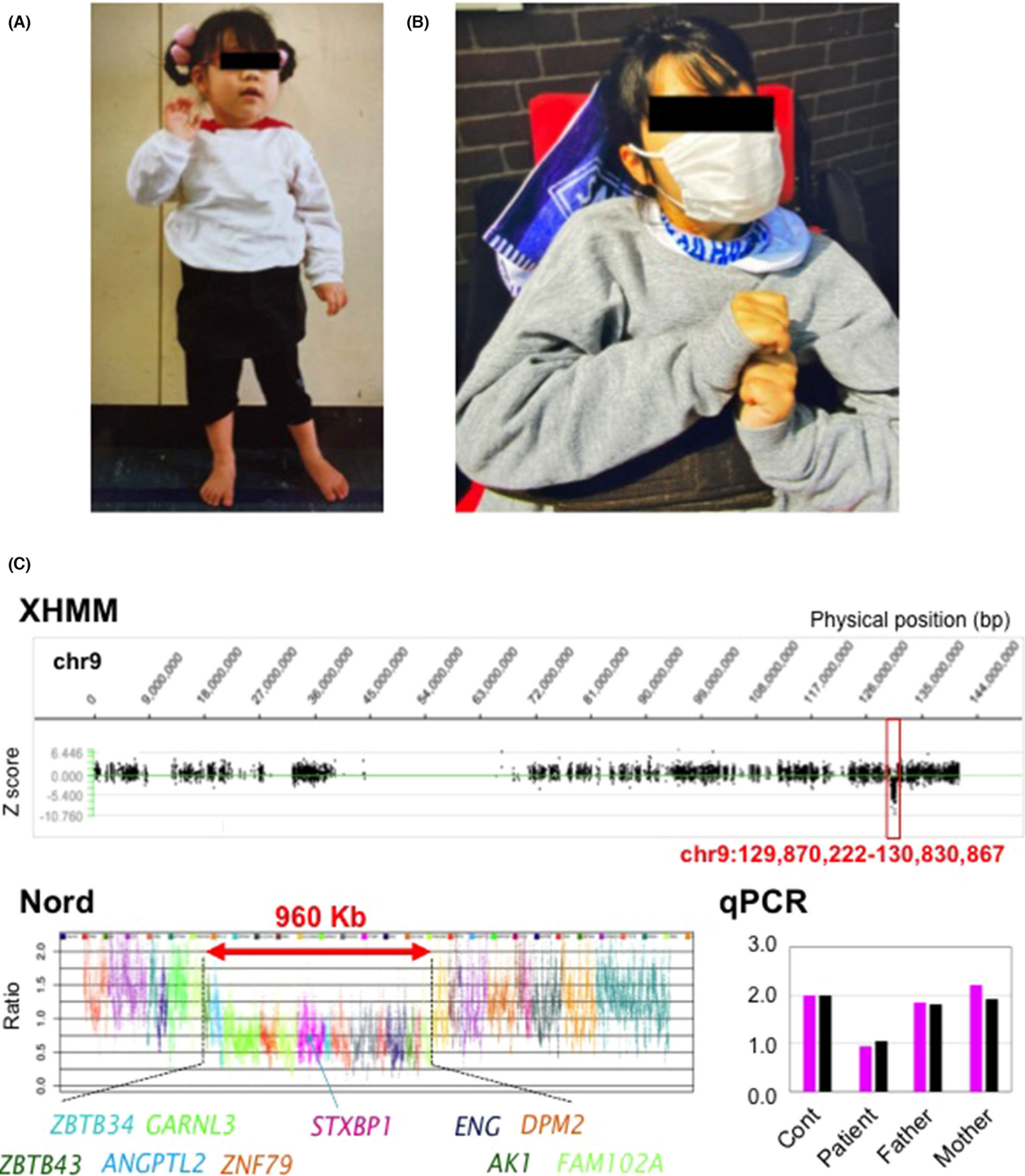
FIGURE 1 (A) The patient standing independently at 2 years of age. (B) She presented typical stereotypic hand movements beginning at 2 years 6 months of age, which continued throughout her development (shown at 22 years of age). Parental permission was obtained to publish the patient's images. (C) eXome Hidden Markov Model (XHMM) identified a 960-kb at 9q34.11 in this patient (red box). Nord's method (Nord) identified the deletion of *STXBP1* and *ENG*, and 8 other genes (red double-headed arrow). Quantitative PCR (qPCR) for *STXBP1* (purple bar) and *ENG* (black bar) of patient showed decreased copy number compared to the parents, which suggest de novo mutation of *STXBP1* and *ENG*

(A) EEG at 27 years old
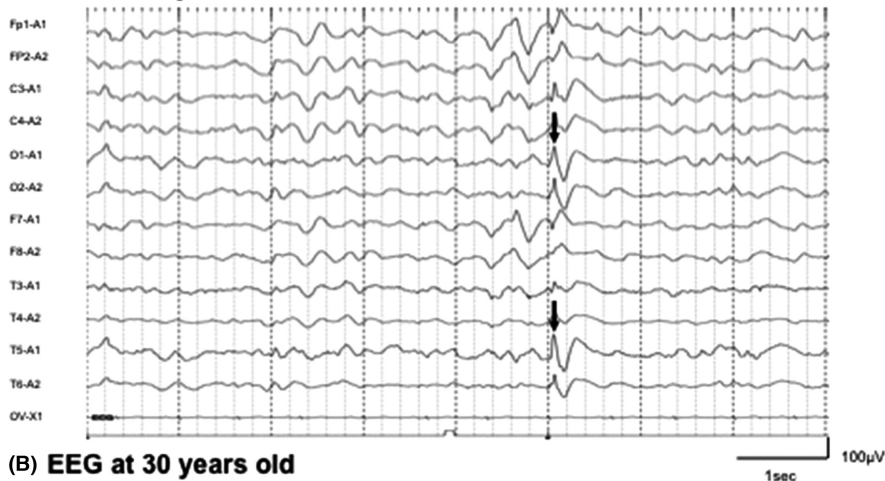
(B) EEG at 30 years old
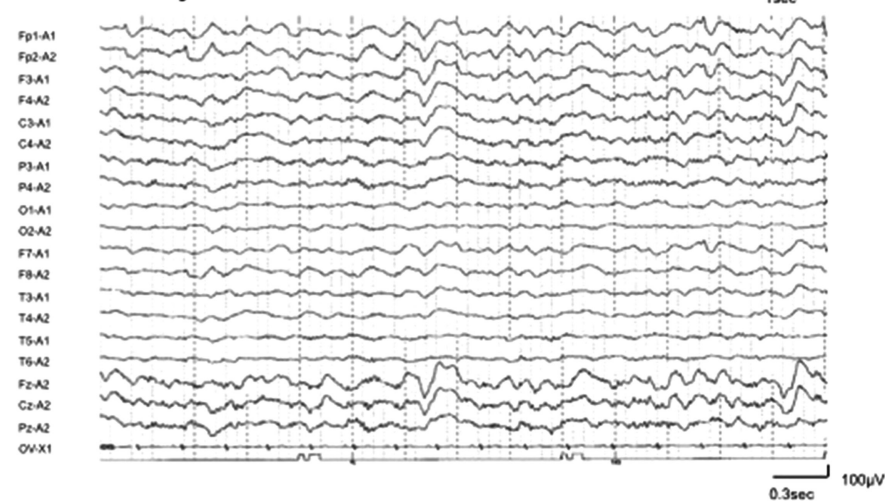
FIGURE 2 (A) Sleep electroencephalogram (EEG) of the 27-year-old patient showed spike and wave discharges in the O1, O2 and T5, T6 regions (arrows). (B) There were no spike and wave discharges after daily administration of 8 mg of perampanel (PER) at 30 years of age
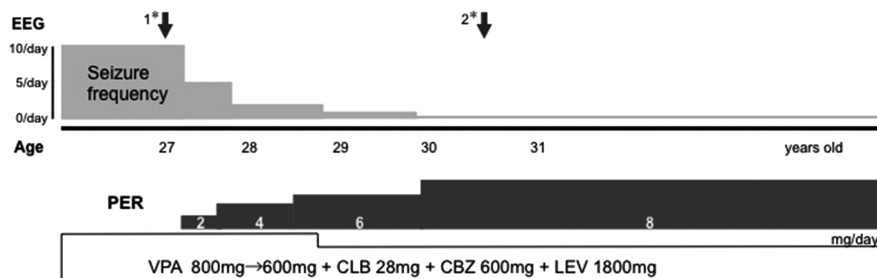
FIGURE 3 After the introduction of perampanel (PER), the seizure frequency decreased by >50%. Increasing the dosage of PER from 4 mg/day to 6 mg/day resulted in almost complete control of seizures. At this stage, seizures occurred 2–3 times/month. Seizures were completely controlled by treatment with 8 mg/day of PER. CBZ, carbamazepine; CLB, clobazam; LEV, levetiracetam; PER, perampanel; VPA, valproic acid. First EEG (Figure 2A), Second EEG (Figure 2B)

computed tomography showed diffuse cerebral atrophy. The patient was diagnosed with West syndrome at 5 months of age. She was treated with adrenocorticotropic hormone and a combination of 5 mg of nitrazepam and 400 mg of pyridoxal phosphate. However, her seizures remained intractable. The developmental milestones achieved were as follows: head control was obtained at 4 months, unaided sitting at 7 months, and delayed independent standing at 2 years of age (Figure 1A). However, the acquired motor abilities were then lost. The patient transiently attained only babbling at 2 years of age, which was subsequently lost. Stereotypic hand movements were observed at the

age of 2 years and 6 months. The patient was suspected of having autism spectrum disorder (ASD) because she disliked being hugged by her mother and having other people touching her skin and showed a poor response to family members. She deteriorated and developed further hand stereotypies at the age of 2 years and 6 months, which have continued into adulthood (Figure 1B). Her developmental quotient was <20 at 2 years of age.

3 | DISCUSSION

Here, we report for the first time that PER was effective in treating clinical seizures in a Japanese female patient with RTT-P caused by an *STXBP1* gene abnormality. Four individuals with RTT phenotypes and *STXBP1* mutations have previously been described,[5–9] three of whom also presented with West syndrome. Furthermore, we identified five patients with RTT-P caused by *STXBP1* mutations, including the current patient (R008), who initially developed West syndrome that ultimately evolved into intractable epilepsy.[5] Patients with *STXBP1* mutations often suffer from severe intellectual disability, ASD, and epilepsy, and *STXBP1* mutations may also be the cause of Ohtahara and West syndromes, which result in refractory epilepsy.[5,9–11] Patients with Ohtahara syndrome have intractable seizures with a characteristic suppression-burst pattern on their EEG and present with severe psychomotor retardation; the prognosis is extremely poor with a high mortality rate. Several of the previously identified patients progressed to West Syndrome, which is characterized by hypsarrhythmia on an EEG and exists on a continuum with Ohtahara syndrome.[9,10]

STXBP1 encodes syntaxin-binding protein 1, a neuron-specific protein of the Sec1 family of membrane-trafficking proteins. *STXBP1* is a multifunctional protein expressed throughout the brain that participates in the regulation of synaptic vesicle docking, fusion, and calcium-dependent neurotransmitter release. It is also involved in synaptic vesicle release at both glutamatergic and GABAergic synapses.[9] STXBP1 is strongly expressed at GABAergic synapses, and suppression of inhibitory neurons by *STXBP1* mutations has been proposed as a mechanism of epileptic seizures.[5,9–11] *STXBP1* mutations occur frequently in a wide spectrum of disorders, including West syndrome (25%), early-onset epileptic encephalopathies (EOEE, 23.6%), Ohtahara syndrome (14.6%), and Rett syndrome (3.2%).[9]

Recent studies have shown that seizures in unexplained West and Lennox–Gastaut syndromes were reduced by approximately 50% after LEV administration.[14–16] In addition, inhibitory effects of LEV on EOEE caused by *STXBP1* mutations have been reported, suggesting that LEV administration may be effective in treating EOEE accompanied by *STXBP1* mutations.[17,18] As a mechanism of action, LEV binds to the synaptic vesicle protein SV2A located on the surface of synaptic vesicles and may be a therapeutic agent for intractable epilepsy cases caused by *STXBP1* gene mutations that mediate synaptic vesicle release.[14–18] However, our patient did not respond sufficiently to LEV at the age of 27 years. The lack of response may have been due to the long duration of epilepsy. In all of the previous studies, LEV treatment was initiated between the first few months of life and less than 2 years of age.[14,15,17,18]

One therapeutic target for epilepsy is the postsynaptic AMPA glutamate receptor.[19,20] This receptor has been considered a rational target for epilepsy treatments because it mediates most fast excitatory synaptic transmissions in the central nervous system and has been implicated in multiple disorders characterized by neuronal overexcitation. Antagonism of AMPA receptors has been associated with antiseizure effects. PER is a novel antiepileptic drug that selectively inhibits the postsynaptic AMPA receptor and is effective for treating drug-resistant epilepsy.[21–26] PER efficacy has been demonstrated in focal epilepsy and, more recently, in primary generalized tonic-clonic seizures.[23,24] A recent open-label study indicated that PER treatment was effective in adults with Lennox–Gastaut syndrome.[25] Furthermore, post hoc analysis of 6 randomized trials demonstrated that supplemental PER treatment was effective in adolescent patients with focal epilepsy, secondary generalized or partially generalized tonic-clonic seizures, and uncontrolled epilepsy and was generally well-tolerated.[26] Recently, two studies reported the efficacy of PER for treating refractory epilepsy complications in various neurodevelopmental disorders.[21,22] However, the previous two reports did not report genotypic data for RTT-P, such as mutations of *MECP2*, *FOXG1*, and *CDKL5*.

In our patient with RTT-P caused by an *STXBP 1* gene abnormality, several antiepileptic drugs were ineffective. Nonetheless, intractable epilepsy was suppressed by a low dose and well-controlled by a higher maintenance dose of PER (Figure 3). Our report suggests that PER is effective for intractable epilepsy patients with RTT-P caused by *STXBP1* genetic abnormalities. Moreover, we believe that improvement of our patient's epilepsy was mainly associated with the PER-mediated control of AMPA receptor activity in the patient's central nervous system. In conclusion, PER exhibits a unique mechanism against epileptic potential and maybe the therapeutic candidate of choice for epilepsy, especially for intractable seizures in patients with *STXBP1* gene mutations, including RTT-P.

There are some limitations to our study that may influence interpretation of the results. The principal limitation is that our findings are based on a single case study. The

second is a lack of a randomized, placebo-controlled study, which is indispensable. Further randomized control studies of intractable epilepsy in patients with *STXBP1* mutations and/or RTT-P will be necessary.

AUTHOR CONTRIBUTIONS

All authors have been involved in drafting the manuscript, have given final approval, and agree to be accountable for all aspects of the work. Each author's individual participation is outlined as follows: SY, AM, TT, KI, NM, and TM performed the conceptualization and design of the study and acquisition, analysis, and interpretation of the data. SY, AM, and IT performed the follow-up examinations.

CONFLICT OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

The research protocol was approved by the Ethics Committees of Kurume University School of Medicine and Yokohama City University School of Medicine.

CONSENT

Written informed consent was obtained from the parents of the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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