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Case Report

PRRT2 mutation in a Japanese woman: Adult-onset focal epilepsy coexisting with movement disorders and cerebellar atrophy

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ABSTRACT

Proline-rich transmembrane protein 2 (*PRRT2*) was confirmed as the causative gene of paroxysmal kinesigenic dyskinesia (PKD) as shown by genome-wide linkage analyses. *PRRT2* mutations are also associated with benign familial infantile seizures, infantile convulsions and choreoathetosis, and childhood absence epilepsy, but few reports have investigated adult-onset epilepsy. We describe here a rare presentation of adult-onset focal epilepsy with a *PRRT2* mutation in a 31-year-old woman who showed cerebellar atrophy, familial paroxysmal kinesigenic dyskinesia, and paroxysmal non-kinesigenic dystonia. Video-electroencephalography (EEG) demonstrated focal impaired awareness seizures, in which ictal EEG changes showed left temporal onset with rhythmic theta activity over the left temporal region. Magnetic resonance imaging showed mild cerebellar atrophy. The administration of lamotrigine 50 mg/day resulted in freedom from her seizures and lamotrigine 150 mg/day reduced paroxysmal non-kinesigenic dystonia. Furthermore, she had a rare frameshift mutation, c.604_607del, p.Ser202fs of which the pathogenicity has been reported in ClinVar, but it has not been reported in Japan. Mutation of the *PRRT2* gene can cause adult-onset epilepsy, paroxysmal non-kinesigenic movement disorder, and cerebellar atrophy, suggesting an expanding clinical phenotypic spectrum associated with *PRRT2* mutations.

1. Introduction

Proline-rich transmembrane protein 2 (*PRRT2*) was confirmed as the causative gene of paroxysmal kinesigenic dyskinesia (PKD) as shown by genome-wide linkage analyses [1]. *PRRT2* mutations are also associated with benign familial infantile seizures, infantile convulsions and choreoathetosis, and childhood absence epilepsy [2]. These features evolve into the phenotypic spectrum associated with a *PRRT2* mutation. However, to the best of our knowledge, no clinical reports have investigated adult-onset focal epilepsy with a *PRRT2* mutation, and no seizure has been documented on electroencephalographic (EEG) monitoring.

The variant c.649dupC, p.Arg217Profs*8, which leads to a premature stop codon, is the most common *PRRT2* mutation. However, c.604_607del, p.Ser202fs is a rarely reported variant of *PRRT2* mutations and has not been described yet in Japan. Previously reported clinical phenotypes of this mutation are a case of PKD without infantile convulsions in Taiwan [3], benign familial infantile seizures in an Italian family [4], and infantile convulsion, and choreoathetosis, and PKD in a three-generation Chinese family [5].

We describe a case of a Japanese woman with the *PRRT2* mutation c.604_607del, p.Ser202fs. She clinically showed familial PKD, paroxysmal non-kinesigenic dystonia (PNKD), mild cerebellar atrophy, and adult-onset focal epilepsy for which seizures were documented by long-term video-EEG monitoring.

Case study

A 31-year-old woman was admitted to our institute because of recurrent seizures and PNKD. She had a family history of PKD (Fig. 1). Her father and sister are currently taking phenytoin and lamotrigine, respectively, for PKD. The patient's birth and neonatal history were unremarkable, and she had developed normally. She

Abbreviations: PRRT2, proline-rich transmembrane protein 2; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia.

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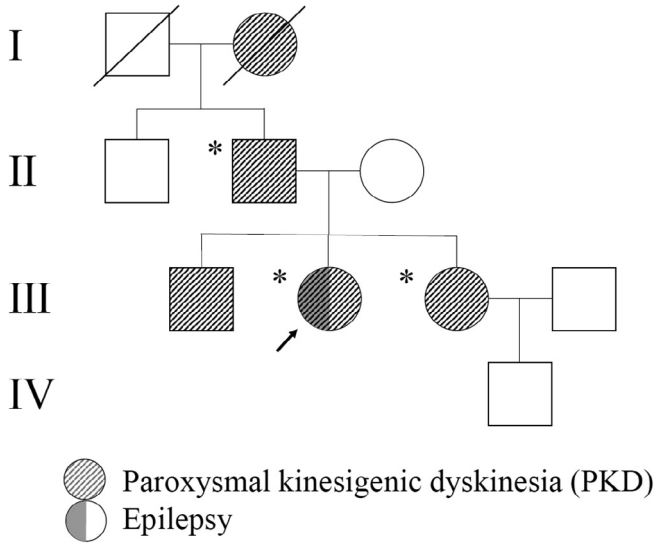

Fig. 1. Pedigree of the family. The arrow indicates the proband. Asterisks indicate the *proline-rich transmembrane protein 2* mutation (c.604-607del).

was intellectually normal, and her final level of education achieved was at a vocational school. She had no history of suspected epileptic seizures, including staring, when she was a child and had no history of known epilepsy risk factors, such as a head injury, encephalitis, and drug exposure. When she was in elementary school, she occasionally became unable to move quickly when she started running, which is concordant with the typical symptoms of PKD. This symptom was mild and remitted spontaneously without treatment. At 11 years old, she was affected by right hip arthropathy, and she then started to limp in the right leg. She had no migraines. At 31 years old, she experienced her first epileptic seizure during sleep. She had a cluster of seizures in which she suddenly groaned and was heavily breathing, followed by thrashing around with a post-ictal headache and vomiting. Similar seizures recurred 1 and 3 months later. She also experienced paroxysmal dystonia in her right or left arm and fingers (right > left) lasting for several to 10 min, which were not triggered by movements (non-kinesigenic). This symptom frequently occurred when she felt stressed. Therefore, she was referred to our hospital for a detailed evaluation.

Neurological examinations showed no abnormal findings, such as symptoms of cerebellar ataxia (e.g., dysmetria, dysdiadochokinesia, dysarthria, and limb/truncal ataxia), except for muscle weakness in her right leg due to the hip arthropathy. An interictal EEG showed sharp waves over the left anterior temporal regions. Video-EEG revealed nine focal impaired awareness seizures and one focal to bilateral tonic-clonic seizure. During the focal impaired awareness seizures, she showed behavioral arrest during awake, and her eyes opened with oral automatism during sleep. One tonic-clonic seizure was followed by her eyes opening with oral automatism during sleep with head version to the right side. The interictal EEG revealed sharp waves over the left temporal regions (Fig. 2A). Ictal EEG started with rhythmic theta activity over the left temporal region with evolution to involve all electrodes over the left hemisphere (Fig. 2B). A symptom that was not triggered by movements (non-kinesigenic) was also captured during video-EEG monitoring, and the EEG showed no ictal change. Brain magnetic resonance imaging (MRI) showed mild cerebellar atrophy (Fig. 3). Because of the presence of paroxysmal dystonia and epileptic seizures, we considered glucose transporter type 1 deficiency syndrome as one of the differential diagnoses. However, blood and cerebrospinal fluid examinations, including the cerebrospinal fluid/blood glucose ratio, were normal. We considered the symptom of transient non-kinesigenic dystonia to be PNKD because this symptom lasted for several to 10 min, it was triggered by emotional stress, and there was no unusual electrical activity on EEG.

She was treated with lamotrigine 50 mg/day, which resulted in freedom from seizures, and with lamotrigine 150 mg/day, which reduced the PNKD. We selected lamotrigine instead of carbamazepine in consideration of a future pregnancy. After obtaining informed consent from the patient, her parents, and her sister, we performed a mutation analysis of the *PRRT2* gene using Sanger sequencing to search for the variant of c.649dupC. Although this variant was not detected, the c.604_607del variant was detected in the father, sister, and the patient, but not in the mother (Fig. 4).

4. Discussion

We report a patient presenting with childhood-onset PKD and adult-onset focal epilepsy with a *PRRT2* mutation. The variant c.649dupC is the most common hotspot of *PRRT2* mutations, and direct sequencing of this site is generally used for *PRRT2* mutation analysis. No variant at this site was detected in our case, while the c.604_607del, p.Ser202fs variant was identified. The patient's father and sister also have the same variant. The patient's sister was previously diagnosed with PKD without a *PRRT2* mutation because the c.649dupC variant was not detected. The laboratory only searched for the c.649dupC variant.

Although a few studies investigated adult-onset tonic-clonic seizures or myoclonic seizures in patients with *PRRT2* mutations [6,7], no reports have investigated adult-onset focal epilepsy associated with *PRRT2* mutations. Additionally, reports on patients with the c.604_607del variant have shown benign familial infantile seizures and PKD with infantile convulsions [3–5]. However there have been no reports showing that this variant is related to adult-onset focal epilepsy. Therefore, our report is the first to describe a patient with the c.604_607del variant presenting with focal epileptic seizures.

PRRT2 is a member of the transmembrane protein family, and truncated PRRT2 proteins cannot anchor to the membrane and may be loss-of-function [1,2]. Despite the fact that many missense, nonsense, and frameshift mutations have been described, no specific genotype–phenotype correlations have been found [8], and the location and type of the mutation in *PRRT2* do not appear to predict the clinical phenotype [2]. *PRRT2* mutations generally induce epilepsy in infancy and PKD in childhood or adolescence with a tendency for remission in adulthood [2]. In contrast, our patient's focal epilepsy appeared in adulthood, and the PKD symptoms of her father and sister have not resolved. These clinical characteristics might have been caused by the c.604_607del variant.

Fruscione et al. found that the activity of voltage-gated Na^+ channels was enhanced in PRRT2-deficient neurons, and that they were important negative modulators of Nav1.2 and Nav1.6 channels [9]. Therefore, *PRRT2* mutations result in an increased voltage-dependent Na^+ current and increased intrinsic excitability. In our case, the epilepsy was considered to be associated with a *PRRT2* mutation, and a low dose of a sodium channel blocker was effective. The favorable response to sodium channel blocker treatment in this patient may be explained by the negative modulatory role of PRRT2.

Our patient also showed symptoms of PNKD. PNKD is characterized by paroxysmal attacks of dystonic or choreiform movements occurring at rest, or it is provoked by alcohol intake, caffeine intake, emotional stress, and fatigue. PNKD attacks usually last longer than those in PKD [10,11]. In the majority of typical PNKD cases, the myofibrillogenesis regulator 1 gene is the main genetic

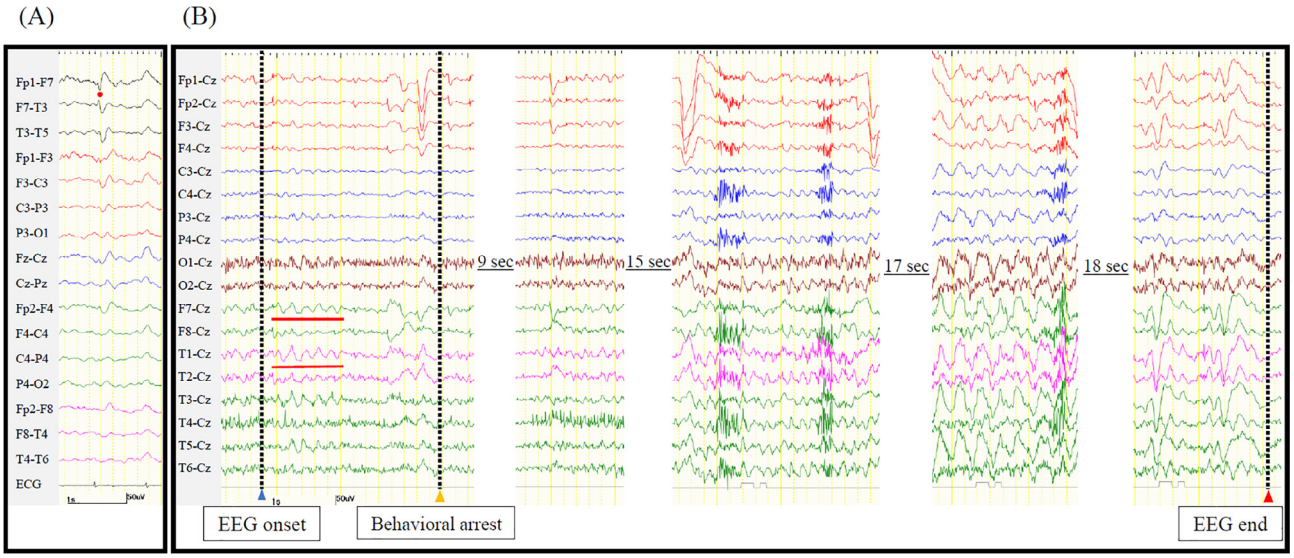

Fig. 2. (A. Interictal electroencephalography (EEG) (bipolar montage, high-pass filter: 1.59 Hz, low-pass filter: 60 Hz) revealed sharp waves over the left temporal region (red dot). (B) EEG of a focal impaired awareness seizure (Cz referential montage, high-pass filter: 1.59 Hz, low-pass filter: 60 Hz). This seizure started during wakefulness. The ictal EEG change started (blue arrow) with rhythmic activity over the left temporal region (red bars) followed by no apparent change for 10 s. Rhythmic activity then restarted from the left temporal area, followed by evolution over the left hemisphere, and then suddenly stopped (red arrow). Two and one-half seconds after the onset of the ictal EEG change, a clinical seizure appeared (yellow arrow). The patient suddenly stopped motion and lowered her eyes without aura of a seizure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

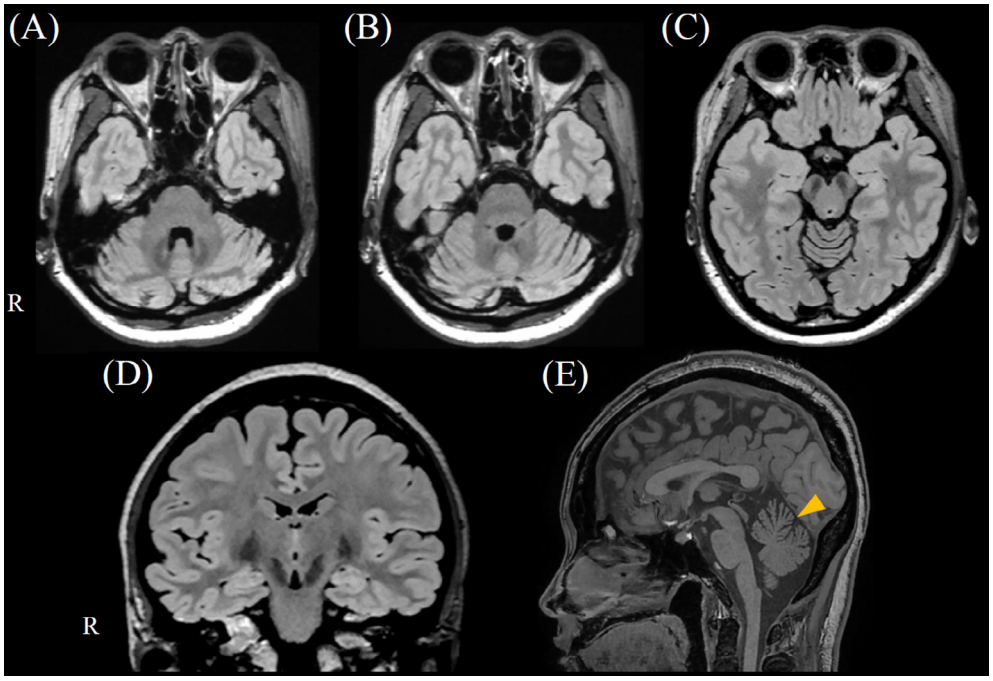

Fig. 3. Brain MRI showing axial fluid-attenuated inversion recovery (FLAIR) images (A, B and C), a coronal FLAIR image (D), and a sagittal spoiled gradient recalled echo image (E). Mild cerebellar atrophy and expansion of the fourth ventricle (A, B and E) were observed, especially in the upper cerebellum (yellow arrow). Although mild cortical atrophy was observed (D and E), bilateral hippocampi and amygdala were normal. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cause [12], but the relationship between PNKD and *PRRT2* mutations remains unclear. However, several studies have reported that PNKD and PNKD-like symptoms are associated with *PRRT2* mutations [2,10,13].

Interestingly, we also found the mild cerebellar atrophy on her brain MRI without ataxia in our patient. Although we could not evaluate MRI in the patient's father and sister, they had no cerebellar ataxia. *PRRT2* mRNA is highly expressed in the Purkinje cell layers of the cerebellum [14,15]. One study showed that PRRT2 was a presynaptic protein of which mutations caused abnormal firing patterns in Purkinje cells [15]. Another study showed reduced parallel fibre transmission and Purkinje cell excitability [16]. Furthermore, episodic ataxia has been reported in some patients with heterozygous *PRRT2* mutations, and two patients with biallelic *PRRT2* mutation showed cerebellar atrophy on MRI [17]. Therefore, these findings indicate that *PRRT2* mutations can affect the cerebellum, leading to not only cerebellar dysfunction, but also to cerebellar atrophy.

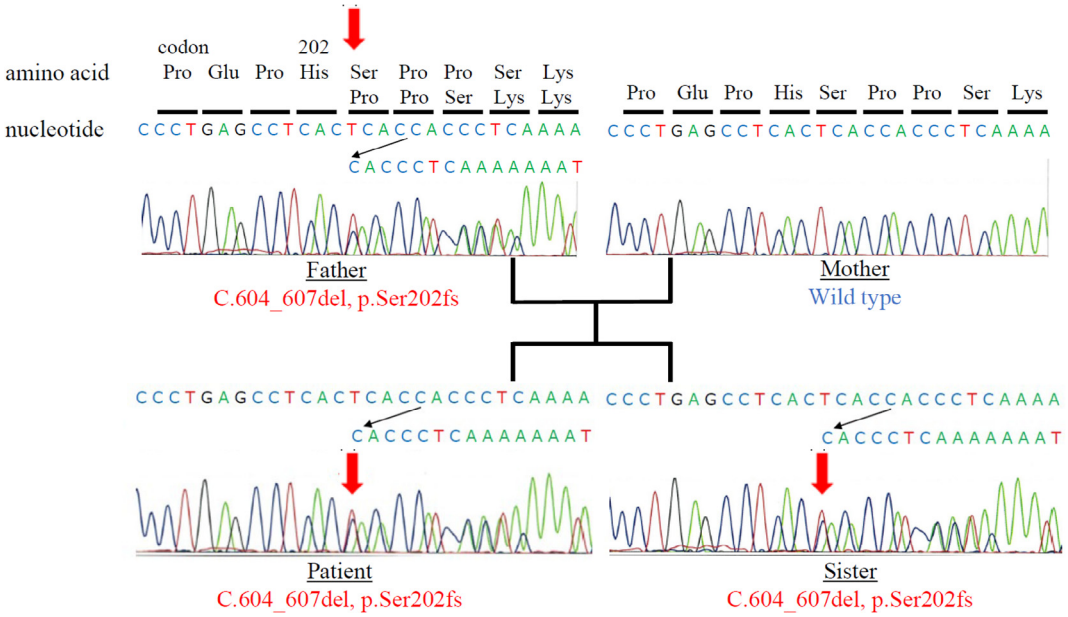

Fig. 4. *Proline-rich transmembrane protein 2* mutations identified in this patient, her father, and her sister. Sanger sequencing shows deletion of TCAC at position 604–607, which changed the reading frame. The red arrows indicate heterozygous. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

One limitation of this study is that we did not test for mutations other than the one that we found. We cannot provide relevant biological evidence that the *PRRT2* mutation contributed to the development of adult-onset epilepsy. Therefore, there might be a dual pathology in our patient. Additionally, the cause of epilepsy may not have only been due to a genetic mutation, but also due to other factors. However, there was no known prior epilepsy risk factors and no epileptogenic lesion in the temporal lobe that could have caused the patient's epilepsy. Additionally, no findings suggested any other known genetic mutation, such as intellectual disability, infantile-onset epilepsy, or physical characteristics. Although her father and sister did not develop epileptic seizures, the existence of epilepsy cannot be ruled out because they have been taking antiepileptic drugs since childhood.

Despite these limitations, the findings in our case indicate the expanding clinical spectrum of *PRRT2*-associated phenotypes. The findings from our case also suggest that not only c.649dupC but also other mutations should be analyzed, even if a patient does not show typical clinical features associated with *PRRT2* mutations. Not only PKD but also various other diseases (e.g., epilepsy) can be associated with *PRRT2* mutations. Therefore, a proactive attitude, such as referring to the family history and other clinical information, is required to identify *PRRT2* mutations. In clinical practice, epileptic seizures and involuntary movements associated with *PRRT2* mutations may respond to low doses of sodium channel blockers.

We present a case of adult-onset temporal epilepsy, cerebellar atrophy, PKD, and PNKD with a *PRRT2* mutation. Further studies are required to examine the associations between *PRRT2* mutation and epilepsy and movement disorders.

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Consent: We have obtained written informed consent from the patient for publication of this case report.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YT received an academic donation from Eisai.

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