Epilepsy Spectrum Associated with *PRRT2* Variants: Case Presentations

Semih Taşdelen[1], Gözde Yeşil Sayın[2], Sibel Aylin Uğur İşeri[3], Nerses Bebek[1], Betül Baykan[1]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Neurology, İstanbul, Turkey

[2]İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey

[3]İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, İstanbul, Turkey

Abstract

Variations in the *PRRT2* gene have been shown to cause a variety of diseases, including benign familial infantile epilepsy (BFIE) and paroxysmal kinesigenic dyskinesia (PKD). Next-generation sequencing techniques have allowed the broadening of this disease spectrum. In this study, we aimed to present patients with epilepsy who were shown to have *PRRT2* variants in our clinic. The characteristics of 13 patients with epilepsy, including two families with *PRRT2* variants and one patient with a sporadic homozygous variant, were reviewed by screening the epilepsy archive. P.R217Pfs∗8 variation was detected in patients of our first family with both BFIE and PKD diseases. This family was included in the article in which this gene was first described in 2012. In the first generation there were 3 patients with BFIE, in the second generation there were 2 patients with BFIE-PKD and one patient with BFIE. The second family had only BFIE. In this family, the c.604_607del (p.Ser202HisfsTer26) variation was detected in the *PRRT2* gene in the index case. In this phenotypically homogeneous family, BFIE was present in all 3 generations. Although the seizures remitted, electroencephalography abnormalities continued for 2 years in our index case. Migration of the epileptogenic focus to the posterior of the hemispheres over time is an interesting observation. Our sporadic case was a patient with a diagnosis of juvenile absence epilepsy, and a homozygous c.67G>A;p.(Glu23Lys) variant was detected in this patient. Findings in *PRRT2*-associated epilepsy patients show the importance of next-generation sequencing techniques. It indicates that different epilepsy phenotypes can be seen in variations associated with a single gene. With better recognition of epilepsy associated with *PRRT2* gene variants, which are considered as synaptopathy, it will be possible to switch from current symptomatic treatments to therapeutic options targeting specific pathophysiological changes.

Keywords: Synaptopathy, benign familial infantile epilepsy, paroxysmal kinesigenic dyskinesia, *PRRT2*

INTRODUCTION

Genetic causes are important in many systemic and neurological diseases. The process, which started with family studies previously, is now progressing much faster with the developments in gene sequencing technologies and bioinformatics. Thus, our knowledge and treatment options are increasing. It becomes clear over time that genetic etiology plays a major role in epilepsy, movement disorders, and migraine.[1] It was first determined that variants in the *PRRT2* gene cause paroxysmal kinesigenic dyskinesia (PKD), which is a distinct phenotype, through genetic linkage analysis and whole-exome sequencing.[2] In the following period, it was shown that the same gene causes benign familial infantile epilepsy (BFIE).[3] Today, the spectrum of *PRRT2*-related diseases has expanded beyond these entities and has included several different diseases, such as neurodevelopmental disorders and hemiplegic migraine. There are not many publications from our country about variants in this gene.

Our aim in this study was to present epilepsy patients in our clinic with variants detected in the *PRRT2* gene and to review the developments in the spectrum of this gene.

CASE PRESENTATIONS

In this article, we will present two families with a *PRRT2* variant and a sporadic case with a homozygous variant in the same gene, followed up in our clinic for epilepsy for years.

Family 1

In the first family diagnosed with BFIE and PKD together, ENST00000358758.12:c.649dup; p.(Arg217ProfsTer8) pathogenic variation (ClinVar: VCV000065758.86) was detected in five patients in 2012. This family was included in a article in which the *PRRT2* gene was first described.[4] In the first generation, three patients had BFIE that resolved spontaneously without the use of medication. Two patients in the second generation had BFIE-PKD, and one patient had BFIE only (Figure 1). All patients had BFIE, and generalized convulsive seizures were observed with daily frequency, starting at the age of 8-10 months. There was moderate cyanosis but no fever. The seizures were controlled with low-dose phenobarbital and ended between the ages of 2 and 4 years, after which the drug treatment was discontinued. In two patients in the second generation, PKD was observed after BFIE, which started at the age of 4-8 years. Involuntary movements in the extremities were observed, triggered by sudden and rapid movements lasting less than 1 min, and without loss of awareness. The movements were unilateral in one patient and bilateral in the other sister.

These involuntary movements were controlled with carbamazepine 100 mg/day. Seizure frequencies and PKD severities vary among patients. Neurological examination and cranial magnetic resonance imaging (MRI) of all patients were normal, and electroencephalography (EEG) examinations of the two index patients showed no significant features other than nonspecific theta paroxysms.

Family 2

The patients from the second family had only BFIE. In the index case, pathogenic ENST00000358758.12:c.604_607del in the *PRRT2* gene; p.(Ser202HisfsTer26) variation (ClinVar: rs1064793851) was detected. The members of this phenotypically more homogeneous family experienced seizures that started at 4-6 months of age and were controlled with phenobarbital (Figure 2). Although the seizures stopped, the EEG abnormality in our index case continued for 2 years (Figures 3a, 3b, 3c). The patient's older sister had a history of similar seizures, which stopped immediately with treatment. Seizures seen in his mother, aunt, maternal uncle, and maternal grandfather ended without medication. Neurological examination and cranial MRI were normal.

Sporadic Case

Our sporadic case was a female patient who was diagnosed with juvenile absence epilepsy and had a generalized convulsion once. EEG showed nonspecific generalized paroxysms and photosensitivity. A homozygous but possibly benign c.67G>A;p.(Glu23Lys) variant (ClinVar: rs140383655) was detected in the patient whose parents were relatives (Figure 4).

MAIN POINTS

- Findings in *PRRT2*-associated epilepsy patients show the importance of next-generation sequencing techniques.
- The *PRRT2* gene is expressed in the central nervous system, especially in the cerebral cortex, basal ganglia and cerebellum.
- BFIE, PKD, and PKD/IC form the basis of the spectrum of *PRRT2*-associated paroxysmal disorders.

DISCUSSION

The *PRRT2* gene is located on chromosome 16p11.2 and encodes the PRRT2 protein, which consists of 340 amino acids. The *PRRT2* gene is expressed in the central nervous system, particularly in the cerebral cortex, basal ganglia, and cerebellum.[2,3] In animals, the expression of PRRT2 has been examined in the developing nervous system. Accordingly, it has been shown that there is a significant increase in gene expression in the early postnatal period and a decrease in adulthood.[5] Age-related changes in gene expression may be important in explaining the onset and termination of symptoms in patients at certain age intervals.

At the cellular level, the PRRT2 protein is localized in axons, especially in glutamatergic synapses, and is associated with the GRIN1A glutamate receptor, which is a member of the AMPA receptor family.[4] It can be thought that variants in this gene are related to the etiopathogenesis of the seizures in our cases. PRRT2 interacts with the synaptic t-SNARE protein SNAP25 (Synaptosomal-Associated Protein), indicating its role in the synaptic vesicle mechanism and neurotransmitter release. Subsequent studies have shown that PRRT2 also interacts with other synaptic proteins involved in neurotransmitter release, such as VAMP2 (Vesicle Associated Membrane Protein 2) and synaptotagmin (Syt1 and 2).[6]
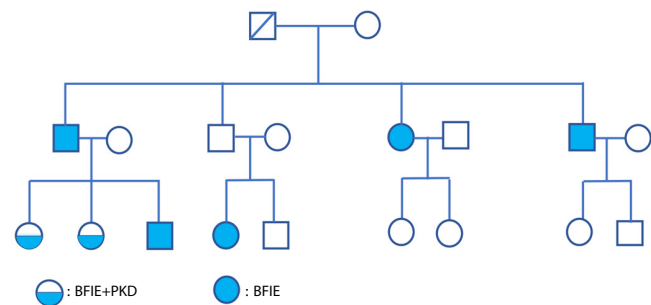

Figure 1. Family 1, in the first generation, 3 patients with the p.R217Pfs∗8 variation had only BFIE, which ended spontaneously without the use of medication, while BFIE-PKD coexistence was noted in 2 patients in the second generation, and the presence of BFIE in one patient
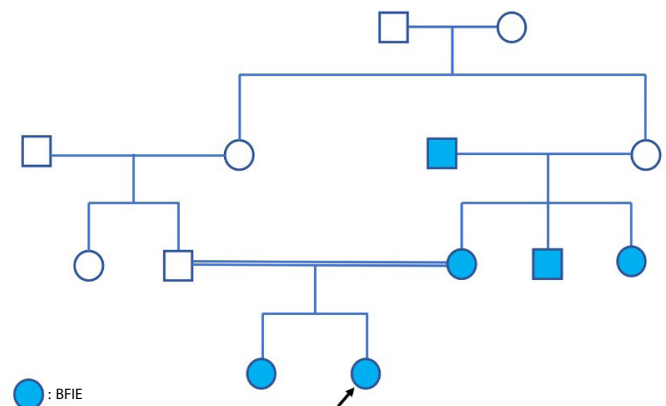BFIE: Benign familial infantile epilepsy, PKD: Paroxysmal kinesigenic dyskinesia

Figure 2. Family 2 was phenotypically homogeneous, with members in three generations having BFIE
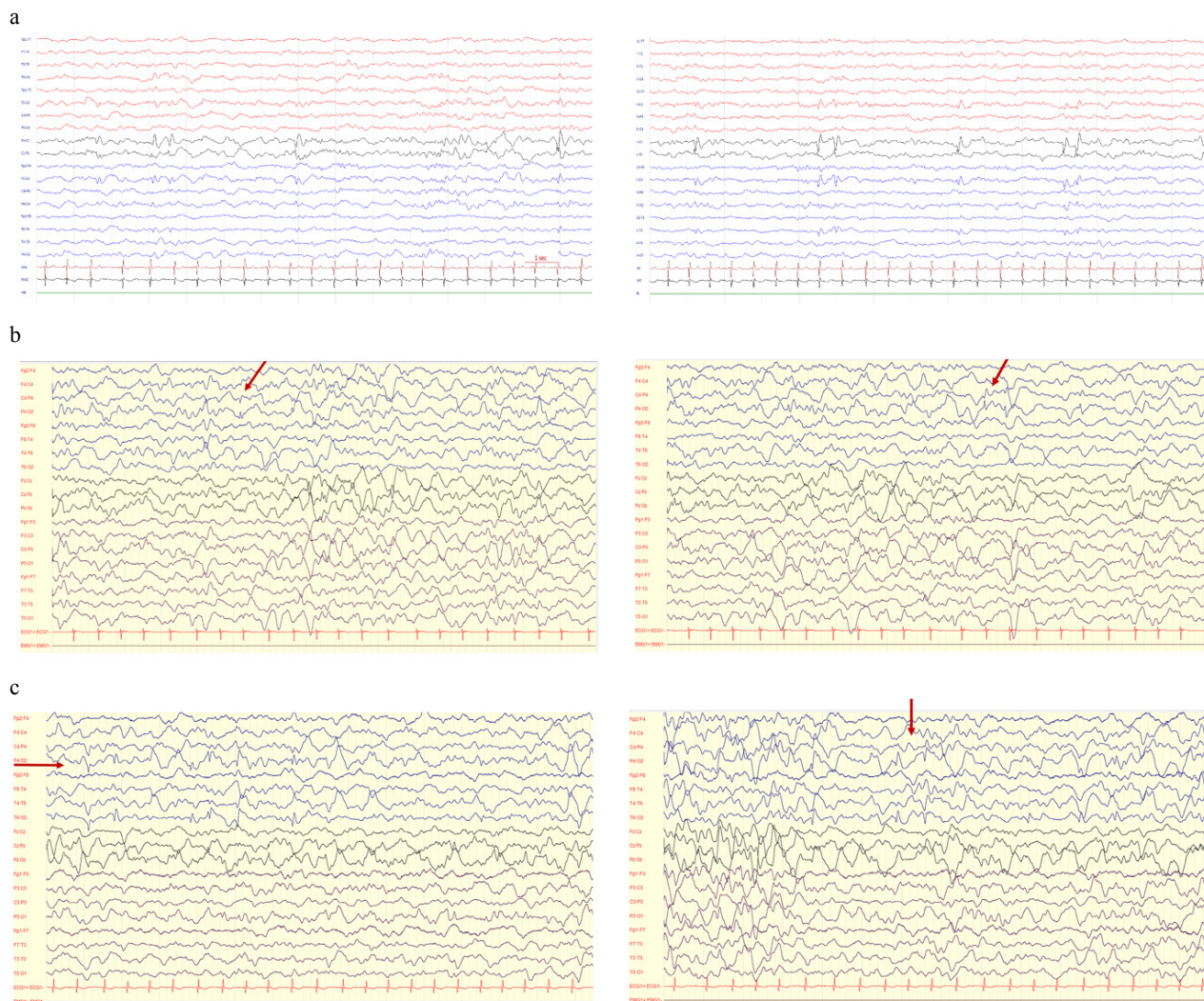BFIE: Benign familial infantile epilepsy

Figure 3. a) Family 2, interictal EEG of the index case shows the presence of epileptogenic foci in the centro-parieto-temporal regions, prominent in the midline and on the right (at the age of 2.5). b) The interictal EEG examination of family 2-index case shows low-amplitude spike-wave activity in the right parietal region during sleep (at the age of 3.5 years). c) Family 2-index case's interictal EEG examination shows epileptiform activity in the right occipital region during sleep. Although the patient's seizures ended over time, the migration of epileptogenic foci towards the posteriors of the hemispheres was impressive (at the age of 4)
EEG: Electroencephalography

SNAP25 is expressed predominantly in neurons and neuroendocrine cells and is extensively involved in presynaptic terminals. SNAP25 regulates calcium-triggered exocytosis in synaptic vesicles by three mechanisms. SNAP25 acts as a t-SNARE protein, plays a role in the molecular mechanism required for synaptic vesicle fusion, contributes to endocytosis at synapses, and negatively regulates voltage-gated channels. Therefore, the inactivation of SNAP25 results in increased activity in glutamatergic neurons. Therefore, impairment or decrease in the function of PRRT2, which interacts with SNAP25, may lead to changes in synaptic vesicle release and neuronal hyperexcitability.[7]

Recent studies have shown that PRRT2 also causes negative modulation of voltage-gated Nav1.2 and Nav1.6 channels.[8] Studies on induced pluripotent stem cell-derived neurons from homozygous patients and neurons from *PRRT2* knockout mice have shown an increase in sodium currents.[8] This causes spontaneous firing when suprathreshold, high-frequency stimulation is applied to neurons. The abnormal firing was completely reversed when *PRRT2* was regained by the cells. Beyond synaptic dysfunction, the impairment in cellular excitability caused by the negative modulation of Na + channels may explain the paroxysmal character of *PRRT2*-related disorders and the effectiveness of molecules acting on the sodium channel.[2,8]

In the review by Ebrahimi-Fakhari et al.[9], patients with 70 different *PRRT2* variations were analyzed. According to this review, 5.5% of the variations were *de novo*, whereas 87.1% were familial. It was highlighted that almost 80% of the patients had the pathogenic c.649dupC; p. Arg217Profs*8 variation, which was also found in the first family in our study. When the variations in the *PRRT2* gene were classified according to their types, it was understood that approximately three quarters of them caused premature stop codons due to missense or frameshift variations. Such variations, including ENST00000358758.12:c.649dupC, may lead to a decrease in mRNA stability or a rapidly degradable protein product.[10]

BFIE, PKD, and PKD/IC form the basis of the spectrum of *PRRT2*-associated paroxysmal disorders (Figure 5).
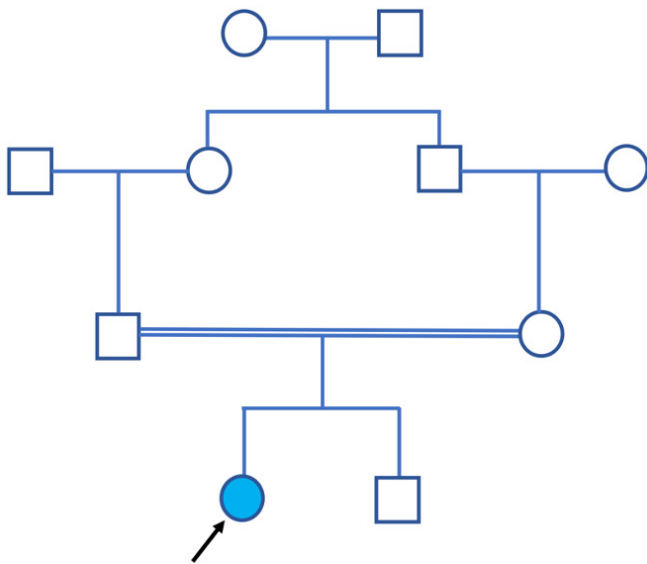
Figure 4. Our sporadic case who was diagnosed with juvenile absence epilepsy and had generalized tonic-clonic convulsion only once. Homozygous but possible benign c.67G>A;p.(Glu23Lys) variant was detected in this case
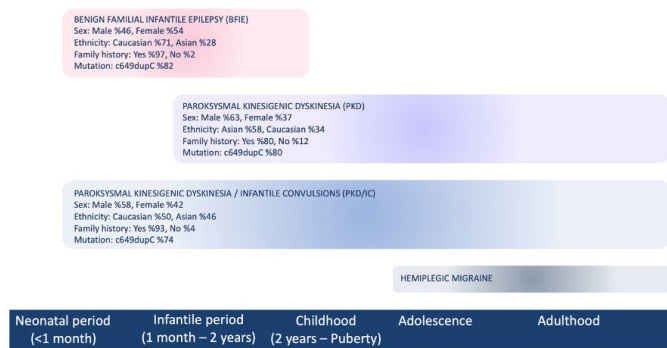

Figure 5. Clinical spectrum of *PRRT2*-associated paroxysmal disorders according to age of onset
BFIE: Benign familial infantile epilepsy, PKD/IC: Paroxysmal kinesigenic dyskinesia/infantile convulsions

BFIE, which we diagnosed in our cases, is a self-limiting seizure disorder characterized by nonfebrile seizures that usually begin between 3 and 12 months of age and end at 2 years of age. BFIE-associated seizures usually occur as focal-onset seizures with impaired awareness or generalized tonic-clonic seizures. The focal features observed in our EEG samples are noteworthy. Interictal neurological examination and MRI are normal, as in our cases. Ictal EEG usually shows parieto-occipital epileptic activity, which then becomes generalized.[11]

In most cases, seizures respond easily to antiseizure medications, with remission rates over 90%. Complete remission in our patients is consistent with the literature. Levetiracetam was found to be significantly ineffective compared with phenobarbital and valproate. While sodium channel blockers such as carbamazepine and oxcarbazepine have a positive effect, the effectiveness of levetiracetam was found to be insufficient.[12]

Although PKD is rare, with a prevalence of 1:150,000, it is still the most common paroxysmal movement disorder. The movement disorder, which would later be defined as paroxysmal PKD, was first described by Shuzo Kure in 1892.[13] Bruno et al.[14] defined the diagnostic criteria for PKD in 2004. These criteria were identified as the kinesigenic trigger for the attacks, short duration of attacks (<1 minute), no loss of consciousness or pain during attacks, exclusion of other organic diseases and normal neurological examination, control of attacks with phenytoin or carbamazepine (if tried), and age at onset between 1 and 20 years (if no family history of PKD).

As typically observed in our cases, symptoms begin between the ages of 5 and 15. Clinically, PKD is characterized by unilateral or bilateral hyperkinetic movements triggered by sudden voluntary movements, such as starting to walk, getting up from a chair, or being startled. Involuntary movements involving one or more extremities may be dystonic contractions of the extremities or may be choreoathetoid or ballistic.

Most patients experience bilateral attacks, the upper limbs are most commonly affected, and the attack lasts approximately 30 s on average. It does not occur during sleep, and there is no loss of consciousness, pain, or weakness. Interictal examination, EEG, and MRI are normal, and no long-term neurological sequelae have been reported. Carbamazepine at low doses (50-200 mg/day) is usually sufficient, and a complete response is observed in approximately 95% of the cases, as observed in our cases.

It has been observed in our cases and in the literature that *PRRT2* variation can cause BFIE alone, PKD alone, or a combination of PKD and BFIE. In addition, the age of onset and disease severity can vary significantly.[4] Patients may have additional symptoms such as mental retardation, attention deficit and hyperactivity disorder, absence epilepsy, migraine, paroxysmal nonkinesigenic dyskinesia, and episodic ataxia.[15] Therefore, it was thought that the homozygous variant detected during research in our sporadic case might be related to epilepsy.

Confirmation of *PRRT2* variations in patients with typical infantile seizures may reassure parents that seizures are probably self-limiting. Early genetic diagnosis can help provide appropriate advice and education to families about the possibility of PKD later in life; thus, it can facilitate early diagnosis and treatment.

There is a need for research on the relationship between *PRRT2* variations and other seizure types and whether they lower the epilepsy threshold. In addition to nonfebrile and febrile seizures, cases of generalized tonic-clonic seizures, absence, nonconvulsive seizures, Dravet syndrome, West syndrome, and Rolandic epilepsy have also been reported.

In summary, although current data have clearly shown the relationship between *PRRT2* variations and BFIE and PKD, further research is needed to obtain information about its role in other types of epilepsy.

CONCLUSION

Findings in *PRRT2*-associated disorders demonstrate the importance of next-generation gene sequencing techniques and indicate that different phenotypes can be observed in single gene-related variations. The spectrum of *PRRT2*-associated disorders is likely to be broader than we currently know. The identification of *PRRT2* variants as the genetic cause of several diseases is an important starting point for a better understanding of the molecular

mechanisms underlying paroxysmal diseases. Comprehensive genetic and phenotypic characterization will elucidate a broad phenotypic spectrum and pave the way for personalized treatments.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B., Concept: B.B., Design: B.B., S.T., Data Collection or Processing: B.B., S.A.U.İ., S.T., N.B., Analysis or Interpretation: B.B., S.A.U.İ., S.T., N.B., Literature Search: B.B., Writing: B.B., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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