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PRRT2 mutations in Japanese patients with benign infantile epilepsy and paroxysmal kinesigenic dyskinesia

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ABSTRACT

Purpose: This study was performed to clarify the clinical features of Japanese patients with *PRRT2* mutations.
Methods: The *PRRT2* gene was analyzed in 135 patients with benign infantile epilepsy (BIE) or paroxysmal kinesigenic dyskinesia (PKD) using a direct sequencing method: 92 patients had BIE alone, 25 had both BIE and PKD, and 18 had PKD alone. Of the cases, 105 were familial, and 30 were sporadic. Clinical information was collected using a structured questionnaire.
Results: *PRRT2* mutations were identified in 104 patients. Among the familial cases, *PRRT2* mutations were found in at least one individual in 21 of 28 families with BIE alone, in 26 of 27 families with infantile convulsions and choreoathetosis, and in 2 of 3 families with PKD alone. Among the sporadic cases, *PRRT2* mutations were observed in 7 of 25 patients with BIE alone, in 1 of 1 patient with BIE and PKD, and in 3 of 4 patients with PKD alone. The c.649dupC mutation was the most frequent, followed by the c.981C > G mutation. Among the patients with epilepsy, the median age at BIE onset was 5 months, the median age at the last seizure was 6 months, and the median number of seizures was 5.
Conclusion: *PRRT2* mutations were found in 68% of Japanese probands with BIE or PKD. The phenotypes of BIE associated with *PRRT2* mutations were consistent with those of BIE diagnosed clinically.

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1. Introduction

Watanabe et al. reported focal epilepsy of infants with favorable outcome [1,2], and proposed an epilepsy syndrome called benign partial epilepsy in infancy [3]. Benign partial epilepsy in infancy was renamed benign infantile epilepsy (BIE) or benign familial infantile epilepsy (BFIE), if familial, and it has been described in the international classification of epilepsy [4]. Additionally, an association of BIE with paroxysmal kinesigenic dyskinesia (PKD) has been reported and called infantile convulsions and choreoathetosis [5].

BIE and/or PKD can all be familial, and genetic factors are assumed to be involved [1,2,5]. In 2011, Chen et al. reported that the proline-rich transmembrane protein 2 (*PRRT2*) gene was responsible for PKD [6]. Subsequently, Heron et al. reported that *PRRT2* caused BIE [7]. *PRRT2* mutations are frequently observed in patients with BIE and/or PKD regardless of race or country [8–12]. Moreover, the clinical spectrum of *PRRT2* mutations has expanded to include other paroxysmal movement disorders, such as hemiplegic migraine [13–15], paroxysmal non-kinesigenic dyskinesia [13,16], paroxysmal torticollis [17], and epilepsies other than BIE or BFIE [14,15,18].

There have been several reports on *PRRT2* mutations in BIE and/or PKD in Japanese children [8–10,19–21]. However, most reports included few patients. Therefore, this multicenter study was conducted to clarify the clinical features of Japanese patients with *PRRT2* mutations and to amass clinical and genetic data.

2. Methods

The study enrolled the patients who were clinically diagnosed to have BIE and/or PKD. In this study, BIE was defied as epilepsy beginning during infancy meeting all the following conditions: (a) focal seizures; (b) normal psychomotor development and neurologic findings before onset; (c) normal interictal EEGs; (d) normal cranial CT and MRI findings; (e) seizure freedom within 2 years of age. PKD was defined as recurrent brief involuntary hyperkinesia, such as choreoathetosis, ballism, athetosis or dystonia, triggered by sudden movements. The relatives of the patients were also included when informed consent was given. A large majority of the subjects were patients who visited the Departments of Pediatrics of Juntendo University Hospital, Aichi Medical University Hospital, Okayama University Hospital, Kyoto University Hospital, Asahikawa Medical University Hospital, and their affiliated hospitals. We also obtained clinical and genetic information from the subjects who requested genetic analysis through the Zao Seminar mailing list, which consists of more than 1000 pediatric neurologists in Japan, and the Japanese Society of Pediatric Neurology. This study was approved by the ethics committee of each facility that performed genetic analyses.

Table 1 lists the 58 families in which *PRRT2* gene analysis was performed in this study: 28 families had BIE alone; 27 families had BIE and/or PKD; and three families had PKD alone. In these families, 67 patients had BIE alone, 24 patients had BIE and PKD, and 14 patients had PKD alone. *PRRT2* gene analysis was also performed in 30 sporadic patients (Table 1): 25 cases with BIE alone, 1 with BIE and PKD, and 4 with PKD alone. When these patients were integrated, 66 probands had BIE alone, 13 had BIE and PKD, and nine had PKD alone.

PRRT2 gene analysis was performed at Tokyo Women's Medical University Integrated Medical Science Institute, Fukuoka University, Okayama University, Kyoto University, and Asahikawa Medical University based on a polymerase chain reaction (PCR)-direct sequencing method described elsewhere [22]. The primers used were the same as those reported by Heron et al. [7]. We focused on all nonsynonymous mutations involving amino acid substitutions. We obtained the following clinical information using a structured questionnaire: family history of epilepsy and PKD; history of convulsions with gastroenteritis (CwG) [23] and febrile seizures; age at the last seizure; total number of seizures; and presence or absence of seizure clusters, PKD, and intellectual disorders.

As to statistical analyses, the Mann-Whitney U test was used to compare numerical variables. A p value < 0.05 was considered to indicate statistical significance.

3. Results

The *PRRT2* gene was analyzed in 135 patients, and mutations were identified in 104 patients. Table 1 shows the *PRRT2* mutation rate according to the phenotypes. Among familial cases, *PRRT2* mutations were found in at least 1 patient in 21 of 28 families with BIE alone, in 26 of 27 families with BIE and/or PKD, and in 2 of 3 families with PKD alone. Within all families with *PRRT2* mutations, all patients who participated in gene analysis shared single *PRRT2* mutation within their family. In the sporadic cases, *PRRT2* mutations were observed in 7 of 25 patients with BIE alone, in 1 of 1 patient with BIE and PKD, and in 3 of 4 patients with PKD alone. According to the phenotypes of the probands, *PRRT2* mutations were present in 41 of 66 probands with BIE alone, in 13 of 13 with BIE and PKD, and in 6 of 9 with PKD alone.

Table 2 lists the *PRRT2* mutations in the probands. The c.649dupC mutation, which is common, was observed in 50 probands. The c.981C > G mutation was found in four cases, and the other mutations were seen in one case each. The c. 318 delA mutation was a novel unreported mutation. A homozygous c.981C > G mutation was identified in one sporadic patient with BIE and PKD, whereas the other mutations were present at one allele. The patient with a homozygous c.981C > G mutation had a typical clinical phenotype of BIE and PKD: the first seizure at 5 months of age, a total of 4 seizures until 12 months of age. He also had PKD since 2 years of age, whereas other neurological symptoms or intellectual disorder had not been observed.

Of the 104 patients with *PRRT2* mutations, 90 had BIE. In the 81 patients for whom the age at epilepsy onset was recorded, the median age at the onset of BIE was 5 (range 2–14) months (Fig. 1). The age at the last seizure age was available for 72 patients, and their median age was 6 (range 2–19) months (Fig. 1). The total number of seizures was recorded in 73 patients. Their median number of seizures was 5; 64

Table 1
PRRT2 mutations according to the phenotypes.

	Number of families	Families with *PRRT2* mutation	Families with no *PRRT2* mutation	A total number of patients tested	Patients with *PRRT2* mutation	Patients with no *PRRT2* mutation
BIE family	28	21 (75%)	7 (25%)	41	33 (80%)	8 (20%)
PKD family	3	2 (67%)	1 (33%)	6	4 (67%)	2 (33%)
BIE and/or PKD family	27	26 (96%)	1 (4%)	58	56 (97%)	2 (3%)
				BIE alone 26	25 (96%)	1 (4%)
				PKD alone 8	7 (88%)	1 (13%)
				BIE and PKD 24	24 (100%)	0
Sporadic BIE	NA			25	7 (28%)	18 (72%)
Sporadic PKD	NA			4	3 (75%)	1 (25%)
Sporadic BIE and PKD	NA			1	1 (100%)	0

BIE: benign infantile epilepsy, PKD: paroxysmal kinesigenic dyskinesia, NA: not applicable.

Table 2
The list of the *PRRT2* mutations according to the phenotype of the probands.

PRRT2 mutations		phenotype of the proband			
		BIE	PKD	BIE and PKD	ExAC (East Asia)
c.649dupC	p. Arg 217 Pro fs*8	37	5	8	0.004626
heterozygous c.981C > G	p. Ile 327 Met	1	1	1	–
homozygous c.981C > G	p. Ile 327 Met	0	0	1	–
c.318delA	p. Glu 107 Lys fs*8	1	0	0	–
c.522 T > G	p. Ser 174 Arg	1	0	0	0.00012
c.1012 + 3_4insT	Splicing	1	0	0	–
c.503_504delCT	p. Pro 168 Arg fs*5	0	0	1	0
c.650delG	p.Arg217Gln fs*12	0	0	1	0.01287
c.880-2_-3delCA	Splicing	0	0	1	–
None		25	3	0	

ExAC : Exome Aggregation Consortium (http://exac.broadinstitute.org/, accessed on Aug 1, 2018).

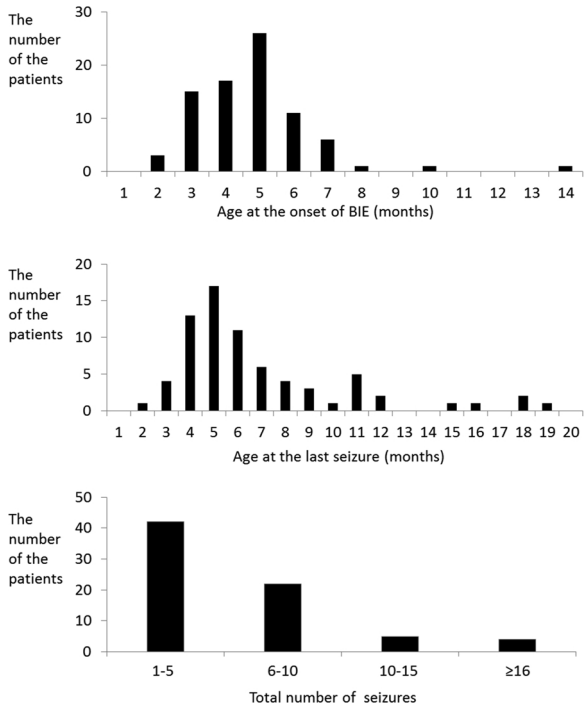

Fig. 1. Age at the first and last seizure, and total number of seizures in patients with *PRRT2* mutations having benign infantile epilepsy.

patients had 10 seizures or less, whereas 4 patients had 16 or more seizures (Fig. 1). A cluster of seizures was seen in 50 of 78 patients from whom information was available. Status epilepticus was noted in 2 of 84 patients. The antiepileptic drugs given to these patients were carbamazepine in 33 patients, valproic acid in 6, phenobarbital in 2, phenytoin in 1, and zonisamide in 1; the drugs were unidentified in 42 patients. When comparing patients treated with carbamazepine and those treated with valproic acid, there was no significant difference in the age at the onset, age at the last seizure, or total number of seizures.

PKD was observed in 39 patients with *PRRT2* mutations. The median age at the onset of PKD was 9 (range 2–16) years in the 34 patients for whom information was obtained. No patients with *PRRT2* mutations had CwG, whereas 11 had a history of febrile seizures. Migraine was reported in three patients, one of whom had hemiplegic migraine associated with the c.649dupC mutation. Intellectual disorders were seen in three patients.

4. Discussion

We recruited patients with BIE and/or PKD from throughout Japan and analyzed the presence or absence of *PRRT2* mutations to examine the phenotypes of Japanese patients with *PRRT2* mutations. *PRRT2* mutations were frequently identified in familial cases, whereas *PRRT2* mutations were less frequent in sporadic patients with BIE. Although a novel *PRRT2* mutation was found in our cohort, types of *PRRT2* mutations and phenotypes of patients were comparable to those in previous reports. One patient with homozygous missense mutation had a typical phenotype of BIE and PKD.

The epilepsy phenotypes in the patients with *PRRT2* mutations in this study were similar to those reported in patients with clinically defined BIE. Our previous study of clinically diagnosed BIE based on long-term follow up found that the median age at the first and last seizures were 5 and 8 months, respectively; the median number of seizures was seven; and a cluster of seizures was observed in 79% of the patients [24,25]. These findings are similar to those of the present study. Although the rate of PKD was higher in the present study, this was related to the fact that the present study included more families with BIE and/or PKD. There have been several reports on the phenotypes of cases with *PRRT2* mutations. The age at onset of BIE averaged 4.9 months in our study and 6.0 months in the review by Ebrahimi-Fakhari et al. [26]. These results suggest that the phenotypes of BIE associated with *PRRT2* mutations do not differ among races.

In a review of 1444 cases, Ebrahimi-Fakhari et al. reported approximately 70 different mutations, and the *PRRT2* mutations identified here were similar to those they described [26]. In our study, 83% of the probands with *PRRT2* mutations had the c.649dupC mutation compared with 81% in the review. In this study, the c.981C > G mutation was the next most frequent mutation. The c.981C > G mutation was uncommon in previous reports and has been limited in Japan and China [27,28]. This suggests that the pattern of *PRRT2* mutations differs among races, and the c.981C > G mutation may be unique to East Asia. The c.981C > G mutation is located in the transmembrane region of the PRRT2 protein. The prediction made by the Combined Annotation Dependent Depletion Tool [29] gave a score of 24.30 (> 15 indicates a potentially pathological mutation), implying that the c.981C > G mutation is deleterious.

Several authors have reported that homozygous mutations and compound heterozygous mutations can result in severe neurological symptoms other than BIE or PKD [13,27,30]. Patients with *PRRT2* mutations in both alleles often have intellectual disorders, hyperactivity, absence seizures, migraine, paroxysmal non-kinesigenic dyskinesia, and periodic ataxia. Most of these patients had homozygous c.649dupC mutations, implying that the PRRT2 protein is lost completely. Logically, such patients would have severe phenotypes. In this study, one patient had a homozygous c.981C > G mutation. Contrary to previous reports, our patient with the homozygous c.981C > G mutation had the common BIE and PKD phenotype. The c.981C > G mutation is a missense mutation causing the amino acid change Ile327Met. The differences in the phenotypes may be explained by the

types of *PRRT2* mutations. Homozygous c.649dupC mutations imply complete loss of the PRRT2 protein, whereas homozygous c.981C > G mutations may lead to modified PRRT2 protein and not to its absence. Delcourt et al. reported 5 patients with biallelic *PRRT2* mutations [13]. Phenotype of a patient with homozygous missense c.913 G > A mutations was milder that the other four patients with homozygous nonsense c.649dupC mutations. Liu et al. also reported a patient with compound heterozygous mutation of c.510dupT and c.647C > G [31]. This patient had the common BIE and PKD phenotype. Although the father and mother of this patient were asymptomatic, each had c.510dupT and c.647C > G mutation, respectively, suggesting a pattern of autosomal recessive inheritance. Data on more patients are necessary to clarify the phenotype of patients with *PRRT2* mutations in both alleles.

The rate of febrile seizures in patients with *PRRT2* mutations was 11% in this study, which is higher than that in the Japanese population (around 5%) [32]. Several authors have also reported an association between febrile seizures and *PRRT2* mutations [18,33–35]. These facts suggest that *PRRT2* mutations increase susceptibility to febrile seizures. On the other hand, Djémié et al. detected no *PRRT2* mutations in patients with febrile seizures and stated that *PRRT2* mutations do not seem to be involved in the etiology of febrile seizures [15]. Further studies are necessary to clarify the relationship between *PRRT2* mutations and febrile seizures.

No CwG was observed in any patient with *PRRT2* mutations. This result was quite different from that in clinically defined BIE [24]. BIE and CwG are similar in the age at the onset, tendency toward seizure clusters, and efficacy of carbamazepine [23]. In our previous study of patients with clinically diagnosed BIE, 3 of 33 patients subsequently developed CwG [24]. Espeche and Caraballo reported two patients with BIE: one had CwG followed by BIE, and the other had BIE followed by CwG related to anti-rotavirus vaccine [36]. However, there have been no reports of *PRRT2* mutations in patients with CwG [9,33]. Therefore, BIE and CwG are presumed to be genetically different.

The strength of this study is the large number of patients from all over Japan. The results of this study will provide useful basic information for genetic counseling regarding clinical symptoms, time course, and prognosis. The rarity of severe phenotypes in epilepsy due to *PRRT2* mutations will help to alleviate the anxiety of patients and caregivers. However, BIE and PKD due to *PRRT2* mutations show autosomal dominant inheritance. Therefore, it is also important to discuss the possibility of inheritance. Additionally, there are several limitations to this study. First, the follow-up period was insufficient in some patients. A majority of patients were infants and young children, although the data of age at the evaluation were insufficient. As it is not uncommon for PKD to develop after childhood, PKD might appear later in the lives of patients currently classified as BIE alone. Sufficient clinical information was not always obtained because the clinical information was collected retrospectively. Especially in adults, it was difficult to obtain accurate information from infancy through childhood. Moreover, it is difficult to obtain precise information on intellectual disorders. Therefore, mild intellectual disorders may have been overlooked. We only performed direct sequencing of a single gene as genetic analysis. Thus, the patients with *PRRT2* copy number variants or 16p11.2 deletion were not included in this study.

5. Conclusion

PRRT2 mutations were found in 68% of Japanese probands with BIE or PKD. The BIE phenotypes associated with the *PRRT2* mutations were consistent with those of clinically diagnosed BIE. In our cohort, c.981C > G was more frequent than that in previous reports, suggesting possible racial differences. The results of this study will be useful when counseling patients with *PRRT2* mutations on phenotype and prognosis.

Declaration of interest

None.

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