Paroxysmal hypnogenic dyskinesia is associated with mutations in the *PRRT2* gene

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ABSTRACT

Objective: To explore the potential causative genes of paroxysmal hypnogenic dyskinesia (PHD), which was initially considered a subtype of paroxysmal dyskinesia and has been recently considered a form of nocturnal frontal lobe epilepsy (NFLE).

Methods: Eleven patients with PHD were recruited. Mutations in proline-rich region transmembrane protein-2 (*PRRT2*), myofibrillogenesis regulator 1 (*MR-1*), solute carrier family 2, member 1 (*SLC2A1*), calcium-activated potassium channel alpha subunit (*KCNMA1*), cholinergic receptor, nicotinic, alpha 4 (*CHRNA4*), cholinergic receptor, nicotinic, beta 2 (*CHRNB2*), cholinergic receptor, nicotinic, alpha 2 (*CHRNA2*), and potassium channel subfamily T member 1 (*KCNT1*) were screened by direct sequencing.

Results: Two *PRRT2* mutations were identified in patients with typical PHD. A mutation of c.649dupC (p.Arg217ProfsX8) was identified in a patient with PHD and his father who was diagnosed with paroxysmal kinesigenic dyskinesia. An additional mutation of c.640G>C (p.Ala214Pro) was identified in a sporadic patient and his asymptomatic mother. No mutations were found in the other screened genes.

Conclusions: The present study identified *PRRT2* mutations in PHD, extending the phenotypic spectrum of *PRRT2* and supporting the classification of PHD as a subtype of paroxysmal dyskinesia but not NFLE. Based on the results of this study, screening for the *PRRT2* mutation is recommended in patients with PHD. ***Neurol Genet* 2016;2:e66; doi: 10.1212/NXG.0000000000000066**

GLOSSARY

ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; **CBZ** = carbamazepine; ***CHRNA2*** = cholinergic receptor, nicotinic, alpha 2; ***CHRNA4*** = cholinergic receptor, nicotinic, alpha 4; ***CHRNB2*** = cholinergic receptor, nicotinic, beta 2; **GTCS** = generalized tonic-clonic seizures; **NREM** = non-REM sleep; **OXC** = oxcarbazepine; **PD** = paroxysmal dyskinesia; **PED** = paroxysmal exercise-induced dyskinesia; **PHD** = paroxysmal hypnogenic dyskinesia; **PKD** = paroxysmal kinesigenic dyskinesia; **PNKD** = paroxysmal nonkinesigenic dyskinesia; ***PRRT2*** = proline-rich region transmembrane protein-2; ***SLC2A1*** = solute carrier family 2, member 1; **VPA** = valproate.

Paroxysmal hypnogenic dyskinesia (PHD) is characterized by paroxysmal involuntary dystonic, choreoathetoid, and ballistic attacks during sleep without triggers.[1–3] PHD was initially considered a subtype of paroxysmal dyskinesia (PD), which also includes paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED). However, PHD is distinguished from the other subtypes of PD by the characteristic of nocturnal attacks without triggers. To date, proline-rich region transmembrane protein-2 (*PRRT2*) has been proven to be a common causative gene for the 3 subtypes of PD.[4,5] Mutations in solute carrier family 2, member 1 (*SLC2A1*), myofibrillogenesis regulator 1 (*MR-1*), and calcium-activated potassium

Supplemental data at Neurology.org/ng

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channel alpha subunit (*KCNMA1*) have been proven to cause PED and PNKD.[6,7] However, the genetic causes of PHD remain unknown.

From another perspective, the high frequency and short duration of nocturnal attacks of PHD make it challenging to differentiate from epileptic seizures.[8] Ictal alterations of diffuse irregular sharp waves or slowing with anterior predominance on EEG have been recorded in some patients with PHD.[9] Therefore, PHD is speculated to be a form of nocturnal frontal lobe epilepsy.[10] Mutations in *CHRNA4* (cholinergic receptor, nicotinic, alpha 4), *CHRNB2* (cholinergic receptor, nicotinic, beta 2), *CHRNA2* (cholinergic receptor, nicotinic, alpha 2),[11–14] and *KCNT1* (potassium channel subfamily T member 1)[15,16] have been identified in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In the present study, we screened 11 patients with PHD for mutations in *PRRT2*, *MR-1*, *SLC2A1*, *KCNMA1*, *CHRNA4*, *CHRNB2*, *CHRNA2*, and *KCNT1*. Two *PRRT2* mutations were identified, suggesting that PHD is potentially a subtype of PD.

METHODS

Participants. Eleven patients with PHD were recruited from a cohort of 108 patients with PD who were diagnosed and followed for more than 2 years in the Second Affiliated Hospital of Guangzhou Medical University. The collected clinical data included semiology and evolution of the disorder, family history, and results of general and neurologic examinations. Brain MRI was performed to exclude symptomatic PD. Video-EEG monitoring that included hyperventilation, intermittent photic stimulation, and sleep recordings was obtained. All EEGs were reviewed by 2 qualified electroencephalographers. Any disagreements about EEGs were resolved through discussion or consulting a third electroencephalographer when necessary.

PHD was diagnosed according to Lugaresi and Demirkiran's descriptions.[1,3,8] Diagnoses were classified as typical PHD and atypical PHD. A diagnosis of typical PHD was made if a patient presented with paroxysmal dyskinetic movements (including choreoathetosis, ballistic, and dystonia) predominantly while sleeping and if the duration of the attack was shorter than 1 minute. Atypical PHD was characterized by 1 of the following features: the duration of attacks was longer than 1 minute, attacks occurring at wakefulness were more frequent than or at the same frequency as those during sleep, and any generalized tonic-clonic seizures (GTCS) after dyskinesia. Exclusion criteria were as follows: (1) presence of focal neurologic deficits; (2) abnormal brain imaging; (3) dyskinetic attacks secondary to a clear etiology or lesion, such as brain tumor, cerebrovascular disease, metabolic disturbances, and endocrine disorders; and (4) clinical and EEG manifestations of frontal lobe epilepsy, such as asymmetric extremities tonic movement, paroxysmal fear, loss of consciousness, and ictal or interictal epileptic discharges in the frontal lobe region.

Molecular analysis. Blood samples were obtained from the probands, their parents, and other family members when available. Genomic DNA was extracted from peripheral blood using a QuickGene DNA whole-blood kit L (Fujifilm, Tokyo, Japan). Mutations in *PRRT2* were screened using the methods described in our previous study.[5] Mutations of *SLC2A1*, *MR-1*, *KCNMA1*, *CHRNA4*, *CHRNB2*, *CHRNA2*, and *KCNT1* genes were screened by PCR and direct Sanger sequencing on an ABI3730 XL sequencer (Applied Biosystems, Foster City, CA) using the primers designed according to the sequences available through GenBank (table e-1 at Neurology.org/ng). Parental DNA was used to determine the origin of the mutation. Six hundred healthy volunteers were recruited as controls.

Standard protocol approvals, registrations, and patient consents. The ethics committee of the hospital approved the study protocol, and written informed consent was obtained from the participants or their guardians.

RESULTS

Genetic findings. Of the 11 patients with PHD, 5 were diagnosed as typical PHD and 6 as atypical PHD (table 1). Two *PRRT2* mutations were identified in 2 patients with typical PHD. An insert mutation, c.649dupC (p.Arg217ProfsX8), was identified in patient 1 and his father with PKD (figure 1A). This was a hot-spot mutation of *PRRT2* resulting in a stop codon and has previously been identified in the other 3 subtypes of PD.[17–22] Another mutation, c.640G>C (p.Ala214Pro), was detected in patient 2 and his asymptomatic mother (figure 1B). This mutation was a missense mutation and has previously been reported in patients with PKD.[23,24]The mutation was predicted to be "probably damaging" by PolyPhen (score = 0.999) and "deleterious" by SIFT (score = 0). The 2 mutations were not found in 600 normal controls. The amino acid sequence alignment of the *PRRT2* family showed that A214 and R217 were highly conserved from various species (figure 1C). No mutations in the coding exons of *MR-1*, *SLC2A1*, *KCNMA1*, *CHRNA4*, *CHRNB2*, *CHRNA2*, or *KCNT1* were identified in any of the 11 patients with PHD.

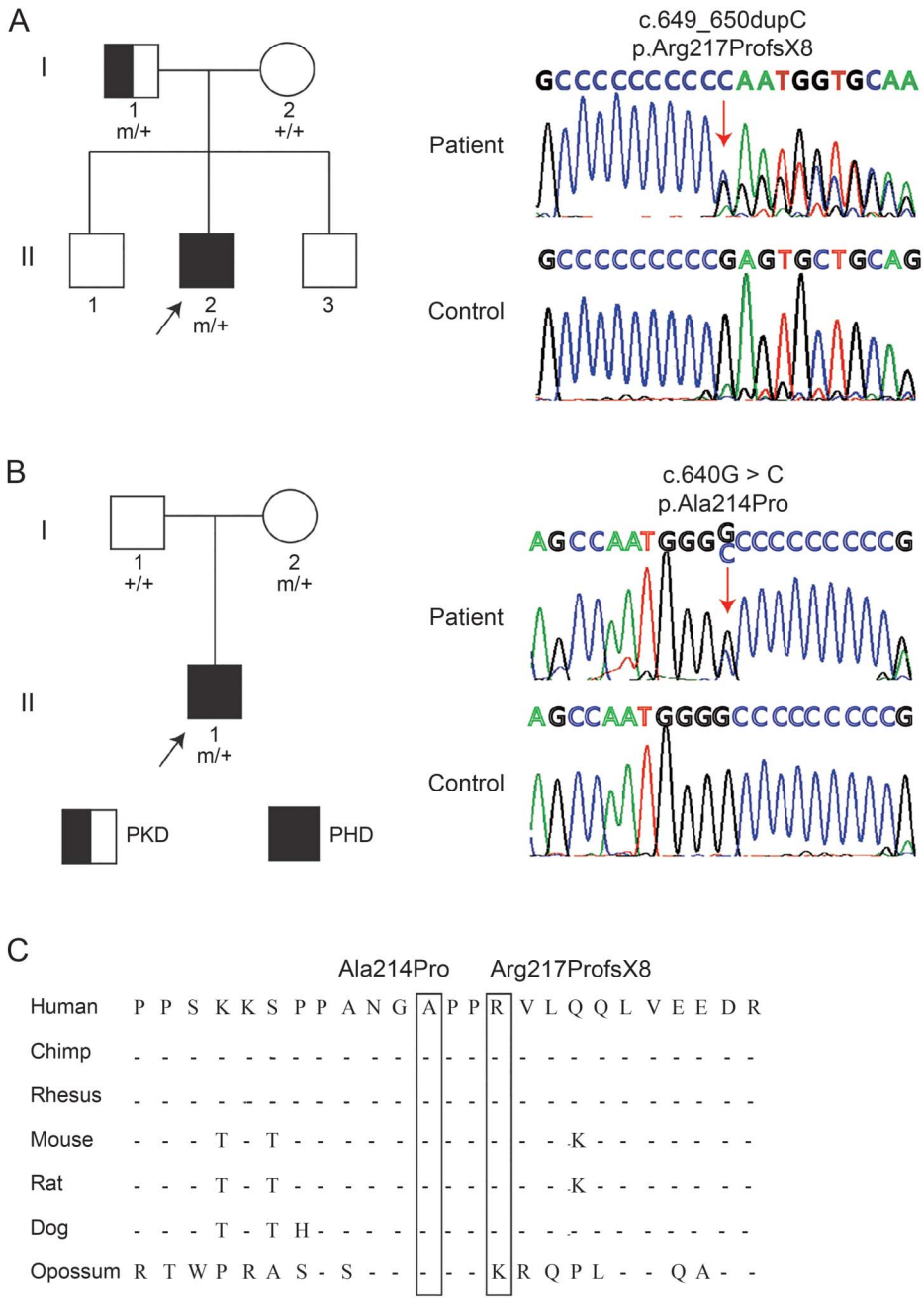
Clinical presentation of the patients with *PRRT2* mutations. Patient 1 was a 24-year-old man who presented with episodic dyskinesia since the first year of life. He experienced ballistic or choreoathetoid attacks while sleeping. The attacks lasted 10–60 seconds and were usually exacerbated by sleep deprivation. The patient was aware during the attacks. The frequency was 5 to 8 times per year and then increased to daily after the age of 13. He had 4 GTCS during wakefulness without any triggers after the age of 15. His father had PKD attacks

Table 1 Clinical characteristics of the patients with PHD

Patient	Sex	Age at onset	Present age	Frequency of dyskinesia	Epileptic seizure	Family history	Triggers	Clinical features	EEG		Drug therapy		Outcome	Gene mutations
									Interictal	Ictal	Effective	Ineffective		
Typical PHD														
1	M	10 mo	20 y	3-4 attacks per day	4 GTCS	PKD (father)	SD	Chorea, ballism	Bifrontal slowing	Generalized slowing	CBZ	VPA	Improved	c.649dupC
2	M	2 y	18 y	3-8 attacks per day	3 GTCS	No	SD, alcohol, fatigue	Chorea	Generalized and focal SW	Normal	CBZ, PHT, OXC, LTG	VPA	Attack free	c.640G>C
3	F	2 mo	25 y	2-3 attacks per day	No	Epilepsy (uncle)	SD	Chorea	Normal	Normal	CBZ	LTG, PHT, VPA	Improved	–
4	M	3 y	7 y	7-8 attacks per day	No	PKD (father)	SD	Chorea	Normal	Normal	OXC, PHT, CBZ	VPA, LTG	Improved	–
5	M	1 y, 9 mo	7 y	4-5 attacks per day	No	No	SD	Chorea, dystonia	R temporal SW	Normal	LTG, CBZ	VPA	Improved	–
Atypical PHD														
6	M	1 y, 4 mo	11 y	5-6 attacks per month	3 GTCS	No	No	Chorea	Normal	Normal	CBZ, LTG	VPA	Improved	–
7	M	31 y	32 y	2-3 attacks per month	No	No	SD, starvation	Dystonia	Normal	NA	NA	NA	Improved	–
8	M	2 y	6 y, 4 mo	7-8 attacks per day	No	No	SD, stress	Chorea	Normal	Normal	NA	OXC	Improved	–
9	M	17 y	29 y	20-30 attacks per month	No	No	No	Chorea	R frontal slowing	NA	OXC	NA	Attack free	–
10	M	5 y	13 y	2 attacks per month	No	Epilepsy (brother)	SD	Chorea	R central SW	NA	CBZ	NA	Attack free	–
11	F	12 y	14 y	2 attacks per month	1 GTCS	No	No	Chorea	Normal	Normal	OXC	NA	Attack free	–

Abbreviations: CBZ = carbamazepine; GTCS = generalized tonic-clonic seizures; LTG = lamotrigine; NA = not available; OXC = oxcarbazepine; PHD = paroxysmal hypnogenic dyskinesia; PHT = phenytoin; PKD = paroxysmal kinesigenic dyskinesia; SD = sleep deprivation; SW = spike and slow waves; VPA = valproate.

Figure 1 Genetic data on the patients with paroxysmal hypnogenic dyskinesia (PHD) with gene mutations in *PRRT2*



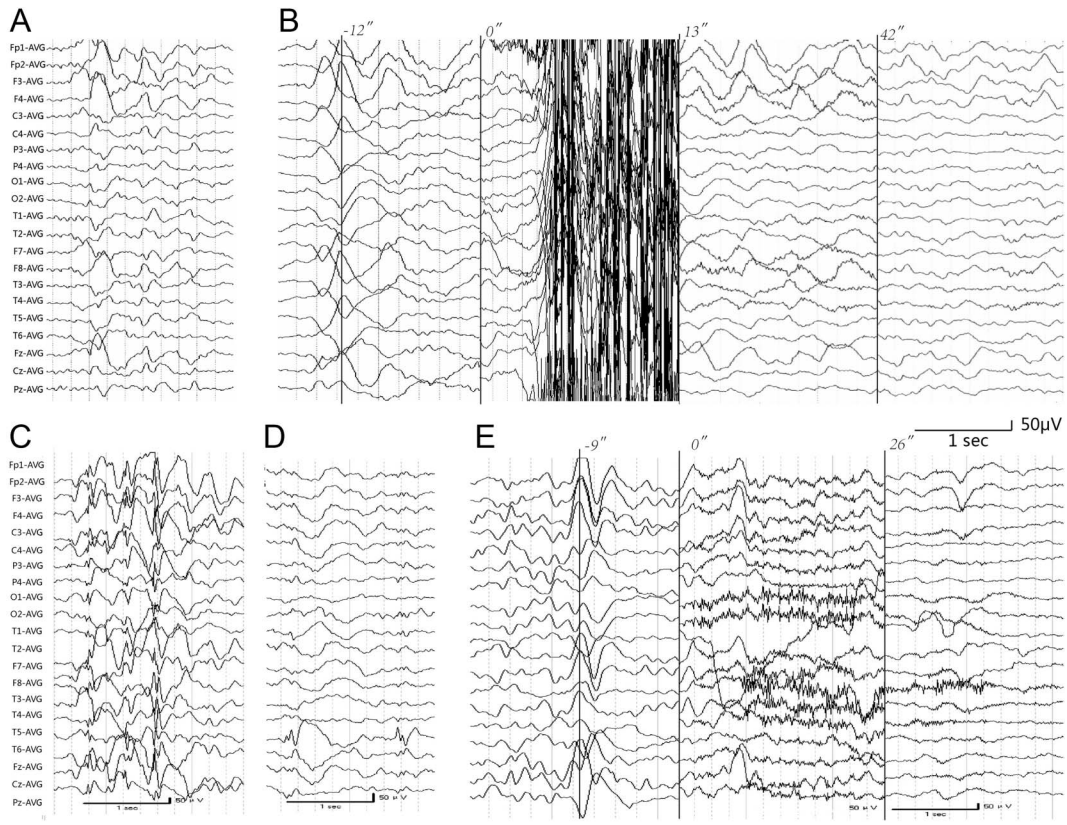
(A) The pedigree (left) and *PRRT2* sequence (right) of the patient with mutation of c.649dupC (patient 1). The patient carried the heterozygous mutation of the *PRRT2* gene c.649dupC (p.Arg217ProfsX8), inherited from his father with paroxysmal kinesigenic dyskinesia (PKD). (B) The pedigree (left) and *PRRT2* sequence (right) of the patient with mutation c.640G>C (patient 2). The patient carried the heterozygous mutation of the *PRRT2* gene c.640G>C (p.Ala214Pro), inherited from his asymptomatic mother. (C) The amino acid sequence alignment of the PRRT2 family showed the evolutionary conservation of the residues. Ala214 and Arg217 were highly conserved in various species.

since the age of 12, and the attacks remitted spontaneously at the age of 41.

EEG monitoring performed at the age of 20 showed interictal intermittent high-voltage delta slow waves in the bifrontal region (figure 2A). An attack was recorded during non-REM sleep (NREM) stage II, which manifested as sudden stiffening and massive jerk movements of extremities lasting for 12 seconds. Then the patient fell asleep again (video 1). The ictal EEG showed muscle artifacts in all channels and then postictal high-voltage slow waves, dominant in the bifrontal lobe, lasting until the 180th second and followed by NREM-IV (figure 2B).

The patient did not respond to valproate (VPA, 15 mg/kg/d). Carbamazepine (CBZ, 12 mg/kg/d) decreased

Figure 2 EEG changes in the patients with paroxysmal hypnogenic dyskinesia with *PRRT2* mutations



(A) Interictal EEG of patient 1 obtained at the age of 20 years showed irregular delta activities in the bifrontal lobe, more dominant in the right frontal lobe. (B) Ictal EEG of patient 1. The attack started with rhythmic convulsions during non-REM sleep (NREM) stage II accompanied by muscle artifacts on EEG recording. It lasted 12 seconds, followed by slow waves in the bifrontal lobe, and returned to the sleeping background (NREM-IV) 1 minute later. (C) Interictal EEG of patient 2 obtained at the age of 10 years showed irregular generalized spikes and slow waves and (D) focal spike and waves in the right posterior temporal lobe. (E) Ictal recording of patient 2 showed that the patient awakened suddenly from NREM-II and presented irregular bilateral arm and leg choreoathetoid movements, accompanied by movement artifacts and generalized low- and medium-voltage theta slowing. The movements lasted 26 seconds, and the slowing continued for 1 minute.

the frequency of attacks from 5 to 8 times per day to 1 to 2 times per month.

Patient 2 was an 18-year-old man who presented with choreoathetoid movements during sleep since the age of 2. He experienced uncontrollable extremities and a bizarre sequence of movements with awareness at a frequency of 1 to 12 times per night. The attacks occurred predominantly during sleep but occasionally during wakefulness with precipitating factors, including fatigue, stress, sleep deprivation, and alcohol. He had 3 GTCS during daytime between ages 6 and 8.

His mother carried the same mutation and did not present any dyskinetic symptoms. There was no family history of paroxysmal disorders in his family.

Video-EEG monitoring at age 9 showed irregular generalized spikes, slow waves (figure 2C), and focal spike slow waves in the right posterior temporal lobe interictally (figure 2D). One episode was recorded, which was a sudden wake up accompanied by choreoathetoid movement of the extremities and lasted for 26 seconds (video 2). He maintained consciousness during the event. The ictal EEG showed an arousal from NREM-II sleep followed by movement artifacts and generalized slowing that lasted about 1 minute (figure 2E).

The patient did not respond to VPA (30 mg/kg/d). CBZ, phenytoin, or oxcarbazepine (OXC) monotherapy markedly reduced the attacks from more than 10 times per night to 2 to 3 times per night. At the age of 17, the attacks were controlled by a combination of lamotrigine (2.5 mg/kg/d) and OXC (20 mg/kg/d).

Comparison of clinical features of typical and atypical PHD. Because *PRRT2* mutations were detected in typical cases but not in atypical cases, we analyzed their clinical difference to isolate the potential clinical biomarkers for *PRRT2* mutations. The demographic and clinical features of the cases are summarized in table 1. As defined in the diagnosis criteria, attacks in typical cases have a shorter duration and are

predominantly nocturnal. Typical cases tend to have an earlier onset (1.55 ± 4.88 years, ranging from 2 months to 3 years in typical cases vs 11.4 ± 4.64 years, ranging from 1 year 4 months to 31 years in atypical cases) and more frequent family history of PKD (2/5 vs 0/6 in typical and atypical cases, respectively), but no statistical significances were detected. There was no significant difference between typical and atypical cases with regard to trigger factors, concurrency of GTCS, EEG abnormalities, or family history of epilepsy.

Regarding the response to antiepileptic drug therapy, patients with PHD generally had good responses to antiepileptic drugs with the action of sodium channel blocking, especially CBZ. Typical cases tended to have lower attack-free rates with monotherapy than atypical cases (0/5 vs 3/5, respectively), and 1 typical case achieved remission with a combination of OXC and lamotrigine. VPA was applied in 6 cases and was ineffective in all of them.

DISCUSSION PHD is a paroxysmal disorder with unknown etiology. In the present study, *PRRT2* mutations were identified in patients with PHD, which established an association between the *PRRT2* gene and PHD and expanded the phenotypic spectrum of *PRRT2* mutations. This study also highlights that PHD is a genetic disorder similar to other types of PD such as PKD, PNKD, and PED.

PRRT2 is a presynaptic protein that potentially plays an important role in exocytosis and neurotransmitter release.[25] Mutations in the *PRRT2* gene have recently been proven to be a major cause of PD. In the present study, an insert mutation c.649dupC and a missense mutation c.640G>C (p.Ala214Pro) were identified in the patients with PHD. The mutation c.649dupC causes frameshift and a premature stop codon (p.Arg217ProfsX8) and leads to loss of function and haploinsufficiency. This mutation is a hotspot mutation and is responsible for 57% of the cases with different phenotypes.[20] The missense mutation p.Ala214Pro changed a highly conserved amino acid residue and potentially damages the protein (score = 0 by SIFT and score = 0.999 by PolyPhen). It was also previously reported in PKD cases,[23,24]supporting its possible role in pathogenesis. A recent study has shown that truncated or missense mutation could affect glutamate signaling and glutamate receptor activity through their weakened interaction with SNAP25, resulting in increased glutamate release and subsequent neuronal hyperexcitability.[26] However, the mutations c.649dupC and c.640G>C are present at frequencies of 0.004626 and 0.004827, respectively, in East Asians (ExAC database), raising suspicion about their pathogenicity. It is noted that p.Ala214Pro was detected in the asymptomatic mother of the patient with PHD. In our previous study, incomplete penetrance was observed in 26.5% of PD individuals with *PRRT2* mutations, including those with truncated mutations, and even led to recessive inheritance.[5] Incomplete penetrance was reported to be 18% in families with benign familial infantile convulsion.[27] Our recent study on *SCN1A* has demonstrated that lower penetrance was associated with fewer pathogenic mutations.[28]It is therefore possible that *PRRT2* mutations were relatively less pathogenic, explaining their frequencies in the general population.

In the present study, c.649dupC was identified in the patient with PHD and his father with PKD. The mutation c.649dupC was previously detected in patients with PKD, PED, PNKD, and other paroxysmal disorders.[17–22] Similarly, the missense mutation p.Ala214Pro was also identified in patients with PKD previously.[23,24] The striking pleiotropic phenotypic expression of the *PRRT2* mutation indicates that the *PRRT2* genotype likely does not predict clinical phenotype. The underlying mechanism of phenotype variations should be examined in ways other than genotype of *PRRT2*. Clinically, PHD shares similar clinical characteristics with other subtypes of PD, especially PKD, such as dyskinetic symptoms, short duration of attacks, and good response to sodium channel blockers. The present study suggests that PHD may have a similar genetic etiology to the other types of PD. However, each of the PD subtypes differs with regard to precipitating factors. Sudden movement is the most common trigger observed in PKD, and prolonged exercise usually induces attacks in patients with PED. Our previous study demonstrated that 4 of the 9 children with infantile convulsions and paroxysmal choreoathetosis had attacks during feeding,[5] suggesting that suction is a possible kinesigenic trigger in infants. In the present study, the majority of dyskinetic attacks occurred during NREM, suggesting that NREM is potentially a trigger for PHD symptoms. Future studies should focus on detecting internal and external precipitating factors in patients with PD and identifying the relationship between triggers and attacks.

The nocturnal and movement features of PHD and ADNFLE attacks are similar and difficult to differentiate. The present study identified mutations in *PRRT2* but not in ADNFLE-associated genes in patients with PHD. This suggests that PHD is potentially PD but not ADNFLE by nature. It should also be considered that the clinical characteristics presented in the patients with PHD in the present study, such as dyskinetic attacks not followed by GTCS, no discharges in the frontal region, attacks during NREM-II to NREM-IV, and a lack of ictal epileptic patterns in EEG, may be helpful in distinguishing PHD from ADNFLE. In

contrast, the seizures in ADNFLE may occur at any stage of sleep, and there is evidence of localized discharges in the frontal region.

The 2 patients with *PRRT2* mutations also exhibited occasional GTCS, suggesting a susceptibility to seizures. Previously, occasional, mild, and benign epileptic seizures were observed in patients with PD with *PRRT2* mutations, such as benign family infant convulsions, febrile seizures, absence seizures, and occasional GTCS.[5,22,25,27,29,30] Taken together, this suggests that *PRRT2* mutations are potentially associated with an increased neuronal excitability and susceptibility to seizures as opposed to a distinct type of epilepsy, such as ADNFLE.

In a previous study, *PRRT2* mutations were commonly clustered in the patients with epilepsy with onset in the first year of life.[31] In the present study, *PRRT2* mutations were identified in the 2 patients with PHD with relatively earlier age at onset (age of 10 months and 1 year). Therefore, patients with earlier onset may be an important clue to address *PRRT2* gene testing.

Although *PRRT2* mutations were identified in the patients with PHD in this study, it is not clear whether PHD is PD or epilepsy. The etiology for the patients without *PRRT2* mutation is still unknown. Recently, more causative genes associated with epilepsy and PD were identified, such as *DEPDC5* mutations in familial cases with the symptoms of ADNFLE.[32,33] Further and wider genetic screening/testing should be performed in patients with PHD without *PRRT2* mutation to find potential causative genes.

AUTHOR CONTRIBUTIONS

Dr. Xiao-Rong Liu: design and conceptualization of the study, analysis and interpretation of data, drafting the manuscript. Dr. Dan Huang: analysis and interpretation of data. Dr. Jie Wang: analysis and interpretation of data. Dr. Hui Sun: analysis and interpretation of data. Dr. Yi-Fan Wang: analysis and interpretation of data. Dr. Bin Tang: analysis and interpretation of data. Dr. Wen Li: analysis and interpretation of data. Dr. Jin-Xing Lai: analysis and interpretation of data. Dr. Na He: analysis and interpretation of data, drafting the manuscript. Dr. Mei Wu: analysis and interpretation of data. Dr. Tao Su: analysis and interpretation of data, revising the manuscript. Dr. Heng Meng: analysis and interpretation of data. Dr. Yi-Wu Shi: analysis and interpretation of data. Dr. Bing-Mei Li: analysis and interpretation of data, revising the manuscript. Dr. Bei-Sha Tang: analysis and interpretation of data. Dr. Wei-Ping Liao: design and conceptualization of the study, analysis and interpretation of data, drafting the manuscript.

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DISCLOSURE

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