Published Ahead of Print on October 7, 2015 as 10.1212/WNL.0000000000002079

Paroxysmal kinesigenic dyskinesia

Clinical and genetic analyses of 110 patients

Xiao-Jun Huang, MD*
Tian Wang, MM*
Jun-Ling Wang, MD, PhD*
Xiao-Li Liu, MM
Xiang-Qian Che, MD
Jin Li, MM
Xiao Mao, MD
Mei Zhang, MB
Guang-Hui Bi, MD
Li Wu, MD, PhD
Yu Zhang, MD, PhD
Jing-Yi Wang, MM
Jun-Yi Shen, MM
Bei-Sha Tang, MD, PhD
Li Cao, MD, PhD
Sheng-Di Chen, MD, PhD

Correspondence to Dr. Chen: chen_sd@medmail.com.cn or Dr. Cao: caoli2000@yeah.net or Dr. Tang: bstang7398@163.com

ABSTRACT

Objective: We aimed to investigate the clinical and genetic features of paroxysmal kinesigenic dyskinesia (PKD) in a large population and to analyze the genotype–phenotype correlation of PKD.

Methods: We analyzed clinical manifestations and conducted *PRRT2* screening in 110 patients with PKD. Clinical data were compared between 91 probands with and without *PRRT2* mutations.

Results: Among the enrolled participants (45 from 26 families, 65 sporadic cases), 8 *PRRT2* mutations were detected in 20 PKD families (76.9%) and 14 sporadic cases (21.5%), accounting for 37.4% (34/91) of the study population. Five mutations (c.649dupC, c.649delC, c.487C>T, c.573dupT, c.796C>T) were already reported, while 3 mutations (c.787C>T, c.797G>A, c.931C>T) were undocumented. A patient harboring a homozygous c.931C>T mutation was shown to have inherited the mutation via uniparental disomy. Compared with non-*PRRT2* mutation carriers, the *PRRT2* mutation carriers were younger at onset, experienced longer attacks, and tended to present with complicated PKD, combined phenotypes of dystonia and chorea, and a positive family history. A good response was shown in 98.4% of the patients prescribed with carbamazepine.

Conclusions: *PRRT2* mutations are common in patients with PKD and are significantly associated with an earlier age at onset, longer duration of attacks, a complicated form of PKD, combined phenotypes of dystonia and chorea, and a tendency for a family history of PKD. A patient with uniparental disomy resulting in a homozygous c.931C>T mutation is identified in the present study. Carbamazepine is the first-choice drug for patients with PKD, but an individualized treatment regimen should be developed. ***Neurology*® 2015;85:1–8**

GLOSSARY

BFIS = benign familial infantile seizures; **EKD** = episodic kinesigenic dyskinesia; **PKD** = paroxysmal kinesigenic dyskinesia; **PxD** = paroxysmal dyskinesia; **SNP** = single-nucleotide polymorphism; **UPD** = uniparental disomy.

Paroxysmal kinesigenic dyskinesia (PKD) (MIM 128200) is a rare movement disorder characterized by transient and recurrent dystonic or choreoathetoid attacks triggered by sudden voluntary movements.[1] Three EKD (episodic kinesigenic dyskinesia) loci have been identified in PKD and are defined as EKD1 (16p11.2-q12.1), EKD2 (16q13-q22.1), and EKD3.[2] In 2011, genome-wide linkage analyses confirmed *PRRT2* (proline-rich transmembrane protein 2) as the causative gene of PKD, which clarified the EKD1 loci.[2–4] Thus far, 71 *PRRT2* mutations have been reported,[5–7] accounting for approximately 61.5% to 100% of patients with familial PKD and 12.5% to 50% of sporadic PKD cases.[5,8,9] Of note, *PRRT2* gene mutations have also been identified in other paroxysmal disorders such as benign familial infantile seizures (BFIS), paroxysmal nonkinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, hemiplegic migraine, paroxysmal torticollis, episodic ataxia, childhood absence epilepsy, and febrile seizures.[10–17] Such disorders are collectively referred to by the label *PRRT2*-related paroxysmal disorders.[18] Considering the remarkable pleiotropy of the *PRRT2* gene with the still-expanding

Supplemental data at Neurology.org

*These authors contributed equally to this work.

From the Department of Neurology and Institute of Neurology (X.-J.H., T.W., X.-L.L., L.W., Y.Z., J.-Y.W., J.-Y.S., L.C., S.-D.C.), Rui Jin Hospital & Rui Jin Hospital North, Shanghai Jiao Tong University School of Medicine; Department of Neurology (J.-L.W., X.-Q.C., J.L., X.M., B.-S.T.), Xiangya Hospital, Central South University, Changsha, Hunan Province; Department of Neurology (M.Z.), Huainan First People's Hospital affiliated to Bengbu Medical College, Huainan, Anhui Province; and Department of Neurology (G.-H.B.), Dongying People's Hospital, Dongying, Shandong Province, China.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

clinical spectrum and the limited researches into the genotype–phenotype analysis of PKD,[19–22] we analyzed the clinical manifestations and genetic features of our patients with PKD and conducted the genotype–phenotype correlation analysis.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study was approved by the ethics committee of Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, and all participants or their guardians provided written informed consents. Signed patient consent-to-disclose forms were obtained from the 2 patients who provided videos of their attack.

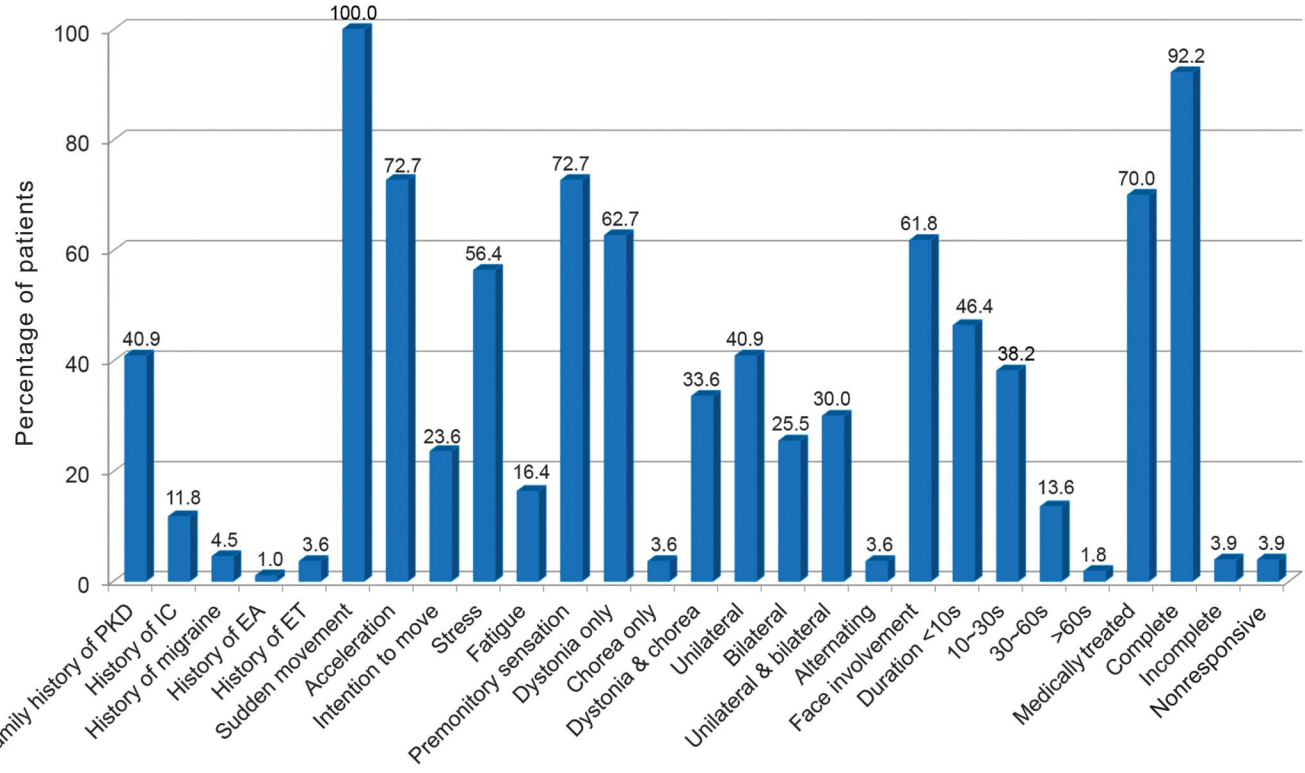
Clinical and genetic analyses. One hundred ten patients diagnosed with PKD during 2008 to 2014 were recruited after being evaluated by 2 or more movement disorder specialists. The diagnosis of PKD was determined according to Bruno's criteria.[1] In addition, 200 genetically unrelated individuals were enrolled as healthy controls.

Genomic DNA was isolated from the peripheral blood by using a standard phenol/chloroform extraction protocol. Sanger sequencing was performed to identify *PRRT2* (NM_145239) mutations (table e-1 on the *Neurology*® Web site at Neurology.org). Considering the remarkable overlap in clinical and genetic underpinnings of paroxysmal dyskinesias (PxDs),[23,24] the participants who did not reveal *PRRT2* mutation were subjected to *MR-1* (NM_015488), *SLC2A1* (NM_006516), or *CHRNA4* (NM_000744) and *CHRNB2* (NM_000748) gene screening, which was responsible for paroxysmal nonkinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, and paroxysmal hypnogenic dyskinesia, respectively. SIFT software (http://sift.jcvi.org/) was applied to predict the function of novel missense mutations. Single-nucleotide polymorphism (SNP) array analysis was conducted in one patient (PA0234) and her parents.

Genotype–phenotype analysis was performed on 91 probands with and without *PRRT2* gene mutations. The differences between the 2 groups were evaluated by means of the unpaired Student *t* test in the case of continuous variables and the χ^2 test in the case of categorical variables. The Fisher exact test was used for categorical variables if one or more cells had an expected frequency of ≤5, and Wilcoxon rank sum test was used for nonparametric data. All tests were 2-tailed, and the level of statistical significance was set at $p < 0.05$. All statistical analyses were conducted using Statistical Analysis System version 8.2 (SAS Inc., Cary, NC).

RESULTS **Clinical features.** One hundred ten patients with PKD, including 89 males and 21 females, were recruited in the present study. The mean age at onset was 11.8 ± 3.7 years (range 4 months to 27 years). Symptom onset occurred after 18 years of age in only 4 patients. The clinical features of these patients are summarized in figure 1, and 2 typical episodes are presented in videos 1 and 2. Fifty-seven of the 110 patients experienced complete or partial remission of the disease, and the mean age at remission was 21.3 ± 4.8 years. A total of 77 patients required anticonvulsant treatment, including 64 patients with

Figure 1 **Clinical features of 110 patients with PKD**



For each clinical manifestation, the proportion of the patients is indicated. EA = episodic ataxia; ET = essential tremor; IC = infantile convulsions; PKD = paroxysmal kinesigenic dyskinesia.

carbamazepine, 5 patients with oxcarbazepine, and 8 patients with other anticonvulsants (phenobarbital, valproate, clonazepam, topiramate, flunarizine, and lamotrigine). Because of the wide use of carbamazepine as the therapeutic drug, we classified the response to anticonvulsant treatment into 3 levels: complete (attacks vanished, with or without premonitory sensation), incomplete (occasional attacks at a low frequency), and nonresponsive/insensitive (attacks showed a decrease less than 25% vs the previous level when the dosage was increased to 400 mg daily). Of the 64 patients, 98.4% benefited from carbamazepine with complete response in 61 patients (50–100 mg, daily) and incomplete response in 2 cases. The 5 patients receiving oxcarbazepine (75–150 mg, daily) were event-free on the treatment. Overall, 96.1% of the patients who had received anticonvulsant treatment reported a great benefit from the medications, with complete response in 71 patients and incomplete response in 3 patients. The remaining 3 patients who showed slight relief of their attacks (nonresponsive) were prescribed with valproate in 2 cases and carbamazepine in 1 case.

***PRRT2* sequencing.** We detected 8 *PRRT2* mutations in 34 probands; the remaining 57 patients were negative for *PRRT2* mutations. In total, 76.9% (20/26) of familial PKD cases were attributable to *PRRT2* mutations while only 21.5% (14/65) of sporadic PKD cases harbored pathogenic variants of the *PRRT2* gene. The most frequently described mutation, c.649dupC (p.R217PfsX8),[23] was identified in 70.6% (24/34) of the patients with *PRRT2* mutations. Four patients were found to harbor the mutation c.649delC (p.R217EfsX12). Three other mutations that had been reported in our previous work, namely, c.487C>T (p.Q163X), c.573dupT (p.G192WfsX8), and c.796C>T (R266W)[2,25] were identified in one family each. Three undocumented mutations, one nonsense mutation, c.787C>T (p.Q263X), and 2 missense mutations, c.797G>A (p.R266Q) and c.931C>T (p.R311W), were identified in the present study (figure 2, A–C). None of these 3 *PRRT2* mutations has been reported in the SNP Database or the 1000 Genomes Project, or was detected in the 200 healthy volunteers. SIFT software revealed a score of 0.03 for c.797G>A and 0.00 for c.931C>T. The 57 non-*PRRT2* mutation carriers did not reveal any mutation in the *MR-1*, *SLC2A1*, *CHRNA4*, and *CHRNB2* genes.

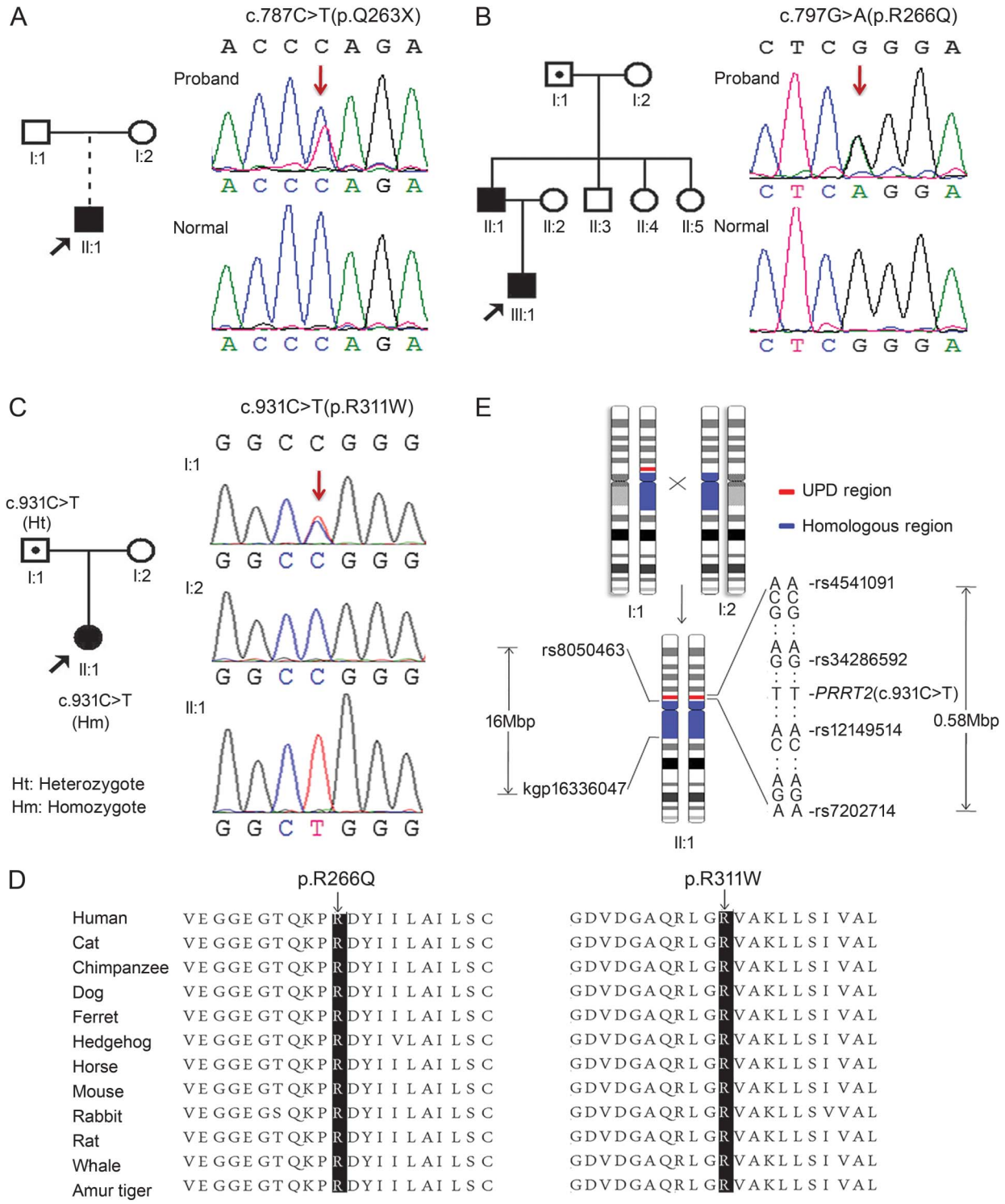
Genotype–phenotype analysis. Analysis of the genotype–phenotype correlation (table 1) revealed that *PRRT2* mutation carriers had an earlier age at onset and a longer duration of attacks than did non-*PRRT2* mutation carriers. In addition, *PRRT2* mutation carriers tended to present with complicated PKD as well as combined phenotypes of dystonia and chorea. Patients with familial PKD were more likely to harbor *PRRT2* mutations. Assessment of other clinical manifestations and the response to anticonvulsant treatment revealed no significant difference between patients with PKD who did and did not carry *PRRT2* mutations.

Case PA0234. Patient PA0234 is a complicated PKD case with a homozygotic c.931C>T mutation resulting from the inheritance of uniparental disomy (UPD). Upon doctor visit in 2012, she was a 25-year-old woman who had involuntary chorea mainly affecting the left side since the age of 2 years (video 1). She had no history of consanguinity and no family history of PKD. She developed infantile convulsions at the age of 7 months and experienced 2 attacks of cerebellar ataxia lasting for 1 week each, with spontaneous remission at the ages of 12 and 14 years. She would experience increased muscular tension before an episode, and slowing down occasionally relieved the attack. The chorea, which was mostly triggered by sudden movements, usually involved the left limb and occurred 6 to 10 times per day. It occasionally alternated between the left and right sides and sometimes involved the trunk. Each attack lasted for less than 30 seconds and consciousness remained normal during the attacks. She experienced an incomplete remission at the age of 18 years, with persistent occasional minor attacks. After bearing her first kid at the age of 26 years, her attacks completely ceased. The interictal neurologic examination was absolutely normal, and brain MRI and EEG showed no abnormalities. Direct Sanger sequencing of *PRRT2* revealed a homozygous mutation of c.931C>T in the patient and a paternal heterozygous c.931C>T; no mutations were found in her mother (figure 2C). To determine the origin of the mutations at c.931C>T, SNP array genotyping was conducted for a further exploration of the mode of inheritance. The results indicated that the patient inherited 2 copies of paternal DNA and no maternal contributions in the region from rs4541091 to rs7202714 on chromosome 16 (denoted as the UPD region hereafter), which covered the *PRRT2* mutation locus at c.931C>T. In addition, there was a large homologous region (16 Mbp) from rs8050463 to kgp16336047 just following the UPD region in both parents (figure 2E). This UPD type of inheritance resulted in a homozygous genotype of the c.931C>T mutation in *PRRT2* in the patient.

DISCUSSION

PKD is the most frequently described type of PxD.[6] Although the identification of *PRRT2* as the causative gene of PKD promises to deepen our understanding of the pathogenesis of the disease, the

Figure 2 Three undocumented mutations identified in the *PRRT2* gene



(A–C) The 3 undocumented *PRRT2* mutations identified in present study. The pedigrees are shown in the left half, and the corresponding chromatograms are shown in the right half. (A) c.787C>T (p.Q263X); (B) c.797G>A (p.R266Q); (C) c.931C>T (p.R311W). (D) The 2 missense mutations located in the highly conserved region at the C-terminal of the PRRT2 protein. (E) Schematic diagram of uniparental disomy. The red rectangle denotes the UPD region (rs4541091 to rs7202714), which encompasses the c.931C>T mutation in the *PRRT2* gene. The blue rectangle denotes the homologous region (rs8050463 to kgp16336047) in both parents. UPD = uniparental disomy.

role of the PRRT2 protein remains unknown. PRRT2 interacts with SNAP 25 (synaptosomal-associated protein 25 kDa), a presynaptic protein involved in vesicle docking and fusion, suggesting that synaptic dysfunction and abnormal neurotransmitter releasing are involved in the pathogenesis of PKD.[26]

In the present study, the mean age at onset and remission demonstrate the age-dependent

Table 1 Clinical manifestations in 110 patients with PKD and genotype-phenotype correlation in 91 PKD probands with and without *PRRT2* mutations

		91 Probands			
Variable	Total (n = 110)	Total (n = 91)	*PRRT2* (+) (n = 34)	*PRRT2* (–) (n = 57)	*p* Value
Demographics					
Age at onset, y, mean ± SD	11.8 ± 3.7	12.1 ± 3.2	10.9 ± 3.5	12.9 ± 2.8	0.0030[a]
Sex, n (%)					
Male	89 (80.9)	77 (84.6)	27 (79.4)	50 (87.7)	
Female	21 (19.1)	14 (15.4)	7 (20.6)	7 (12.3)	
Male to female	4.2:1	5.5:1			
Family history of PKD, n (%)	45 (40.9)	26 (28.6)	20 (58.8)	6 (10.5)	<0.0001[b]
Complicated PKD, n (%)[c]	14 (12.7)	11 (12.1)	8 (23.5)	3 (5.3)	0.0171[b]
Infantile convulsions	13 (11.8)	10 (11.0)	8 (23.5)	2 (3.5)	
Migraine	5 (4.5)	4 (4.4)	2 (5.9)	2 (3.5)	
Episodic ataxia	1 (1.0)	1 (1.1)	1 (2.9)	0 (0.0)	
Essential tremor, n (%)	4 (3.6)	4 (4.4)	0 (0.0)	4 (7.0)	
Nature of attacks, n (%)					
Premonitory sensation	80 (72.7)	70 (76.9)	29 (85.3)	41 (71.9)	0.1029
Duration of attacks, s					0.0060[b]
<10	51 (46.4)	45 (49.5)	9 (26.5)	36 (63.2)	
10–30	42 (38.2)	33 (36.3)	18 (52.9)	15 (26.3)	
30–60	15 (13.6)	12 (13.2)	6 (17.6)	6 (10.5)	
>60	2 (1.8)	1 (1.1)	1 (2.9)	0 (0.0)	
Phenomenology					0.0036[b]
Dystonia only	69 (62.7)	59 (64.8)	15 (44.1)	44 (77.2)	
Chorea only	4 (3.6)	4 (4.4)	2 (5.9)	2 (3.5)	
Dystonia and chorea	37 (33.6)	28 (30.8)	17 (50.0)	11 (19.3)	
Laterality					0.8142
Unilateral	45 (40.9)	38 (41.8)	12 (35.3)	26 (45.6)	
Bilateral	28 (25.5)	20 (22.0)	8 (23.5)	12 (21.1)	
Unilateral and bilateral	33 (30.0)	30 (33.0)	13 (38.2)	17 (29.8)	
Unilateral, alternating	4 (3.6)	3 (3.3)	1 (3.0)	2 (3.5)	
Face involvement	68 (61.8)	62 (68.1)	24 (70.6)	38 (66.7)	0.6977
Response to medication					0.0599
Medically treated patients, n	77	70	25	45	
Complete, % (n)	92.2 (71)	91.4 (64)	100 (25)	86.6 (39)	
Incomplete, % (n)	3.9 (3)	4.3 (3)	0.0 (0)	6.7 (3)	
Nonresponsive, % (n)	3.9 (3)	4.3 (3)	0.0 (0)	6.7 (3)	

Abbreviation: PKD = paroxysmal kinesigenic dyskinesia.
[a] Significant difference ($p < 0.05$) between *PRRT2* mutation carriers and noncarriers, detected using the unpaired Student *t* test.
[b] Significant difference ($p < 0.05$) between *PRRT2* mutation carriers and noncarriers, detected using the χ^2 test.
[c] Complicated PKD is defined as PKD accompanied by infantile convulsions, migraine, or episodic ataxia.

development and alleviation pattern of the disease, which corresponds with the temporal expression pattern of *PRRT2* observed in the developing mouse brain.[3] The male to female ratio of 6.2:1 in sporadic cases and 2.7:1 in familial cases suggests the apparent male predilection, especially in sporadic cases.[1,27] This finding implies that some sex-related regulatory factors are involved in the disease. In our study, 12.7% of patients had a complicated form of PKD, manifesting as paroxysmal movement disorders accompanied

by a personal history of infantile convulsions, migraine, or episodic ataxia. We noticed that essential tremor was a complaint in 4 patients with PKD who did not carry the *PRRT2* mutation in the present study, whereas it had been reported only in the family members of patients with PKD.[1] There is no report revealing *PRRT2* mutation in patients with essential tremor without PKD.[28] Considering the high prevalence of essential tremor, whether the coexistence is attributable to coincidence or an unknown relation requires further investigation and longer patient follow-up. Dystonia is the most common movement disorder (video 2), as well as in published patients with clinically diagnosed PKD.[29] In our study, almost all patients reported a clear kinesigenic trigger, and the attacks lasted for less than 1 minute. The 2 patients who experienced attacks of longer than 1 minute had a positive family history and each harbored a *PRRT2* mutation (c.649dupC and c.649delC). This suggests that the attack duration can occasionally be somewhat longer than the typical duration of 1 minute in patients with PKD.

Up to one-third of patients did not require/take medications, as they had minor clinical manifestations or concerns about the side effects of anticonvulsants. We found that 98.4% of patients prescribed with carbamazepine showed a good response, suggesting that carbamazepine is the first-choice drug for patients with PKD. A low dose of 50 to 100 mg per night is recommended; this dose can adequately control the attacks and also avoids the side effects such as drowsiness and dizziness. The treatment should be individualized according to the frequency of attacks, effect on daily life, and needs specific to the patient's occupation. Considering the high incidence of Stevens-Johnson syndrome/toxic epidermal necrolysis induced by carbamazepine in the Chinese Han population, it is important to implement HLA-B*15:02 screening before initiating the treatment to reduce the risk of adverse cutaneous reactions.[30] Furthermore, a referral patient who was initially misdiagnosed as dystonia experienced continued attacks of dyskinesia when prescribed with only one dose of haloperidol (2 mg), an inverse agonist of dopamine, and the symptoms alleviated to his normal level 24 hours later. This phenomenon indicates that haloperidol worsens the symptoms of PKD and that a dysfunction in neurotransmitter releasing, especially dopamine releasing, might underlie the pathogenesis of the disease.

Analysis of genotype–phenotype correlation revealed that *PRRT2* mutations were significantly correlated with an earlier age at onset, longer duration of attacks, a complicated form of PKD, combined phenotypes of dystonia and chorea, and a tendency for a family history of PKD. The correlation between earlier onset of disease and genetic factors has also been described in several studies on patients with different ethnic backgrounds.[19–22] *PRRT2* mutation carriers experienced longer attacks than did noncarriers, in whom attacks typically lasted for less than 1 minute. The correlation of *PRRT2* mutations with combined phenotypes of dystonia and chorea and a family history of PKD has been demonstrated in a recent report of 374 genetically proven *PRRT2*-related PxDs.[23] All 8 *PRRT2* mutation carriers with complicated PKD had a personal history of infantile convulsions, suggesting that infantile convulsions and PKD are allelic conditions caused by *PRRT2* mutations.[31,32]

The c.649dupC mutation was present in 70.6% of the 34 probands who were identified to harbor *PRRT2* mutations, which further confirmed the conclusion of our and other studies that c.649dupC (p.R217PfsX8) was a hotspot mutation in PKD.[2–4,25,33] Together with the other 2 reported mutations c.649delC and c.649C>T, which occur at the same locus, the high frequency of mutations at this site may be related to the natural characteristics of the sequence, which has a homopolymer tract with 4 guanines followed by 9 successive duplicated cytosine residues prior to the mutation locus.[5] This sequence has the potential to form a hairpin loop, which may cause polymerase slippage or the insertion/deletion of a base during DNA replication. The remaining 57 probands who did not have any *PRRT2* mutation may be due to a contribution of yet to be identified genes, which needs to be further investigated in future studies.

The nonsense mutations, which are responsible for 57.7% of *PRRT2* mutations (41/71), introduce premature termination codons in messenger RNA. Through the nonsense-mediated RNA decay pathway, the nonsense mutations of *PRRT2* lead to a quantitative deficiency at the messenger RNA level, thus resulting in haploinsufficiency; this pathway has recently been confirmed to be involved in the pathogenesis of PKD.[34] The 2 undocumented missense mutations identified in our patients are located in a region at the C-terminal that is highly conserved throughout different species, which suggests the significant functional role of this region (figure 2D). The new mutation c.797G>A (p.R266Q) introduces a different amino acid change at the same locus of the already reported mutation c.796C>T (p.R266W).[2] Patients harboring these 2 mutations displayed similar clinical manifestations, indicating that this novel mutation is reliably pathogenic. Furthermore, the SIFT scores also suggested that the 2 mutations were deleterious.

We confirmed a rare inheritance mode of UPD in a patient with complicated PKD. The notion of UPD was first proposed by Engel,[35] referring to the

situation in which both homologs of a chromosomal region or segment have originated from a single parent. The occurrence of UPD can be explained by models postulating postfertilization error, gamete complementation, monosomic conception with subsequent chromosome gain (monosomy rescue), or trisomic conception followed by chromosome loss (trisomy rescue).[36,37] In our patient, mitotic recombination may have contributed to UPD. The SNP array results demonstrated a 16-Mbp homologous region on chromosome 16 close to the UPD region in both parents, suggesting that homologous genetic regions in parents with distant consanguinity may be the genetic basis for UPD. The homologous region exactly encompasses the pericentromeric region of chromosome 16, which is enriched in duplicated areas and prone to chromosomal rearrangement, further supporting our hypothesis. In previous reports, 2 brothers with a homozygous c.649dupC mutation in *PRRT2* displayed mental retardation, episodic ataxia, and absence seizures in addition to the PKD/BFIS phenotype,[38] and a patient with a compound heterozygous *PRRT2* mutation (c.604delT and c.609_611delACC) was educationally subnormal.[21] Our patient with PKD who carried a homozygous c.931C>T mutation had 2 attacks of cerebellar ataxia lasting longer than typical episodic ataxia and was intellectually normal. The normal phenotype in the father of the patient may be attributable to the incomplete penetrance of PKD. The different phenotypes of patients with PKD may result from the remarkable pleiotropy of the *PRRT2* gene.

The present study characterizes the clinical and genetic features of PKD in 110 patients, and presents the results of a genotype–phenotype correlation analysis. A patient harboring a homozygous c.931C>T mutation is identified to have acquired the mutation via the inheritance mode of UPD. We detect 8 mutations including 3 undocumented ones in the *PRRT2* gene, and confirm that *PRRT2* mutations account for 37.4% of PKD cases. Carbamazepine is recommended as the first-choice drug when treatment is needed, but an individualized treatment regimen should be used.

AUTHOR CONTRIBUTIONS

Dr. Huang: data acquisition, analysis and interpretation of data, drafting the manuscript. Dr. T. Wang: data acquisition, analysis and interpretation of data, statistical analysis, drafting the manuscript. Dr. J.-L. Wang: data acquisition, analysis and interpretation of data. Dr. Liu: data acquisition. Dr. Che: data acquisition. Dr. Li: data acquisition. Dr. Mao: data acquisition. Dr. M. Zhang: data acquisition. Dr. Bi: data acquisition. Dr. Wu: data acquisition. Dr. Y. Zhang: funding, data acquisition. Dr. J.-Y. Wang: data acquisition. Dr. Shen: data acquisition. Prof. Tang: funding, data acquisition, analysis and interpretation of data, manuscript revision. Prof. Cao: funding, study design and conceptualization, data acquisition, analysis and interpretation of data, statistical analysis, manuscript revision. Prof. Chen: study design and conceptualization, data acquisition, analysis and interpretation of data, manuscript revision.

ACKNOWLEDGMENT

The authors thank the participants for taking part in the study and Yong Huang (Shanghai, China) for help with SNP array analysis.

STUDY FUNDING

Supported by the State Key Program of the National Natural Science Foundation of China (81130021), Shanghai Municipal Natural Science Foundation (12ZR1418500), and National Natural Science Foundation of China (81271262 and 81301081).

DISCLOSURE

X. Huang, T. Wang, J.-L. Wang, X. Liu, X. Che, J. Li, X. Mao, M. Zhang, G. Bi, and L. Wu report no disclosures relevant to the manuscript. Y. Zhang is in charge of National Natural Science Foundation of China (81301081). J.-Y. Wang and J. Shen report no disclosures relevant to the manuscript. B. Tang is in charge of State Key Program of National Natural Science Foundation of China (81130021). L. Cao is in charge of Shanghai Municipal Natural Science Foundation (12ZR1418500) and National Natural Science Foundation of China (81271262). S. Chen reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received January 6, 2015. Accepted in final form July 1, 2015.

REFERENCES

1. Bruno MK, Hallett M, Gwinn-Hardy K, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology 2004;63:2280–2287.
2. Wang JL, Cao L, Li XH, et al. Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. Brain 2011;134:3493–3501.
3. Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet 2011;43:1252–1255.
4. Li J, Zhu X, Wang X, et al. Targeted genomic sequencing identifies PRRT2 mutations as a cause of paroxysmal kinesigenic choreoathetosis. J Med Genet 2012;49:76–78.
5. Heron SE, Dibbens LM. Role of PRRT2 in common paroxysmal neurological disorders: a gene with remarkable pleiotropy. J Med Genet 2013;50:133–139.
6. Méneret A, Gaudebout C, Riant F, et al. PRRT2 mutations and paroxysmal disorders. Eur J Neurol 2013;20:872–878.
7. Becker F, Schubert J, Striano P, et al. PRRT2-related disorders: further PKD and ICCA cases and review of the literature. J Neurol 2013;260:1234–1244.
8. Lee YC, Lee MJ, Yu HY, et al. PRRT2 mutations in paroxysmal kinesigenic dyskinesia with infantile convulsions in a Taiwanese cohort. PLoS One 2012;7:e38543.
9. Liu XR, Wu M, He N, et al. Novel PRRT2 mutations in paroxysmal dyskinesia patients with variant inheritance and phenotypes. Genes Brain Behav 2013;12:234–240.
10. Ono S, Yoshiura K, Kinoshita A, et al. Mutations in PRRT2 responsible for paroxysmal kinesigenic dyskinesias also cause benign familial infantile convulsions. J Hum Genet 2012;57:338–341.
11. Liu Q, Qi Z, Wan XH, et al. Mutations in PRRT2 result in paroxysmal dyskinesias with marked variability in clinical expression. J Med Genet 2012;49:79–82.
12. Dale RC, Gardiner A, Antony J, Houlden H. Familial PRRT2 mutation with heterogeneous paroxysmal disorders including paroxysmal torticollis and hemiplegic migraine. Dev Med Child Neurol 2012;54:958–960.
13. Riant F, Roze E, Barbance C, et al. PRRT2 mutations cause hemiplegic migraine. Neurology 2012;79:2122–2124.

14. Gardiner AR, Bhatia KP, Stamelou M, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology 2012;79: 2115–2121.
15. Marini C, Conti V, Mei D, et al. PRRT2 mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine. Neurology 2012;79:2109–2114.
16. Cloarec R, Bruneau N, Rudolf G, et al. PRRT2 links infantile convulsions and paroxysmal dyskinesia with migraine. Neurology 2012;79:2097–2103.
17. Scheffer IE, Grinton BE, Heron SE, et al. PRRT2 phenotypic spectrum includes sporadic and fever-related infantile seizures. Neurology 2012;79:2104–2108.
18. Wang JL, Mao X, Hu ZM, et al. Mutation analysis of PRRT2 in two Chinese BFIS families and nomenclature of PRRT2 related paroxysmal diseases. Neurosci Lett 2013;552:40–45.
19. Li HF, Chen WJ, Ni W, et al. PRRT2 mutation correlated with phenotype of paroxysmal kinesigenic dyskinesia and drug response. Neurology 2013;80:1534–1535.
20. Mao CY, Shi CH, Song B, et al. Genotype-phenotype correlation in a cohort of paroxysmal kinesigenic dyskinesia cases. J Neurol Sci 2014;340:91–93.
21. Tan LC, Methawasin K, Teng EW, et al. Clinico-genetic comparisons of paroxysmal kinesigenic dyskinesia patients with and without PRRT2 mutations. Eur J Neurol 2014; 21:674–678.
22. Youn J, Kim JS, Lee M, et al. Clinical manifestations in paroxysmal kinesigenic dyskinesia patients with proline-rich transmembrane protein 2 gene mutation. J Clin Neurol 2014;10:50–54.
23. Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. Mov Disord 2014;29:1108–1116.
24. Pourfar MH, Guerrini R, Parain D, Frucht SJ. Classification conundrums in paroxysmal dyskinesias: a new subtype or variations on classic themes? Mov Disord 2005;20: 1047–1051.
25. Cao L, Huang XJ, Zheng L, Xiao Q, Wang XJ, Chen SD. Identification of a novel PRRT2 mutation in patients with paroxysmal kinesigenic dyskinesias and c.649dupC as a mutation hot-spot. Parkinsonism Relat Disord 2012;18: 704–706.
26. Lee HY, Huang Y, Bruneau N, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep 2012;1:2–12.
27. Bhatia KP. Paroxysmal dyskinesias. Mov Disord 2011;26: 1157–1165.
28. Kuhlenbäumer G, Hopfner F, Deuschl G. Genetics of essential tremor: meta-analysis and review. Neurology 2014;82:1000–1007.
29. Groffen AJ, Klapwijk T, van Rootselaar AF, Groen JL, Tijssen MA. Genetic and phenotypic heterogeneity in sporadic and familial forms of paroxysmal dyskinesia. J Neurol 2013;260:93–99.
30. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004; 428:486.
31. Caraballo R, Pavek S, Lemainque A, et al. Linkage of benign familial infantile convulsions to chromosome 16p12-q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. Am J Hum Genet 2001; 68:788–794.
32. Swoboda KJ, Soong B, McKenna C, et al. Paroxysmal kinesigenic dyskinesia and infantile convulsions: clinical and linkage studies. Neurology 2000;55:224–230.
33. Méneret A, Grabli D, Depienne C, et al. PRRT2 mutations: a major cause of paroxysmal kinesigenic dyskinesia in the European population. Neurology 2012;79:170–174.
34. Wu L, Tang HD, Huang XJ, et al. PRRT2 truncated mutations lead to nonsense-mediated mRNA decay in paroxysmal kinesigenic dyskinesia. Parkinsonism Relat Disord 2014;20:1399–1404.
35. Engel E. A new genetic concept: uniparental disomy and its potential effect, isodisomy. Am J Med Genet 1980;6: 137–143.
36. Spence JE, Perciaccante RG, Greig GM, et al. Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 1988;42:217–226.
37. Yamazawa K, Ogata T, Ferguson-Smith AC. Uniparental disomy and human disease: an overview. Am J Med Genet 2010;154C:329–334.
38. Labate A, Tarantino P, Viri M, et al. Homozygous c.649dupC mutation in PRRT2 worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences. Epilepsia 2012;53:e196–e199.

Paroxysmal kinesigenic dyskinesia: Clinical and genetic analyses of 110 patients

Xiao-Jun Huang, Tian Wang, Jun-Ling Wang, et al.

Neurology published online October 7, 2015
DOI 10.1212/WNL.0000000000002079