PRRT2 gene mutations

From paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine

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ABSTRACT

Objective: The proline-rich transmembrane protein (*PRRT2*) gene was recently identified using exome sequencing as the cause of autosomal dominant paroxysmal kinesigenic dyskinesia (PKD) with or without infantile convulsions (IC) (PKD/IC syndrome). Episodic neurologic disorders, such as epilepsy, migraine, and paroxysmal movement disorders, often coexist and are thought to have a shared channel-related etiology. To investigate further the frequency, spectrum, and phenotype of *PRRT2* mutations, we analyzed this gene in 3 large series of episodic neurologic disorders with PKD/IC, episodic ataxia (EA), and hemiplegic migraine (HM).

Methods: The *PRRT2* gene was sequenced in 58 family probands/sporadic individuals with PKD/IC, 182 with EA, 128 with HM, and 475 UK and 96 Asian controls.

Results: *PRRT2* genetic mutations were identified in 28 out of 58 individuals with PKD/IC (48%), 1/182 individuals with EA, and 1/128 individuals with HM. A number of loss-of-function and coding missense mutations were identified; the most common mutation found was the p.R217Pfs*8 insertion. Males were more frequently affected than females (ratio 52:32). There was a high proportion of *PRRT2* mutations found in families and sporadic cases with PKD associated with migraine or HM (10 out of 28). One family had EA with HM and another large family had typical HM alone.

Conclusions: This work expands the phenotype of mutations in the *PRRT2* gene to include the frequent occurrence of migraine and HM with PKD/IC, and the association of mutations with EA and HM and with familial HM alone. We have also extended the *PRRT2* mutation type and frequency in PKD and other episodic neurologic disorders. ***Neurology*® 2012;79:2115–2121**

GLOSSARY

ADHD = attention-deficit/hyperactivity disorder; **EA** = episodic ataxia; **HM** = hemiplegic migraine; **IC** = infantile convulsions; **ICCA** = infantile convulsions with choreoathetosis; **PKD** = paroxysmal kinesigenic dyskinesia; **PNKD** = paroxysmal non-kinesigenic dyskinesia.

Paroxysmal kinesigenic dyskinesia (PKD) is the most common type of paroxysmal dyskinesia. The disorder was first reported in 1892 by Shuzo Kure[1] in a 23-year-old Japanese man who had frequent movement-induced paroxysmal attacks, typical of PKD, starting from age 10 years. In 1901, Gowers[2] described a similar child, and in 1967, Kertesz[3] and Weber[4] described families with this condition. Idiopathic or familial attacks often occur in childhood induced by sudden movements, accelerating from walking to running, or infrequently other stimuli such as sound, stress, or hyperventilation. There is often a warning of an impending attack such as numbness or paraesthesia in the affected limb or face, which then develops into pure or mixed dystonic, choreic, ballistic, or athetotic

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manifestations. In most patients up to 20 attacks per day occur, lasting between 30 seconds and 2 minutes.[5–7]

PKD is often associated with infantile convulsions (IC) or convulsions with choreoathetosis (ICCA). Attacks respond well to anticonvulsant therapy, indicating an overlap in the pathologic mechanisms that underlie these episodic disorders.[6,7] In 1997, genetic linkage analysis identified a locus for IC or ICCA on chromosome 16p12-q12.[8] A number of family members later developed attacks typical of PKD. Subsequently, multiple families with either PKD or ICCA syndrome from multiple populations were linked to chromosome 16, within or near the original ICCA linkage, suggesting that these disorders are allelic with variable expression, although other studies have demonstrated heterogeneity.[8–17]

Over the last 15 years, a considerable amount of work has been expended on the identification of the PKD/IC gene[17–20] until recently, when mutations in the *PRRT2* gene were identified as an important cause using exome sequencing.[21–25] This is consistent with a recent report of PKD in 2 cases associated with a microdeletion of this region.[26] These were mainly heterozygous loss-of-function mutations. In the homozygous state one case has been reported to cause nonsyndromic intellectual disability.[27] In addition, missense *PRRT2* mutations were also reported that could also be loss-of-function or consistent with a dominant-negative effect.[22,23] The *PRRT2* gene encodes a proline-rich transmembrane protein that is highly expressed in the CNS. Using yeast 2-hybrid screening, the *PRRT2* protein has been shown to interact with the synaptosomal-associated protein 25 (SNAP25), suggesting a role in the fusion of synaptic vesicles to the plasma membrane.[28]

To assess the *PRRT2* mutation frequency, spectrum, and associated phenotype, we analyzed this gene in 3 series of episodic neurologic disorders identifying mutations in 28 out of 58 PKD/IC, 1 out of 182 episodic ataxia (EA), and 1 out of 128 probands or sporadic cases with hemiplegic migraine (HM). There were 27 loss-of-function and 3 missense mutations identified; they were in males more frequently than females (male to female ratio 52:32). A number of families with *PRRT2* mutations and PKD had associated migraine or HM, 1 family had EA with HM, and another large family had HM alone in several individuals, extending the phenotype of this disorder to involve other types of episodic neurologic conditions such as EA, migraine, and HM.

METHODS

Standard protocol approvals, registrations, and patient consents. We have ethical approval for this research and patients and unaffected family members were recruited with informed consent (NHNN studies 06/N076 and 07/Q0512/26). The diagnosis of PKD or IC/ICC, migraine/HM, and EA was made using recognized criteria[5,16,29–32] by the clinicians who are authors on this publication (tables 1 and 2). The EA cases are part of the channel gene UK service and had already been screened as negative for the *KCNA1* and *CACNA1A* gene by Sanger sequencing and MLPA. The PRRT2-positive cases were also negative for these 2 genes.

Genetic analysis. DNA was extracted by a standard phenol chloroform method from blood in affected and unaffected patients. PCR was employed to analyze the coding exons of the *PRRT2* gene. The longest *PRRT2* transcript was used for primers design and sequencing, Genbank NM_145239, Ensemble (*PRRT2* ENSG00000167371) transcript *PRRT2*-001–ENST00000358758. Primers were designed to exons and flanking introns of the coding exons 2 and 3 of the *PRRT2* gene. Synthesized primers were from Sigma Genesis (Sigma-Aldrich Co. LLC, USA) (Prrt2_2f CCTATCTCCTCCTCTTCCAG, Prrt2_2r CTCCAGAGGCTCTATTGCAG, Prrt2_3f CTTACCCGCCATCTATGG, Prrt2_3r AGGCTCCCTTGGTCCTTAGG). PCR analysis was performed using 10 pmol of both forward and reverse genomic primers and FastStart Taq DNA polymerase (www.roche-applied-science.com). Then each purified product was sequenced using forward or reverse primers, as well as sequencing primers to sequence the middle part of exon 2 (Prrt2_2fmid AAGAGGCC ACTGCAGACCAG and Prrt2_2rmid TGGTTGAAGGGCT GGCTTG) with Applied Biosystems BigDye terminator v3.3 sequencing chemistry as per the manufacturer's instructions.[33] The resulting reactions were resolved on a ABI3730XL genetic analyser (Applied Biosystems, Foster City, CA) and analyzed with SeqScape v2.5 software (Gene Codes, VA). Mutations were verified in both directions, repeat sequencing carried out for specific exons in the proband and other family members to confirm and verify segregation. Mutation position was labeled from the start ATG of the *PRRT2* gene according to the standard nomenclature,[34,35] Genbank accession number NM_145239, Ensemble transcript *PRRT2*-001–ENST00000358758. None of these mutations were present on sequencing the *PRRT2* gene in 475UK and 96 Asian controls. Several reported SNPs were identified and these include P75P, P138A, P216L, and C276C.

RESULTS

The *PRRT2* gene was sequenced in 58 PKD/IC, 182 EA, and 128 HM family probands or sporadic cases (tables 1 and 2). The majority of families and sporadic individuals were of English origin but mutations were also identified in families from Malaysia, India, Wales, Somalia, Pakistan, Kenya, Poland, Malta, Austria, Philippines, Ireland, Scotland, and Australia (table 1). Families 6, 11, and 20 were used in the initial identification of the *PRRT2* gene.[24] Few patients had associated IC or ICC, reflecting a bias toward adult movement disorders in our department. The p.R217Pfs*8

Table 1 Mutations identified in the *PRRT2* gene

Pedigree	Gender	Phenotypes	Additional features	*PRRT2* mutation	Ethnic origin
1	1M	PKD	—	p.R217Pfs*8	English Caucasian
2	1M	PKD	—	p.R217Pfs*8	English Caucasian
3	1M	PKD	—	p.R217Pfs*8	Malaysia
4	1M	PKD	—	p.R217Pfs*8	English Caucasian
5	1M	PKD	—	p.R217Pfs*8	English Caucasian
6	10M, 7F	PKD	GTCS	p.R217Pfs*8	India Asian
7	2M, 1F	PKD	Migraine	p.R217Pfs*8	India Asian
8	3M, 4F	PKD/HM	Several with severe migraine and 2 with hemiplegic migraine	p.R217Pfs*8	Wales Caucasian
9	2M	PKD/IC	—	p.332insGAC	India Asian
10	2M	PKD	Migraine	p.R217Pfs*8	English Caucasian
11	7M, 2F	PKD	Migraine in several members	p.R217Pfs*8	English Caucasian
12	1F	PKD	Migraine and depression	P215R	English Caucasian
13	1M	PKD	GTCS	p.R217Pfs*8	Somalia Asian
14	1M, 1F	PKD	—	p.L171Lfs*3	Pakistan Asian
15	2M	PKD/IC	Seizures late	p.R217Pfs*8	Kenya Asian
16	1F	PKD	Migraines	p.R217Pfs*8	Polish Caucasian
17	2M, 1F	PKD	—	p.R217Pfs*8	English Caucasian
18	2F	EA and HM	Hemiplegic migraine	p.R217Pfs*8	English Caucasian
19	1M, 1F	PKD	Migraine	p.R217Pfs*8	Malta Caucasian
20	2M, 1F	PKD	Severe migraine in the affected and parent carrier	p.R217Pfs*8	Austria Caucasian
21	1M, 1F	PKD	NA	p.R217Pfs*8	Ireland Caucasian
22	2M	PKD	Seizures in 30s	p.R217Pfs*8	Scotland Caucasian
23	1F	PKD	—	P216H	English Caucasian
24	3M	PKD	Migraine with aura	p.R217Pfs*8	Philippines Asian
25	1F	PKD	Attention-deficit/hyperactivity disorder	p.R217Pfs*8	Australian Caucasian
26	2F	PKD	—	Exon 3 splice site: c.1011C>T	Scottish Caucasian
27	1F	PKD	NA	p.R217Pfs*8	English Caucasian
28	1F	PKD	NA	G305W	English Caucasian
29	2M	PKD	Headaches, migraine type	p.R217Pfs*8	Pakistan Asian
30	4M, 3F	HM	Early seizures and then hemiplegic migraine	p.R217Pfs*8	Scottish Caucasian

Abbreviations: EA = episodic ataxia; GTCS = generalized tonic-clonic seizures; HM = hemiplegic migraine; IC = infantile convulsions; NA = not available; PKD = paroxysmal kinesigenic dyskinesia.

mutation was by far the most common change, identified in 24 cases/probands from multiple ethnic origins (table 1) as previously reported.[21–24] Fifteen of these were in families where the mutation segregated with the disease and was also present in 2 clinically unaffected members, suggesting incomplete penetrance. Males were more often affected with *PRRT2* mutations compared to females (ratio 52:32). Additional loss-of-function heterozygous mutations were identified in one PKD family with a heterozygous p.C332insGAC, one sporadic PKD patient had a p.L171Lfs*3 mutation, and an additional family with PKD had an exon 3 mutation, c.1011C>T, that results in abnormal splicing. Three missense mutations were identified, a P215R and a P216H mutation in different sporadic PKD cases and a G305W mutation in a child with early onset PKD very responsive to carbamazepine. Although all 3 were predicted to be damaging using SIFT and Polyphen,[36] these families were not large enough for segregation and the *PRRT2* mutations should be considered as variants of unknown significance on this basis until further proof is obtained. None of these mutations were present on sequencing the *PRRT2* gene in 475 UK and 96 Asian control individuals.

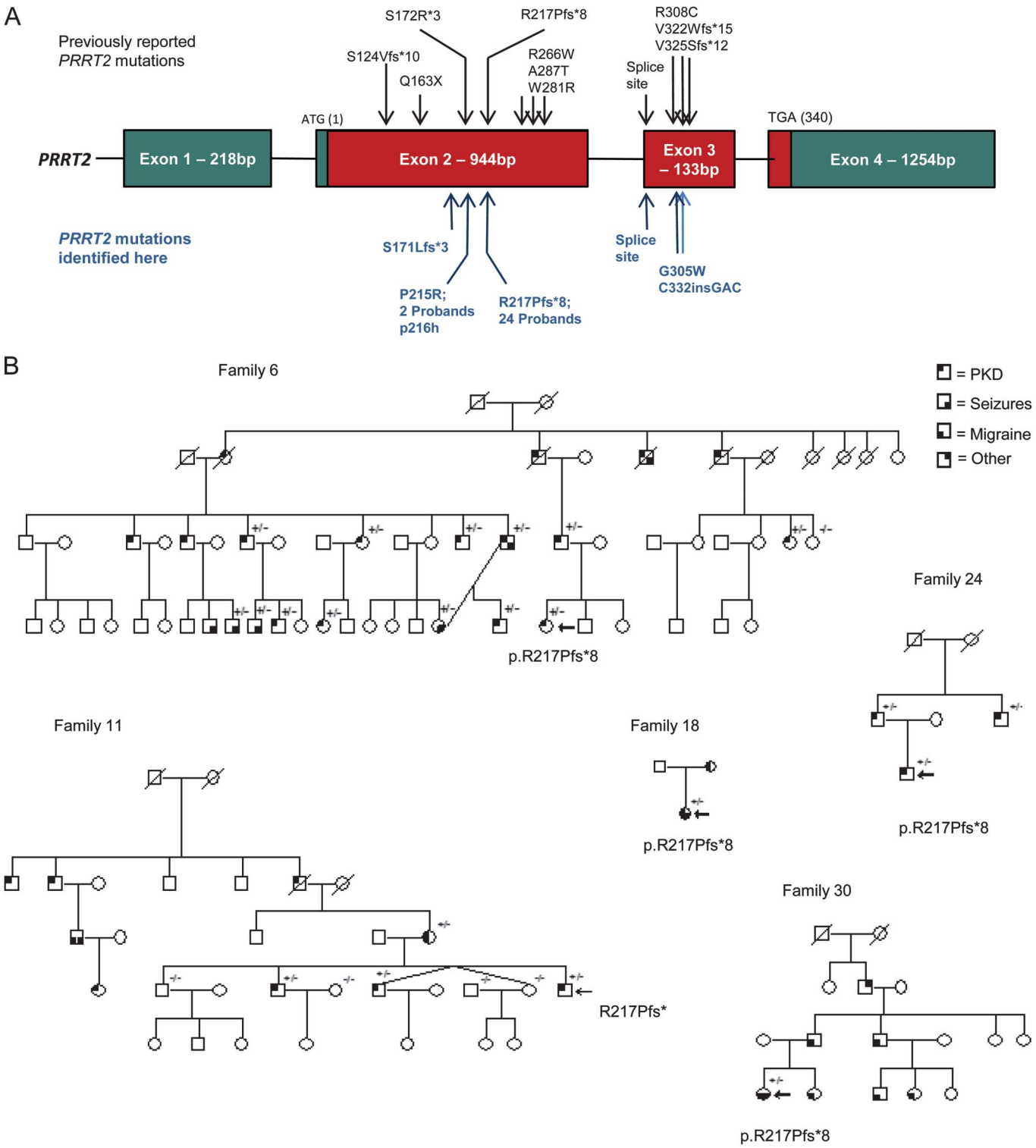
Table 2 Age at onset, family history, and phenotype details of cases/families with *PRRK2* mutations

Case/family	Age, y	Age at onset, y	Family history of PKD, IC, or other episodic problems	Obligate carriers	Past medical history	MRI/EEG
1	27	12	Negative for any attacks	No	Negative	Normal
2	36	14	Negative	No	Negative	Normal
3	47	Child	Daughter 6 months to 5 years seizures, then no follow-up	No	Negative	Normal
4	47	11	Negative	No	Negative	Normal
5	48	27	Negative	No	Negative	Normal
6	7–58	7–13	Autosomal dominant family history; seizures present in 2 cases	Yes, 1	Seizures present in 5 cases	Normal MRI, EEG low spikes
7	42	17	Father and son affected; seizures in one paternal aunt	No	Migraine in one affected case	Normal
8	25–73	8–12	Autosomal dominant family history; seizures present in 4 cases; family history of depression	No	Severe migraine in 3 affected cases; hemiplegic migraine in 2	Normal
9	15–44	5	Autosomal dominant, father and son affected	No	IC as a child in the father	Normal
10	22–40	10	Autosomal dominant, mother and daughter affected	No	IC in the daughter; migraine in the mother	Normal
11	20–68	6–11	Autosomal dominant family history; seizures present in one case	No	Migraine in several individuals with PKD	Normal
12	31	22	Negative	No	Depression, migraine with aura	Normal
13	24	13	Negative	No	Seizures	Normal
14	33	14	Brother and sister affected	No	Negative	Normal
15	40	8	Twin brothers affected	No	Seizures	Normal
16	44	11	Migraine, sister has migraine	No	Migraine/seizures	Normal
17	49	6	Two affected relatives	No	No	Normal
18	56	12	Affected mother had severe hemiplegic migraines; children also with hemiplegic migraine	No	Hemiplegic migraine	Normal
19	48	8–14	Affected mother and son	No	Migraine	Normal
20	27–51	6 mo and 29 y	Two siblings affected, father unaffected mutation carrier	Yes, 1	Seizures, migraine in affected and father	Normal
21	45–51	8–11	Brother and sister affected, parents said to be unaffected	Not proven	No	Normal
22	35	6	Cousin similar attacks, father severe migraine	No	Seizures in 30s	Normal
23	4	9	Negative	No	Attacks affect limbs, tongue/mouth twisting	Normal
24	12–42	6–14	Three affected in family; family history of seizures	No	Migraine in the probed	Normal
25	Child	Child	Asperger syndrome and ADHD; family details NA	No	Negative	Normal
26	18	8, 12	Negative	No	Negative	Normal
27	Teens	Child	PKD, good response to carbamazepine	No	NA	Normal
28	Teens	Child	PKD	No	NA	Normal
29	34	6	PKD	No	Headaches	Normal
29	34	6	Paroxysmal movements and dystonia	No	Negative	Normal
30	20	12	Hemiplegic migraine in the proband, father, uncle, cousins and possible early generations	No	Seizures and hemiplegic migraine	Normal

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; NA = not available; PKD = paroxysmal kinesigenic dystonia.

The majority of patients with *PRRT2* mutations had typical PKD, but we observed a number of cases/families with associated migraine. Two PKD cases with HM were observed in the same family (table 2), a mother and child had severe migraine headaches with PKD and ipsilateral hemimotor and sensory features associated with the p.R217Pfs*8 mutation. Two cases with EA and migraine or HM were also identified. The proband with EA and HM (tables 1 and 2, F18) had the p.R217Pfs*8 mutation with episodic balance difficulties starting at the age of 18 years with unilateral headaches and hemiplegic episodes. She had frequent attacks every day of involuntary movement and balance problems, and cerebellar ataxia on examination

Figure The structure of the *PRRT2* gene and the position of the mutations identified (A) and larger families identified with *PRRT2* gene mutations (B)



(A) The structure of the *PRRT2* gene and the position of the mutations identified. The *PRRT2* gene has 4 exons, exon 1 is noncoding, the gene length is 340 amino acids, 1,020 bp. The start ATG (codon 1) is indicated in the figure and all mutations are labeled from this codon up to the stop codon TGA at 340. Reference sequence NM_145239, Ensemble ENST00000358758. Previously reported mutations are written above the protein in black, and mutations identified here are below in blue. (B) Examples of the families identified with *PRRT2* gene mutations. The mutation is given in the proband in the pedigree, −/− indicates no mutation, +/− indicated mutation present.

but normal imaging. The mother had a past history of epilepsy and severe headaches, and one of her daughters had HM.

An additional family (tables 1 and 2, F30) had HM in a number of individuals in association with infantile convulsions in the proband (tables 1 and 2; figure, B) and we also identified a child with PKD, Asperger syndrome, and attention-deficit/hyperactivity disorder (ADHD), associated with the p.R217Pfs*8 mutation.

DISCUSSION The frequency of *PRRT2* mutations in ethnically diverse PKD families and sporadic cases was 28 out of 58 (48%), similar to the previous report of 50.4%.[24] The *PRRT2* mutation frequency in EA (1/182) and in the HM (1/128) series was low, with less than 1% of patients screened in each group. It is still possible that *PRRT2* defects exist in the other 30 PKD cases, as whole gene[26] or exon deletions or as deep intronic or regulating mutations in the untranslated promoter regions of the gene. No large PKD/IC families remain in our series that are negative for *PRRT2*.[15] The previously reported Indian PKD family, linked to a different region of chromosome 16 than the PKD/IC kindreds, was found to have the p.R217Pfs*8 mutation.[14]

The p.R217Pfs*8 mutation was identified in a large number of cases from many different ethnic backgrounds. We identified a number of other novel loss-of-function mutations as well as missense amino acid changing mutations in the *PRRT2* gene. These additional mutations were consistent with the previous reports where other types of indel and nonsense loss-of-function changes were seen, as well as damaging missense mutations. These data suggest that a mechanism of *PRRT2* haploinsufficiency as well as a possible dominant-negative mutational effect is associated with PKD.

The majority of patients with *PRRT2* mutations identified here and before had typical PKD (tables 1 and 2). However, in addition to infantile convulsions, the phenotype is frequently complicated by other episodic neurologic disorders such as epilepsy, migraine, or HM. In total, 12 out of 30 probands/cases had migraine type headaches; 3 of these families had HM. It is possible that these associations are coincidence, given the high incidence of migraine in the general population, although the frequency is high in these cases and migraine associated with hemiplegia is very rare. The association is not surprising as the coexistence of movement disorders, migraine, and epilepsy is often described in the neurologic channelopathies,[37] indicating an overlap in etiologic pathways as well as clinical features.[38]

The function of *PRRT2* is poorly understood. The gene is known to interact with the SNAP25 and both are highly expressed in the basal ganglia. SNAP25 is a presynaptic protein involved in synaptic vesicle release playing an important role in calcium triggered exocytosis.[28] The interaction with SNAP25 and the possible disruption of neurotransmitter release associated with *PRRT2* mutations is consistent with the pathogenic pathways involved in other paroxysmal movement disorders. In paroxysmal nonkinesigenic dyskinesia (PNKD), mutations in the *PNKD* gene are associated with disruption of synaptic protein regulated exocytosis[39] and SNAP25 has also been shown to be associated with ADHD,[40] which was seen in one of our PKD cases with the p.R217Pfs*8 mutation. Although further work is required, the genetic data and extension of the clinical phenotypes associated with the *PRRT2* genes indicates an overlap in the pathways with other similar disorder of channel or synapse dysfunction such as epilepsy, migraine, and PNKD.

AUTHOR CONTRIBUTIONS

This study was designed and funding obtained by HH, KB, NWW, MGH. KB, MS, RCD, MAK, SAS, GMW, TC, SDS, EMV, LSM, AHS, HAT, SR, JWS, AL, TW, DK, NWW, MH, HH collected samples and assessed patients clinically. AG and HH conducted experiments and performed data analysis. The manuscript was written by HH with input and revision from KB, MS, RCD, MAK, TC, SDS, LSM, JWS, DK, NWW and MH.

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DISCLOSURE

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