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Migraine with aura as the predominant phenotype in a family with a *PRRT2* mutation

Una-Marie Sheerin,
Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Maria Stamelou,
Sobell Department of Motor Neuroscience and Movement, Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Gavin Charlesworth,
Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Tamara Shiner,
Sobell Department of Motor Neuroscience and Movement, Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Sian Spacey,
Department of Neurology, St Paul's Hospital, Burrard Street, Vancouver, BC, Canada

Enza-Maria Valente,
Department of Neurology, Istituto CSS-Mendel Viale Regina Margherita, Rome, Italy

Nicholas W. Wood, and
Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK; UCL Genetics Institute, University College London, Gowers Street, London WC1E 6BT, UK

Kailash P. Bhatia

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k.bhatia@ucl.ac.uk.
u.sheerin@ucl.ac.uk, gavin.charlesworth@ucl.ac.uk, n.wood@ucl.ac.uk, m.stamelou@ucl.ac.uk, tamarashiner@gmail.com, spacey@mail.ubc.ca, e.valente@css-mendel.it

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Ethical standard All human study must state that have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Sobell Department of Motor Neuroscience and Movement, Disorders, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

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Paroxysmal kinesigenic dyskinesia (PKD) is characterized by paroxysms of dystonic, choreic, ballistic, or athetoid movements. Attacks usually commence during childhood or early adulthood, typically lasting a few seconds to a few minutes, and they can occur up to 100 times daily. Attacks usually respond to low-dose carbamazepine [1]. Mutations in *PRRT2* have been identified as a cause of autosomal dominant PKD [2] and replicated in other studies [3-7]. It remains important to report the clinical characteristics of genetically defined families in order to fully describe the clinical syndrome, including the presence of additional associated features beyond the movement disorder.

In a large Caucasian family with PKD (Fig. 1), a detailed neurological history and clinical examination were undertaken. Sanger sequencing of *PRRT2* was performed. Three individuals have PKD alone, and three individuals have PKD and infantile convulsions (IC). Two individuals had isolated IC, whilst two other individuals had at least one adolescent seizure but no movement disorder. The age of onset for the movement disorder ranged between 3 and 30 years. Infantile convulsions occurred between the age of 6 and 12 months. In all cases, PKD attacks were choreic or dystonic in nature, lasting less than a minute, and responded well to carbamazepine. Attacks were provoked by sudden movements in all, with stress in II:10 and III:9. Four individuals were treated with low-dose carbamazepine and/or phenytoin for PKD/IC, which abolished symptoms of the movement disorder. Neurological examination was normal (Table 1).

Sanger sequencing of *PRRT2* revealed the recognized pathogenic (c.649_650InsC p.P217fsX7) heterozygous mutation [2-7] in all eight clinically affected individuals as well as in three of the seven clinically unaffected individuals (Fig. 1). *PRRT2* mutations are unlikely to be the cause of adolescent-onset seizures in this family, as individual III:12 did not carry the mutation. Non-penetrance was observed in three individuals. Migraine with aura, as classified using the International Headache Society diagnostic criteria [8], co-segregated in all but one individual with the p.P217fsX7 mutation, including in three individuals who do not have symptoms of IC/PKD, but was not observed in individuals who did not carry the p.P217fsX7 mutation. Visual aura (positive visual phenomena) was most frequently reported, other types of aura including expressive dysphasia, alexia and alien hand syndrome were also described. Migraine frequency ranged from twice a year to three times a month. Reported triggers included stress, sleep deprivation and exercise. Two individuals were treated with low-dose propranolol for several months, which reduced the frequency and severity of migraine attacks, but did not improve symptoms of the movement disorder.

Previously reported linkage studies for this kindred (family 3, Spacey et al.) [9] generated LOD scores that were not significant for the analysis of PKD alone or PKD ± IC. We repeated linkage analysis using Merlin [10], assuming an autosomal dominant mode of inheritance with 80 % penetrance. LOD scores for the *PRRT2* mutation and PKD/IC and the *PRRT2* mutation and migraine with aura are 1.65 and 2.7, respectively. Several kindreds with hemiplegic migraine and *PRRT2* mutations have recently been reported [11]. Migraine

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(with and without aura) is over-represented in individuals with *PRRT2* mutations and clustering of migraine has been identified in small kindred's harboring *PRRT2* mutations [12] In this large family, migraine with aura segregates in a Mendelian fashion in nine of 10 individuals with the *PRRT2* mutation, the remaining individual is still in adolescence and could still go onto develop migraine. Furthermore, it highlights that in some families, migraine with aura may be the predominant phenotype associated with PRRT2 mutations, which is important to bear in mind when determining whether a patient with PKD/IC has a positive family history, to enable appropriate genetic counseling and testing. The association of migraine with *PRRT2* mutations raises the question of whether genetic variation in *PRRT2* might play a role in susceptibility to 'common' migraine with aura.

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References

1. Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, Lynch DR, Mathews KD, Swoboda KJ, Harris J, Soong BW, Ashizawa T, Jankovic J, Renner D, Fu YH, Ptacek LJ. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology. 2004; 63:2280–2287. [PubMed: 15623687]
2. Chen WJ, Lin Y, Xiong ZQ, Wei W, Ni W, Tan GH, Guo SL, He J, Chen YF, Zhang QJ, Li HF, Murong SX, Xu J, Wang N, Wu ZY. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet. 2011; 43:1252–1255. [PubMed: 22101681]
3. 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(5):704–706. [PubMed: 22386217]
4. Lee HY, Huang Y, Bruneau N, Roll P, Roberson ED, Hermann M, Quinn E, Maas J, Edwards R, Ashizawa T, Baykan B, Bhatia K, Bressman S, Bruno MK, Brunt ER, Caraballo R, Echenne B, Fejerman N, Frucht S, Gurnett CA, Hirsch E, Houlden H, Jankovic J, Lee WL, Lynch DR, Mohammed S, Muller U, Nespeca MP, Renner D, Rochette J, Rudolf G, Saiki S, Soong BW, Swoboda KJ, Tucker S, Wood N, Hanna M, Bowcock AM, Szepetowski P, Fu YH, Ptacek LJ. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep. 2012; 1:2–12. [PubMed: 22832103]
5. Li J, Zhu X, Wang X, Sun W, Feng B, Du T, Sun B, Niu F, Wei H, Wu X, Dong L, Li L, Cai X, Wang Y, Liu Y. Targeted genomic sequencing identifies PRRT2 mutations as a cause of paroxysmal kinesigenic choreoathetosis. J Med Genet. 2012; 49:76–78. [PubMed: 22131361]
6. Liu Q, Qi Z, Wan XH, Li JY, Shi L, Lu Q, Zhou XQ, Qiao L, Wu LW, Liu XQ, Yang W, Liu Y, Cui LY, Zhang X. Mutations in PRRT2 result in paroxysmal dyskinesias with marked variability in clinical expression. J Med Genet. 2012; 49(2):79–82. [PubMed: 22209761]
7. Wang K, Zhao X, Du Y, He F, Peng G, Luo B. Phenotypic overlap among paroxysmal dyskinesia subtypes: Lesson from a family with PRRT2 gene mutation. Brain Dev [Epub ahead of print]. 2012
8. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia. 1988; 8(Suppl 7):1–96.
9. Spacey SD, Valente EM, Wali GM, Warner TT, Jarman PR, Schapira AH, Dixon PH, Davis MB, Bhatia KP, Wood NW. Genetic and clinical heterogeneity in paroxysmal kinesigenic dyskinesia: evidence for a third EKD gene. Mov Disord. 2002; 17:717–725. [PubMed: 12210861]

10. Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin–rapid analysis of dense genetic maps using sparse gene flow trees. Nat Genet. 2002; 30(1):97–101. [PubMed: 11731797]
11. Riant F, Roze E, Barbance C, Meneret A, Guyant-Marechal L, Lucas C, Sabouraud P, Trebuchon A, Depienne C, Tournier-Lasserve E. PRRT2 mutations cause hemiplegic migraine. Neurology [Epub ahead of print]. 2012
12. Cloarec R, Bruneau N, Rudolf G, Massacrier A, Salmi M, Bataillard M, Boulay C, Caraballo R, Fejerman N, Genton P, Hirsch E, Hunter A, Lesca G, Motte J, Roubertie A, Sanlaville D, Wong SW, Fu YH, Rochette J, Ptacek LJ, Szepetowski P. PRRT2 links infantile convulsions and paroxysmal dyskinesia with migraine. Neurology [Epub ahead of print]. 2012

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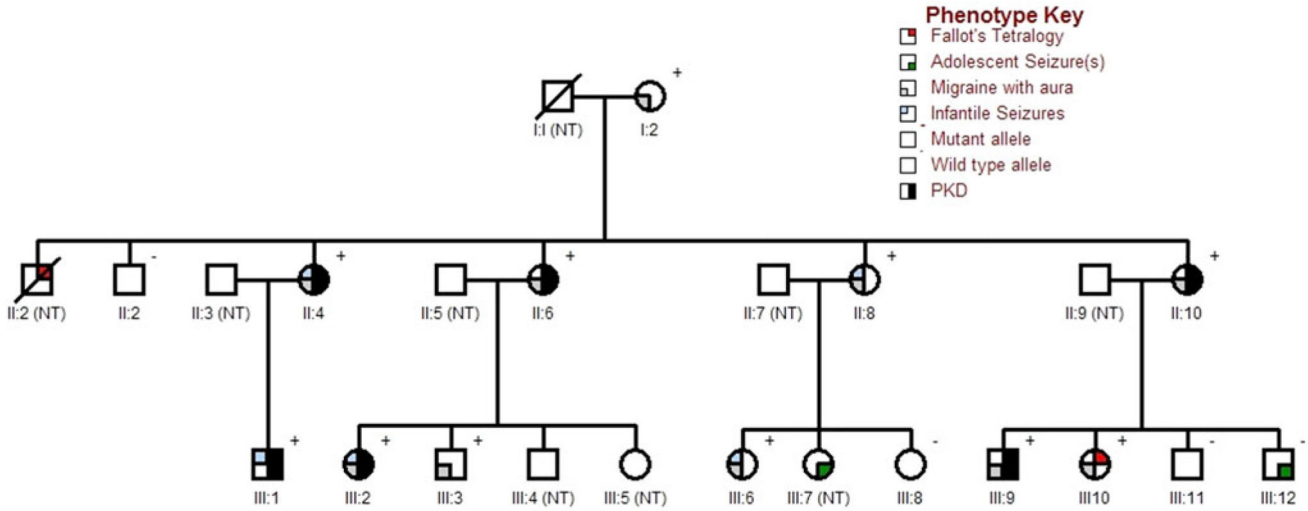

Fig. 1.

Pedigree of Family 1. All individuals with symptoms of PKD, PKD and IC, or isolated IC were found to have a frameshift mutation in PRRT2 (c.649_650InsC p.P217fsX7) indicated by a *plus symbol*; individuals found not to have the mutation are indicated by a *minus symbol*. Deceased members are marked with a *diagonal bar*. The *phenotype key* indicates manifestation of each individual. Individuals who were unavailable for genetic testing are marked *NT*

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Table 1

Clinical descriptions and genotyping results for family members

Individual	Gender	Age currently (years)	Phenotype (age at onset indicated in brackets)	Treatment	Description of IC/PKD attacks	Past medical history/ additional features	Genotype
I:2	F	85	Asymptomatic	N/A		Continuous left sided choreiform movements for a year during an intercurrent illness diagnosed as rheumatic fever. Cardiac valve replacement for rheumatic-fever related valvulopathy. Migraine with visual aura and transient expressive dysphasia	p.P217fsX7
II:4	F	52	IC (6 months)	Phenytoin for IC.	Several IC: 6 afebrile	Migraine with visual aura	p.P217fsX7
			PKD (5 years)	Carbamazepine 200 mg od for PKD attacks commenced age 12 thereafter asymptomatic	generalized tonic–clonic seizures. Dystonic posturing of left arm and left side of the face, and preceded by aura consisting of left arm paraesthesia		
III:1	M	15	IC (from 6–18 months) PKD (3 years)	Carbamazepine 600 mg od for PKD attacks thereafter asymptomatic	Aged 3 years legs turned outwards whilst running. Aged 8 years brief episodes of choreiform movements of both legs and left arm, preceded by a “tingling” sensation in his legs		p.P217fsX7
II:6	F	61	PKD (30 years)	N/A	Several brief episodes of involuntary movements of one arm and facial dystonic posturing	Frequent migraines with visual aura and accompanied by transient expressive dysphasia, treated with propranolol with good response	p.P217fsX7
III:2	F	25	IC (12 months) PKD (10 years)	N/A	Brief recurrent episodes of	Migraine with aura symptoms of transient	p.P217fsX7

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Individual	Gender	Age currently (years)	Phenotype (age at onset indicated in brackets)	Treatment	Description of IC/PKD attacks	Past medical history/ additional features	Genotype
					involuntary arm movements	expressive dysphasia and alexia	
III:3	F	39	Asymptomatic	N/A	N/A	Severe frequent migraine with visual aura since adolescence, triggered by exercise, including episodes associated with transient expressive dysphasia and alexia	p.P217fsX7
III:4	M	40	Asymptomatic	N/A	N/A		Wild type
III:5	F	38	Asymptomatic	N/A	N/A		Wild type
II:10	F	61	PKD (9 years)	Carbamazepine (100 mg od) for PKD attacks	Dystonic posturing of the head and left arm, preceded by a sensation of weakness in the left foot. Attacks more frequent pre-menstrually	Migraine with visual aura since adolescence. Small cerebral haemorrhage	p.P217fsX7
III:9	M	37	PKD (9 years)	Carbamazepine (100 mg od) for PKD attacks	Dystonic posturing of the right arm, preceded by ‘strange sensation spreading down the right side’, lasting 30 s, occurring up to 15 times a day	Migraine with aura and bladder diverticula	p.P217fsX7
III:10	F	36	Asymptomatic			Fallot’s tetralogy. Migraine with visual aura and expressive dysphasia	p.P217fsX7
II:8	F	58	IC (aged 5 months)	NT	Several IC multiple afebrile generalized tonic–clonic seizures	Migraine with visual aura since adolescence, treated with propranolol	p.P217fsX7
III:6	F	30	IC (6–12 months)	NT	Several IC: multiple generalized tonic-clonic seizures	Migraine with visual aura	p.P217fsX7
III:12	M	27	Asymptomatic			Generalized tonic–clonic and partial seizures aged 9 years. Seizures well	Wild type

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Individual	Gender	Age currently (years)	Phenotype (age at onset indicated in brackets)	Treatment	Description of IC/PKD attacks	Past medical history/ additional features	Genotype
						controlled on carbamazepine 200 mg bd. MRI brain normal	
III:7	F	28	Asymptomatic			Single generalized tonic–clonic seizure aged 13 years	NT
II:2	M	45	Asymptomatic				Wild type
III:8	F	20	Asymptomatic				Wild type
III:11	M	34	Asymptomatic				Wild type

PKD paroxysmal kinesigenic dyskinesia, *IC* infantile convulsions, *N/A* not applicable, *NT* indicates that the patient was unavailable genetic testing