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## ***PRRT2* links infantile convulsions and paroxysmal dyskinesia with migraine**

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# PRRT2 links infantile convulsions and paroxysmal dyskinesia with migraine

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See pages 2104, 2109, 2115, 2122, and 2154

Supplemental data at [www.neurology.org](http://www.neurology.org)

Supplemental Data



## ABSTRACT

**Objective:** Whole genome sequencing and the screening of 103 families recently led us to identify *PRRT2* (proline-rich-transmembrane protein) as the gene causing infantile convulsions (IC) with paroxysmal kinesigenic dyskinesia (PKD) (PKD/IC syndrome, formerly ICCA). There is interfamilial and intrafamilial variability and the patients may have IC or PKD. Association of IC with hemiplegic migraine (HM) has also been reported. In order to explore the mutational and clinical spectra, we analyzed 34 additional families with either typical PKD/IC or PKD/IC with migraine.

**Methods:** We performed Sanger sequencing of all *PRRT2* coding exons and of exon-intron boundaries in the probands and in their relatives whenever appropriate.

**Results:** Two known and 2 novel *PRRT2* mutations were detected in 18 families. The p.R217Pfs\*8 recurrent mutation was found in  $\approx 50\%$  of typical PKD/IC, and the unreported p.R145Gfs\*31 in one more typical family. *PRRT2* mutations were also found in PKD/IC with migraine: p.R217Pfs\*8 cosegregated with PKD associated with HM in one family, and was also detected in one IC patient having migraine with aura, in related PKD/IC familial patients having migraine without aura, and in one sporadic migraineur with abnormal MRI. Previously reported p.R240X was found in one patient with PKD with migraine without aura. The novel frameshift p.S248Afs\*65 was identified in a PKD/IC family member with IC and migraine with aura.

**Conclusions:** We extend the spectrum of *PRRT2* mutations and phenotypes to HM and to other types of migraine in the context of PKD/IC, and emphasize the phenotypic pleiotropy seen in patients with *PRRT2* mutations. *Neurology*® 2012;79:2097-2103

## GLOSSARY

**HM** = hemiplegic migraine; **IC** = infantile convulsion; **PKD** = paroxysmal kinesigenic dyskinesia; **PNKD** = paroxysmal nonkinesigenic dyskinesia.

There is a long known relationship between human epilepsies and other paroxysmal brain disorders, such as migraine, episodic ataxia, or paroxysmal dyskinesia—the occurrence of involuntary movements, whether spontaneous or triggered by various types of stimuli. Evidence for shared pathophysiologic mechanisms underlying the concurrence of benign infantile convulsions (IC) and of paroxysmal kinesigenic dyskinesia (PKD) in the same patients or families was obtained more than 15 years ago.<sup>1,2</sup> This defined the autosomal dominant PKD/IC syndrome,<sup>3</sup> formerly known as ICCA (infantile convulsions and paroxysmal choreoathetosis, MIM 602066).<sup>1</sup> IC (or benign infantile seizures) are nonfebrile seizures with onset between 3 and 12 months of age and have a favorable outcome. Patients may develop PKD later in life. In

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PKD/IC families, individuals who inherited the disease haplotypes had PKD, IC, or both. Linkage of pure autosomal dominant IC at the same genetic 16p12-q12 locus was obtained.<sup>4</sup> Familial association of IC with hemiplegic migraine (HM) has also been reported.<sup>5</sup>

Mutations in the *PRRT2* gene were very recently identified via exome or whole genome sequencing in PKD<sup>6–8</sup> and in PKD/IC and IC patients and families.<sup>9,10</sup> *PRRT2* encodes a proline-rich transmembrane protein of unknown function. Interaction with synaptosomal-associated protein 25 (SNAP25)<sup>9</sup> suggests a role in the fusion of synaptic vesicles to the plasma membrane. *PRRT2* mutations identified so far include a recurrent and most frequent frameshift mutation (c.649\_650insC, p.R217Pfs\*8) found in most well-characterized PKD or IC families and in less well-characterized patients or families.<sup>6–10</sup> Lack of mutant protein expression suggested a loss-of-function mechanism.<sup>9</sup>

Altogether, the existence of interfamilial and intrafamilial variability in the phenotypes associated with *PRRT2* mutations, and specifically with the most frequent p.R217Pfs\*8, raised the question of the possible extension of the mutational and phenotypic spectra. In the present study, the phenotype spectrum was extended to PKD with HM and *PRRT2* mutations were also identified in PKD/IC family members with more typical and frequent forms of migraine, and in one sporadic patient having complex migrainous disorder with MRI abnormalities.

**METHODS Patients and families.** Patients and family members reported in this study gave written informed consent and were all collected according to appropriate ethical guidelines and committees (CPPRB 09/40–n°AC-2008-438/n°DC-2009-1002). A subset of the families have been previously reported.<sup>4,11</sup> Inclusion criteria were the variable association of IC (afebrile seizures with onset at age 3–12 months without recognized etiology and with a favorable outcome) with PKD later in life (attacks of involuntary movements, usually of short duration, from seconds to minutes, and precipitated by other sudden movements such as standing up from a sitting position or being startled) (appendix e-1 on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)). Patients with pure PNKD (paroxysmal nonkinesigenic dyskinesia) or with pure paroxysmal exercise-induced dyskinesia were not included. PKD/IC families were classified as typical when no other neurologic symptom was found in any of the patients. For those PKD/IC families with various types of migraine (so-called atypical PKD/IC families), the diagnosis and classification of migraine were performed according to consensus guidelines according to the International classification. Apart from the aforementioned symptoms, neurologic

workups were normal, including interictal EEGs that were performed in a subset of the patients according to the international 10-20 system.

**Sanger sequencing.** DNA was extracted from whole blood according to standard procedures. The coding exons and the exon-intron boundaries of *PRRT2* (Genbank NM\_145239, AK292393) were screened for mutations by Sanger sequencing of genomic DNA. In family P2315 where PKD and HM cosegregated (figure 1), the coding exons and the exon-intron boundaries of the 3 known HM genes<sup>12</sup> (*ATP1A2*: Genbank NM\_000702; *CACNA1A*: Genbank NM\_000068, NM\_023035, NM\_001127221, NM\_001174080, NM\_001127222; *SCN1A*: Genbank NM\_006920, NM\_001165963, NM\_001165964) were also screened. Fifty-microliter PCR reactions were carried out with 80 ng of genomic DNA and 10 pmol of each pair of forward and reverse *PRRT2* primers, using AccuPrime GC-Rich DNA Polymerase (Life Technologies). Primer pairs are available upon request. All PCR products were purified and both strands were sequenced at GATC Biotech (<http://www.gatc-biotech.com/>) and the data were analyzed with the Genalys 3.0 software.

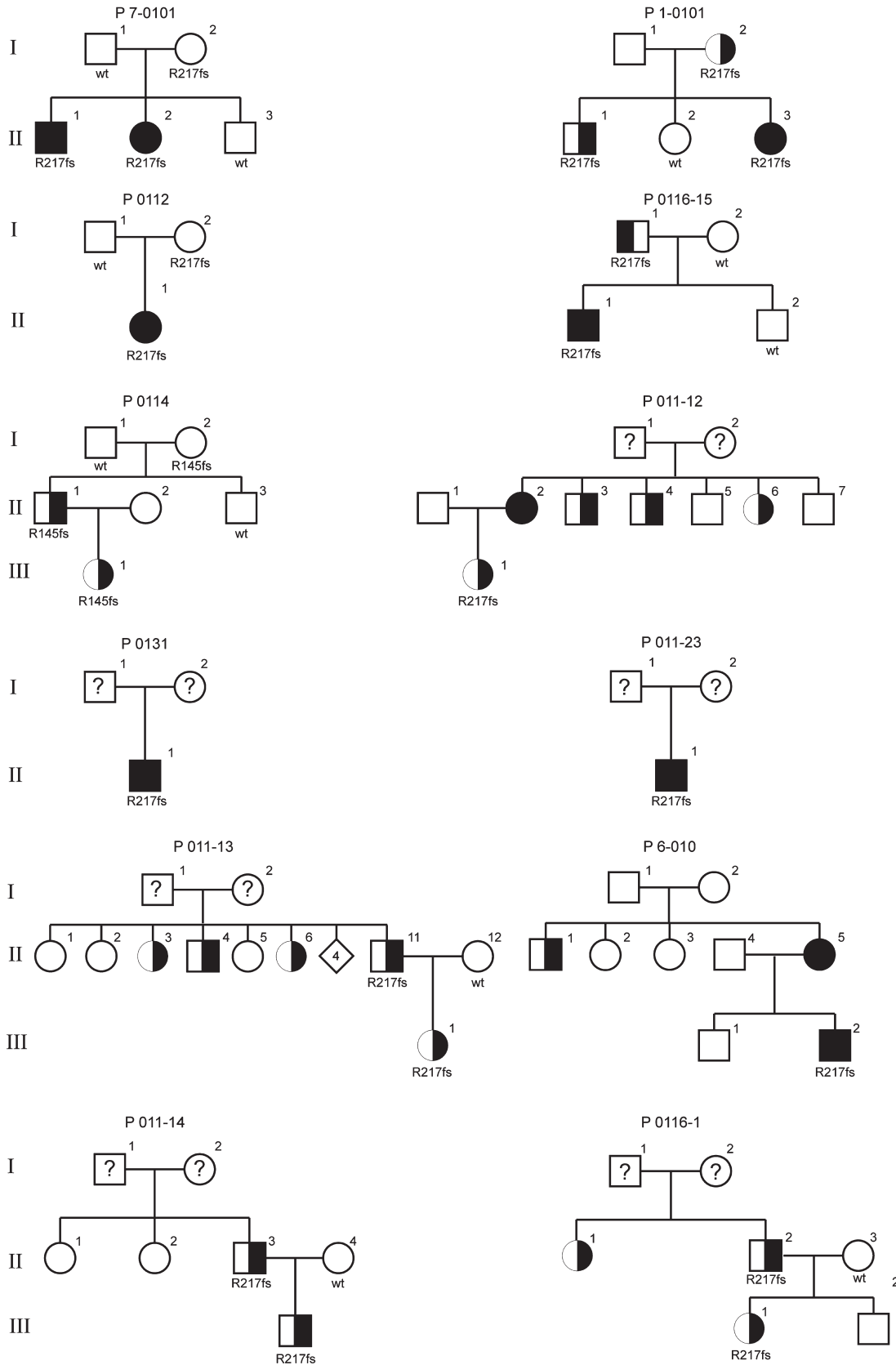
**Array comparative genomic hybridization experiment.** Array comparative genomic hybridization experiment was performed on one patient (II-2) from the P2315 PKD/HM family, using a 180K oligonucleotide microarray (SurePrint G3 Human CGH Microarray Kit, 4 x 180K, Agilent Technologies, CA) as previously described.<sup>13</sup>

**Standard protocol approvals, registrations, and patient consents.** All experiments were conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the subjects, and after approval from the appropriate ethical committees (CPPRB 09/40–n°AC-2008-438/n°DC-2009-1002).

**RESULTS AND DISCUSSION *PRRT2* mutations in typical PKD/IC.** The recurrent frameshift and disease-causing mutation (c.649\_650insC, p.R217Pfs\*8) was found in 11 typical patients and families. A novel frameshift mutation (c.434delC, p.R145Gfs\*31) was detected in family P0114. In total, *PRRT2* mutations were found in 12 of 24 (50%) patients or families with typical PKD/IC syndrome (figure 1, table). This is fully consistent with the formerly reported prevalence (52/103) of *PRRT2* mutations in PKD/IC.<sup>9</sup> PKD and IC showed variable expression and some individuals were also unaffected carriers. Mutations in noncoding sequences or genomic rearrangements of the *PRRT2* gene cannot be excluded in the 12 remaining typical families. In 3 of them, missense variations (c.C413G, p.P138A; c.G687A, p.R229K; c.C836T, p.P279S) were found but did not segregate in other patients (data not shown). Eight of these 12 were pure IC families, where genetic heterogeneity has long been known.<sup>2</sup>

***PRRT2* mutations in PKD/IC with various types of migraine.** The clinical spectrum of the recurrent p.R217Pfs\*8 *PRRT2* mutation was extended to the syndrome of PKD associated with HM in family P2315 (figure 2, figure 3, table). HM is a very rare subtype of migraine that shows sporadic or autosomal dominant

**Figure 1** PRRT2 mutations in 12 families with typical PKD/IC



Females are represented by circles, males by squares. Left half-filled symbols are patients with paroxysmal kinesigenic dyskinesia (PKD). Right half-filled symbols are patients with infantile convulsions (IC). Empty symbols are unaffected individuals. Family number is indicated at the top of each pedigree. DNA from family members with no indication on the mutation status was not available. wt = wild-type. For convenience, names of frameshift mutations have been simplified (R217fs is p.R217Pfs\*8, R145fs is p.R145Gfs\*31).

**Table Summary of *PRRT2* mutations detected in 18 patients and families with PKD/IC and related phenotypes**

Pedigree	Phenotypes	Other features	<i>PRRT2</i> mutation	Ethnic origin
P7-0101	PKD/IC	Poland anomaly (patient II-2)	p.R217Pfs*8	Canadian Caucasian
P1-0101	PKD/IC	—	p.R217Pfs*8	French Caucasian
P0111	PKD/IC/MWA	—	p.R217Pfs*8	French Caucasian
P0112	PKD/IC	—	p.R217Pfs*8	French Caucasian
P0113	PKD/IC/MWOA	—	p.R217Pfs*8	Malaysian Asiatic
P0114	IC	—	p.R145Gfs*31 <sup>a</sup>	French Caucasian
P0115 <sup>a</sup>	PKD/MWA	—	p.R240X	French Caucasian
P0116-1	IC	—	p.R217Pfs*8	Argentinian Caucasian
P0116-12 <sup>a</sup>	PKD/IC/MWA	GTCS (patient IV-1)	p.S248Afs*65 <sup>a</sup>	French Caucasian
P0116-15	PKD/IC	—	p.R217Pfs*8	French Caucasian
P011-12	PKD/IC	—	p.R217Pfs*8	Laotian Asiatic
P011-13	PKD/IC	RE (patient III-1)	p.R217Pfs*8	Argentinian Caucasian
P0131	PKD/IC	—	p.R217Pfs*8	Italian Caucasian
P4604 <sup>a</sup>	PKD/MWOA	GTCS (patient III-1)	p.R217Pfs*8	French Caucasian
P011-14	IC	—	p.R217Pfs*8	Argentinian Caucasian
P6-010	PKD/IC	—	p.R217Pfs*8	Malaysian Asiatic/Canadian Caucasian
P2315 <sup>a</sup>	PKD/HM	—	p.R217Pfs*8	French Caucasian
P011-23	PKD/IC	—	p.R217Pfs*8	Malaysian Asiatic

Abbreviations: GTCS = generalized tonic-clonic seizure; HM = hemiplegic migraine; IC = infantile convulsion; MWA = migraine with aura; MWOA = migraine without aura; PKD = paroxysmal kinesigenic dyskinesia; RE = rolandic epilepsy.

<sup>a</sup>The 6 pedigrees with various types of migraine and the 2 novel mutations reported in the present study.

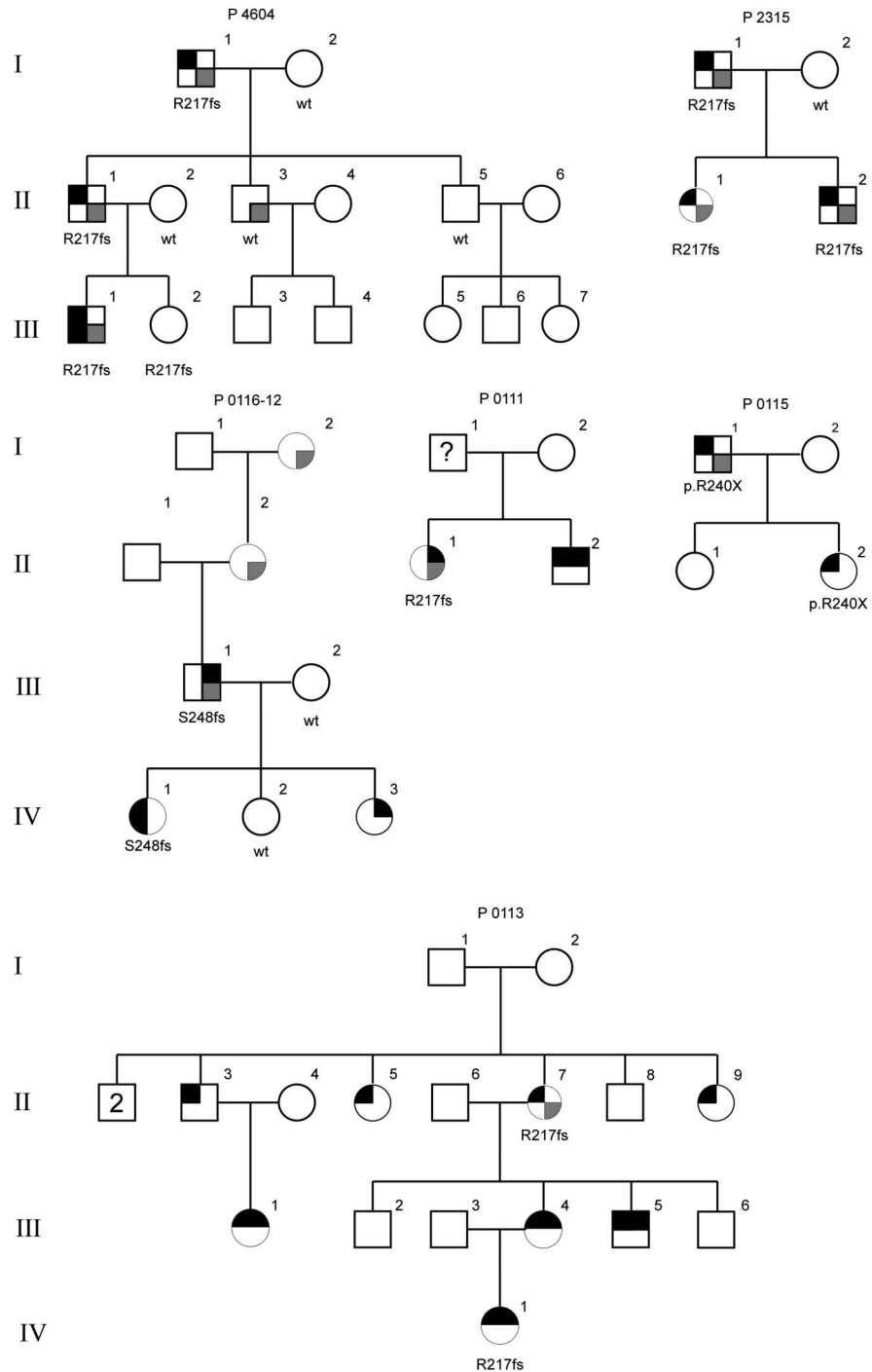
inheritance. Mutations in 3 genes (*ATPIA2*, *CACNA1A*, *SCN1A*) explain about 3/4 of familial patients and a minority of sporadic patients.<sup>12</sup> One *ATPIA2* mutation has also been found in a family with IC and HM.<sup>5</sup> In the P2315 PKD/HM family having the recurrent *PRRT2* mutation, neither a mutation in the 3 aforementioned HM genes nor a pathogenic genomic alteration were detected by Sanger sequencing and by array CGH, respectively (data not shown). The variation in phenotype between families with the same *PRRT2* mutation emphasizes the clinical and genetic links between PKD, IC, and HM. How p.R217Pfs\*8 causes the broad and variable phenotype of pure PKD, pure IC, mixed PKD/IC, and mixed PKD/HM is thus far unknown. The genetic defects reported so far in PKD/IC and in HM, and in PNKD, may all lead to altered synaptic functioning.<sup>9,14</sup>

The recurrent p.R217Pfs\*8 mutation was detected in another family (P4604) in 3 patients with PKD and migraine without aura (figure 2). One more patient in this family (II-3) who experienced migraine without aura did not inherit the mutation; he did not have PKD and might well be a phenocopy (overall prevalence of migraine is 6% in males). p.R217Pfs\*8 was also found in one patient (family P0111) who had IC and migraine with visual aura and with transient speech difficulties. In addition, p.R217Pfs\*8 was detected in one patient (PKD/IC family P0113) having

PKD and reporting migraine without aura. The previously reported p.R240X (c.C719T) nonsense mutation<sup>9</sup> was also found in one family (P0115) member having PKD and migraine without aura. A novel *PRRT2* frameshift mutation (c.742delC, p.S248Afs\*65) was found in 3 patients (family P0116-12): one had IC only, the other had PKD and GTCS, and the third had IC and migraine with visual and aphasic aura. This and the other novel p.R145Gfs\*31 mutation mentioned above were absent from current databases (1000 genomes database, NCBI SNP database) and from an additional series of 95 (p.R145Gfs\*31) and 200 (p.S248Afs\*65) control individuals of same ethnic origin.

The detection of *PRRT2* mutations in 6 PKD/IC-related families with different forms of migraine including the very rare hemiplegic type, the well-known links between IC and HM, and the increased risk of migraine in PNKD patients (Práček, unpublished data) argue in favor of a nonspurious association of typical migraine in the context of familial PKD/IC with *PRRT2* mutations. Indeed, the proportion of migraineurs among *PRRT2* mutation carriers (10/37) was significantly increased as compared with the overall migraine prevalence ( $\approx 12\%$ ) ( $p = 0.02$ , 2-tailed binomial test). This was even highly significant when only the male carriers were considered (7/19 carriers vs  $\approx 6\%$  in general population,  $p = 0.00015$ , 2-tailed binomial test). The link between *PRRT2* and migraine

**Figure 2** *PRRT2* mutations in 6 PKD/IC pedigrees with various types of migraine

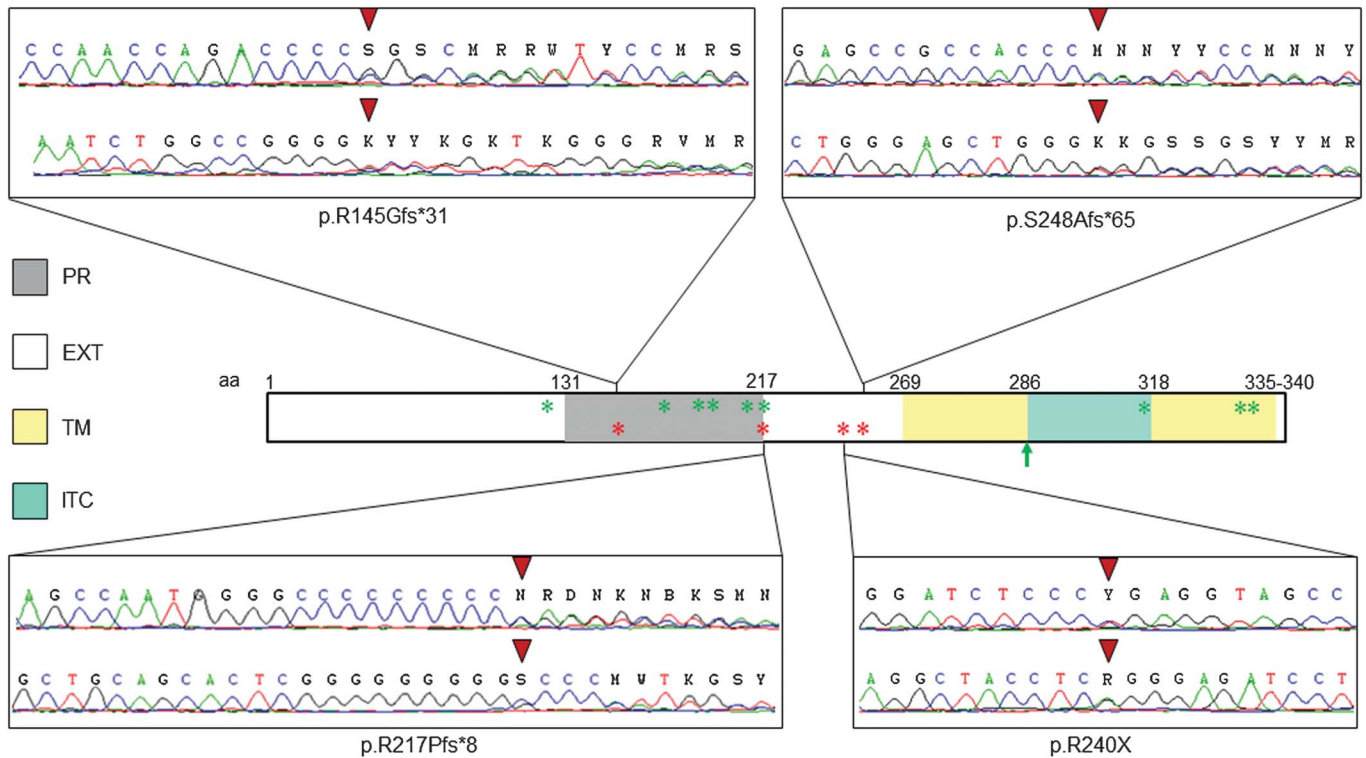


Females are represented by circles, males by squares. Top left quarter-filled symbols are patients with paroxysmal kinesigenic dyskinesia (PKD). Top right quarter-filled symbols are patients with infantile convulsions (IC). Bottom left quarter-filled symbols indicate patients with generalized tonic-clonic seizures. Bottom right quarter-filled gray symbols are patients with various types of migraine: without aura (P0113, P0115, P4604), with visual aura (P0111, P0116-12), hemiplegic (P2315). Empty symbols are unaffected individuals. Family number is indicated at the top of each pedigree. DNAs from family members with no indication on the mutation status were not available. wt = wild-type. For convenience, names of frameshift mutations have been simplified (R217fs is p.R217Pfs\*8, S248fs is p.S248Afs\*65).

was also further strengthened by an independent study where *PRRT2* mutations are also found in several PKD families with various types of migraine, including the rare hemiplegic type (Gardiner et al., unpublished). That *PRRT2* might participate indifferent migraine types is

not surprising, given the previously reported overlaps between HM, migraine with aura, and migraine without aura,<sup>12,16</sup> on the one hand, and the paroxysmal characteristics shared by the other *PRRT2*-related brain disorders on the other hand. To further evaluate the

**Figure 3** Four frameshift and nonsense *PRRT2* mutations detected in the present study



The *PRRT2* protein is from N to C-terminus. Locations of the proline-rich (PR) and transmembrane (TM) domains and of the extracellular (EXT) and intracellular (ITC) parts are indicated. Sequencing traces (both strands) corresponding to each mutation reported here (red asterisks) are shown. The locations of other *PRRT2* mutations reported so far<sup>6–10</sup> are indicated from N to C-terminus. Green asterisks: p.S124Vfs\*10, p.Q163X, p.S172Rfs\*3, p.E173X, p.A211Sfs\*14, p.S317N, p.V325Sfs\*12, p.I327Ifs\*14; green arrow (splice site mutations): c.879+1G>T, c.879+5G>A. aa = aminoacid.

spectrum of *PRRT2* mutations, we screened a cohort of 49 patients with various types of migraine. The recurrent and disease-causing p.R217fs\*8 mutation was detected in one woman (patient DL93) with type I diabetes and having migraine that started at age 48 years with complex sensitive aura (left hemifacial anesthesia), auditory aura (tinnitus), and swallowing difficulties; she had MRI abnormalities consisting of nodular hypersignals in the periventricular white matter (data not shown). Of note, she had no family history of PKD or IC.

In this study, the spectrum of *PRRT2* mutations was expanded to 2 novel mutations: p.R145Gfs\*31 and p.S248Afs\*65. Twelve other *PRRT2* mutations, including the 2 that were also found here (p.R217fs\*8, p.R240X), had been reported so far<sup>6–10</sup> (figure 3). The 2 novel mutations detected here are frameshift and, in line with other *PRRT2* mutations including the recurrent p.R217fs\*8, are thus likely to cause loss of function. The remarkable interfamilial and intrafamilial pleiotropy seen in patients with various *PRRT2* mutations might depend on a complex interplay between a given mutant allele, the genetic background of each individual including genes with synaptic functions, the neighboring genomic context,<sup>13</sup> and the influence of nongenetic factors. Our study also extends the

phenotypic spectrum of *PRRT2* mutations to HM and to other migraine subtypes in the context of PKD/IC families. The recurrent *PRRT2* mutation was also detected in one sporadic migraineur with abnormal MRI. A further search for *PRRT2* mutations in pure HM and in much larger cohorts of patients with more frequent types of migraine will be of great interest. Overall our data add novel insights into the multiple and somehow uncharacterized relationships existing between various paroxysmal brain disorders.

#### AUTHOR CONTRIBUTIONS

R. Cloarec performed the genetic experiments, analyzed the genetic data, and participated in the drafting and revision of the manuscript. N. Bruneau performed the genetic experiments and analyzed the genetic data. G. Rudolf performed the genetic experiments and analyzed the genetic data. A. Massacrier performed the genetic experiments and analyzed the genetic data. M. Salmi performed the genetic experiments and analyzed the genetic data. M. Bataillard performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. C. Boulay performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. R. Caraballo performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. N. Fejerman performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. P. Genton performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. E. Hirsch performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. A. Hunter performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. G.



Lesca performed the phenotyping and genetic analyzes, participated in the DNA collection, and analyzed the clinical and genetic data. J. Motte performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. A. Roubertie performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. D. Sanlaville performed the genetic experiments and analyzed the data. S.-W. Wong performed the phenotyping, participated in the DNA collection, and analyzed the clinical data. Y.-H. Fu participated in the design of the study and the revision of the manuscript. J. Rochette performed the phenotyping, participated in the DNA collection and analyzed the clinical data, and participated in the design of the study. L.J. Ptáček participated in the design of the study and the drafting of the manuscript. P. Szepetowski participated in the design of the study, analyzed the data, and drafted and revised the manuscript.

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## DISCLOSURE

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