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PRRT2-Associated Paroxysmal Movement Disorders

Synonym: *PRRT2*-PxMD

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Summary

Clinical characteristics

PRRT2-associated paroxysmal movement disorders (*PRRT2*-PxMD) include paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), and hemiplegic migraine (HM). In addition, *PRRT2* pathogenic variants have been identified in other childhood-onset movement disorders and different types of seizures, suggesting that the understanding of the spectrum of *PRRT2*-PxMD is still evolving. The paroxysmal attacks in PKD are characterized by dystonia, choreoathetosis, and less commonly ballismus. The seizures of BFIE are usually focal with or without generalization. Thirty percent of *PRRT2*-associated PKD is associated with BFIE and is referred to as PKD/IC.

Diagnosis/testing

The diagnosis of *PRRT2*-PxMD is established in a proband who has one of the following three findings on molecular genetic testing: a *PRRT2* heterozygous pathogenic variant (~99% of affected individuals); the 16p11.2 recurrent deletion that includes *PRRT2* (<1% of affected individuals); or biallelic *PRRT2* pathogenic variants (<1% of affected individuals, typically those with a more severe phenotype).

Management

Treatment of manifestations: PKD attack frequency is reduced or prevented by treatment with low doses of antiepileptic drugs (AEDs). Avoiding stress, sleep deprivation, anxiety, and other triggers that can precipitate PKD episodes can help prevent attacks and can lower attack frequency. For BFIE, seizure frequency is decreased by therapeutic doses of AEDs; seizures lasting longer than five minutes or seizure clusters may respond to use of benzodiazepines. Seizures tend to spontaneously remit by age two years.

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Surveillance: Individuals with PKD or PKD/IC can be monitored clinically every one to two years, particularly with respect to evaluating medication needs and dosing. Individuals with BFIE are monitored clinically for seizures; AEDs are adjusted accordingly.

Agents/circumstances to avoid: PKD: Avoid triggers known to precipitate attacks.

Pregnancy management: Prenatal exposure to AEDs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Discussion of the risks and benefits of using a given AED during pregnancy should ideally take place prior to conception.

Genetic counseling

PRRT2-PxMD caused by a heterozygous *PRRT2* pathogenic variant or, rarely, the 16p11.2 recurrent deletion (that includes *PRRT2*) is inherited in an autosomal dominant manner. Rarely *PRRT2*-PxMD (typically associated with a more severe phenotype) is inherited in an autosomal recessive manner. For autosomal dominant *PRRT2*-PxMD: approximately 90% of pathogenic variants are inherited and 10% are *de novo*. Each child of an individual with *PRRT2*-PxMD has a 50% chance of inheriting the *PRRT2* pathogenic variant. Once the *PRRT2* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible; however, reduced penetrance and variable expressivity lead to phenotypic variability within families.

GeneReview Scope

PRRT2-Associated Paroxysmal Movement Disorders: Included Phenotypes [1]
• Paroxysmal kinesigenic dyskinesia (PKD) • Benign familial infantile epilepsy (BFIE) • Paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC) • Hemiplegic migraine (HM)

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

PRRT2-associated paroxysmal movement disorders (*PRRT2*-PxMD) **should be considered** in individuals with any one of the following four phenotypes and/or in individuals with a paroxysmal movement disorder and a positive family history of any of the four phenotypes:

Paroxysmal Kinesigenic Dyskinesia (PKD)

PKD characterized by the following clinical and supportive findings (adapted from Bruno et al [2004]):

- **Clinical findings.** Sudden attacks of unilateral or bilateral involuntary movements (dyskinesias that can include a combination of dystonia, chorea, ballism, or athetosis) and the following:
  - Onset between ages one and 20 years
  - A kinesigenic trigger (e.g., sudden voluntary movements or being startled)
  - An aura preceding attacks (10% of individuals)
  - Short duration (typically <1 minute)
  - High frequency (sometimes as many as 100 times/day)
  - No loss of consciousness or pain during attacks
  - Prevention or control with phenytoin or carbamazepine

- **Supportive findings**
  - Normal neurologic examination between attacks
  - Normal brain MRI
  - No EEG changes during the attacks

Benign Familial Infantile Epilepsy (BFIE)

BFIE characterized by the following clinical and supportive findings [Watanabe et al 1987, Vigevano 2005, Specchio & Vigevano 2006]:

- **Clinical findings.** Complex partial seizures or localization-related epilepsy (focal, typically with altered awareness, and a unilateral motor component that can involve either side of the body in the same individual) with the following:
  - Onset in the first year of life (most commonly 4-12 months)
  - Either spontaneous or occuring in the context of fever [Scheffer et al 2012]
  - Can occur in clusters of multiple seizures per day: up to eight to ten seizures per day occurring every two to three hours on average
  - Excellent response to antiepileptic drugs (AEDs)
  - Resolution by age two years
- **Supportive findings**
  - Otherwise normal development and normal developmental outcome
  - Normal neurologic examination
  - Normal brain imaging and EEG background signal

Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions (PKD/IC)

PKD/IC characterized by both of the following phenotypes:

- Paroxysmal movement disorder that meets criteria for PKD
- Seizures that meet criteria for BFIE

Hemiplegic Migraine (HM)

HM (The International Classification of Headache Disorders ICHD-3 beta [Headache Classification Committee 2013]) characterized by:

- Migraine with aura
- Aura that includes some degree of hemiparesis and may be prolonged

Note: Heterozygous *PRRT2* pathogenic variants have been described in persons with HM who represent simplex cases (i.e., a single occurrence in a family) [Ebrahimi-Fakhari et al 2015].

Establishing the Diagnosis

The diagnosis of *PRRT2*-PxMD **is established** in a proband who meets clinical criteria and has one of the following on molecular genetic testing (see Table 1):

- A *PRRT2* heterozygous pathogenic variant (~99% of affected individuals) [Chen et al 2011, Wang et al 2011, Ebrahimi-Fakhari et al 2015]
- The 16p11.2 recurrent deletion that includes *PRRT2* (<1% of affected individuals) [Dale et al 2012, Silveira-Moriyama et al 2013, Weber et al 2013, Termsarasab et al 2014, Ebrahimi-Fakhari et al 2015]
- Biallelic *PRRT2* pathogenic variants (<1% of affected individuals) [Ebrahimi-Fakhari et al 2015] observed in rare instances of autosomal recessive inheritance in individuals with a more severe phenotype [Labate et al 2012, Delcourt et al 2015]

Molecular genetic testing approaches can include **gene-targeted testing** (typically targeted sequencing of *PRRT2* or a multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis [CMA] and genomic sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from a wide range of other paroxysmal disorders are likely to be diagnosed using either a multigene panel or genomic testing (i.e., exome sequencing) (see Option 2).

Option 1

When the phenotype and family history suggest the diagnosis of *PRRT2*-PxMD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *PRRT2* is performed first. If no pathogenic variant is found, gene-targeted deletion/duplication analysis should be performed next.
- **A multigene panel** for PKD, BFIE PKD/IC, or HM may also be considered.

  Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of pathogenic variants in genes that do not explain the underlying phenotype. Given the rarity of *PRRT2*-associated paroxysmal disorders, clinicians should ensure that *PRRT2* is included in gene panels for the phenotypes observed in this wide spectrum of neurologic findings. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For more information on multigene panels click here.

Option 2

When the diagnosis of *PRRT2*-PxMD has not been considered, **comprehensive genomic testing** is likely to be the diagnostic modality selected. Genomic sequencing (when clinically available) includes exome sequencing and genome sequencing.

For more information on comprehensive genomic testing click here.

Table 1. Molecular Genetic Testing Used in *PRRT2*-Associated Paroxysmal Movement Disorders

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method [3]
PRRT2	Sequence analysis [4]	99%
	Gene-targeted deletion/duplication analysis [5]	<1%
	CMA [6]	<1%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Ebrahimi-Fakhari et al [2015]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. These methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes, such as the 16p11.2 recurrent deletion, may not be defined by these methods.
6. Chromosomal microarray analysis (CMA) using oligonucleotide or SNP arrays detects copy number variants and defines breakpoints of large deletions, including the 16p11.2 recurrent deletion.

Clinical Characteristics

Clinical Description

The core phenotypes of *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMD) include paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), and hemiplegic migraine (HM). In addition, *PRRT2* pathogenic variants have been identified in other childhood-onset movement disorders and different types of seizures, including a small number of individuals who meet clinical criteria for paroxysmal nonkinesigenic dyskinesia (PNKD) [Liu et al 2012, Becker et al 2013, Liu et al 2013, Wang et al 2013, Delcourt et al 2015], paroxysmal exertion-induced dyskinesia [Liu et al 2012], and episodic ataxia [Gardiner et al 2012, Labate et al 2012, Delcourt et al 2015]. Thus, it is likely that the understanding of the spectrum of associated phenotypes is still evolving [Ebrahimi-Fakhari et al 2015].

Paroxysmal Kinesigenic Dyskinesia (PKD)

To date, the primary paroxysmal movement disorder of *PRRT2*-PxMD is PKD (see Suggestive Findings, PKD). Paroxysmal attacks are often characterized by dystonia, followed by choreoathetosis, and rarely ballism. Attacks often occur bilaterally. The arms are the most commonly involved, followed in decreasing order by involvement of the legs, trunk, face, and neck.

Onset of *PRRT2*-PKD is in childhood or adolescence (mean age: 10.3±4.9 [SD] years; range: 1-20 years) [Ebrahimi-Fakhari et al 2015].

The most common triggers are sudden voluntary movements, stress, being startled, intent to perform a voluntary movement, and sleep deprivation. While caffeine and alcohol are precipitating factors in a few affected individuals and attacks at rest are reported in approximately 2% of affected individuals, both of these triggers are more typical of paroxysmal nonkinesigenic dyskinesia (PNKD) than PKD.

A nonspecific aura precedes PKD attacks in about 10% of individuals. Reported aura symptoms include a crawling sensation in the affected limb, paresthesias, or nonspecific epigastric discomfort.

Attacks are usually brief – in the range of a few seconds – but in some individuals last five minutes or more.

The frequency of attacks is highly variable, ranging from 100 per day to one per week [Ebrahimi-Fakhari et al 2015].

Attacks tend to become less frequent with age and often respond well to anticonvulsants such as carbamazepine.

Benign Familial Infantile Epilepsy (BFIE)

The seizures are complex partial seizures or localization-related epilepsy (see Suggestive Findings, BFIE). Ictal patterns have been described as focal; onset has been reported in temporal, central, parietal, and occipital areas, with or without secondary generalization [Caraballo et al 2002].

Seizures may occur in clusters with multiple complex partial seizures per day. Less common are motor arrest, decreased responsiveness, and automatisms [Watanabe et al 1987]. Seizures rarely progress into status epilepticus. While respiratory depression can occur either during seizures or from medications including benzodiazepines, sudden unexpected death in epilepsy and long-term sequelae have not been reported.

In the vast majority of individuals the interictal EEG is unremarkable. In rare instances interictal focal epileptiform discharges may be seen, including bilateral centrotemporal spikes [Seo & You 2016], bilateral parietotemporal spikes [Torisu et al 2014], and unilateral frontocentral spikes [El Achkar et al 2017].

Epilepsy-related brain MRI abnormalities are not reported.

Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions (PKD/IC)

A seizure disorder in the form of BFIE is present in about 30% of *PRRT2*-PKD, leading to the diagnosis of PKD/IC. It is currently unknown how frequently BFIE evolves into PKD/IC.

Hemiplegic Migraine (HM)

HM falls within the classification of migraines with aura, characterized by an aura that localizes to the cerebral cortex. These auras comprise the following (in order of frequency):

- Visual symptoms or disturbance (e.g., scotoma, photopsia, or diplopia)
- Sensory loss (e.g., numbness or paresthesias)
- Dysphasia

HM additionally presents with motor symptoms in the form of some degree of hemiparesis.

Attack frequency often declines over time. Many affected individuals even report a complete remission during adulthood. Improvement during pregnancy has also been observed [Bruno et al 2004].

Genotype-Phenotype Correlations

No clear evidence for genotype-phenotype correlations exists for PKD, BFIE, PKD/IC, and HM, the four core *PRRT2*-PxMD phenotypes [Ebrahimi-Fakhari et al 2015]. Considerable variation in phenotype is seen both within and between families with the same pathogenic *PRRT2* variant.

Individuals with a 16p11.2 deletion who have *PRRT2*-PKD tend to have additional clinical features including developmental delay, intellectual disability, and/or autism spectrum disorder [Dale et al 2012, Silveira-Moriyama et al 2013, Weber et al 2013, Termsarasab et al 2014].

Individuals with biallelic *PRRT2* pathogenic variants tend to have a more severe phenotype that often includes intellectual disability, episodic ataxia, and different seizure types [Labate et al 2012, Delcourt et al 2015].

Penetrance

The penetrance for *PRRT2*-PKD has been estimated to be 60%-90% [van Vliet et al 2012]; thus, individuals with a known *PRRT2* pathogenic variant may be clinically unaffected.

The penetrance for *PRRT2*-BFIE and *PRRT2*-HM is unknown.

Nomenclature

Paroxysmal kinesigenic dyskinesia (PKD) was formerly known as paroxysmal kinesigenic choreoathetosis (PKC).

Benign familial infantile epilepsy (BFIE) is also known as benign familial infantile seizures (BFIS).

Paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC) was formerly known as infantile convulsions and choreoathetosis (ICCA).

Current recommendations are use of the designation *PRRT2*-PxMD for paroxysmal movement disorders associated with *PRRT2* [Marras et al 2016].

Prevalence

The *PRRT2*-associated paroxysmal movement disorders (*PRRT2*-PxMD) are rare.

Prevalence for PKD, the most common of the paroxysmal movement disorders (including both *PRRT2*-PxMD and PKD of unknown or secondary cause), has been estimated at 1:150,000 individuals [Ebrahimi-Fakhari et al 2015].

To date approximately 600 individuals with *PRRT2*-BFIE, 560 with *PRRT2*-PKD, and 210 with *PRRT2*-PKD/IC have been reported [Ebrahimi-Fakhari et al 2015].

The majority of these individuals are of Asian ethnicity from China and Japan, followed by individuals from North America and Europe.

PRRT2-PKD appears to be more common in males with about 1.5-fold more males reported than females.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PRRT2*.

Differential Diagnosis

PRRT2 pathogenic variants are found in the majority of individuals with paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile epilepsy (BFIE), and paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), confirming a common disease spectrum that had previously been suspected based on linkage analyses [Ebrahimi-Fakhari et al 2015].

Familial hemiplegic migraine, defined as the presence of at least one first-degree relative with identical attacks, has been associated with pathogenic variants in *CACNA1A* (designated FHM1), *ATP1A2* (FHM2), and *SCN1A* (FHM3).

Table 2. Genetic Disorders to Consider in the Differential Diagnosis of *PRRT2*-Associated Paroxysmal Movement Disorders

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/ *PRRT2*-PXMD	Distinguishing from *PRRT2*-PXMD
Paroxysmal nonkinesigenic dyskinesia (PNKD)	*PNKD*	AD	Paroxysmal dyskinesias	No kinesigenic trigger. Attacks: • Occur at rest, often precipitated by caffeine or alcohol; • Last longer (usually mins to hrs) & tend to occur less frequently (a few per day).
Paroxysmal exertion-induced dyskinesia (PED)	*SLC2A1*	AD (*SLC2A1*-PxMD)	Paroxysmal dyskinesias	Attacks: • Triggered by prolonged exertion or exercise for usually 5-15 min • Duration often in the range of mins (often up to 30 min)
GLUT1 deficiency syndrome	*SLC2A1*	AD	Paroxysmal dyskinesias	Includes a spectrum of manifestations: • PED • Classic phenotype w/infantile-onset epileptic encephalopathy • Atypical phenotypes w/out epilepsy incl mixed movement disorders & ID or adult-onset w/minimal symptoms
Episodic ataxia type 1, episodic ataxia type 2 (OMIM 108500)	*KCNA1* *CACNA1A* *SLC1A3*	AD	Paroxysmal ataxia	Brief intermittent episodes of ataxia of variable duration
ADCY5-related dyskinesia	*ADCY5*	AD	Paroxysmal dyskinesias	Attacks: • Involve the limbs, neck, and/or face • Often exacerbated by anxiety • Often also facial "twitches" Hypotonia & delayed motor milestones may be present.
Familial hemiplegic migraine	*CACNA1A* *ATP1A2* *SCN1A*	AD	Paroxysmal hemiplegia	Positive family history
Alternating hemiplegia of childhood (See *ATP1A3*-Related Neurologic Disorders.)	*ATP1A2* *ATP1A3*	AD	Paroxysmal hemiplegia and dystonia	• Attacks last longer. • Recurrent hemiplegia • Onset age <18 mos • Variable other transient neurologic findings • Progressive cognitive deficits
Wilson disease	*ATP7B*	AR	Dyskinesias	• Hepatic, neurologic, and/or psychiatric manifestations • Persistent movement disorder, often incl tremor or rigid dystonia

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Disorder	
			Overlapping w/ *PRRT2*-PXMD	Distinguishing from *PRRT2*-PXMD
Simple febrile seizures, complex febrile seizures, genetic epilepsy with febrile seizures plus (GEFS+) (see *SCN1A*-Related Seizure Disorders)	*SCN1A*, *SCN1B*, and others	AD or multifactorial	Seizures	• Seizures in the setting of fever • Often later onset of seizures
Benign (familial) neonatal infantile epilepsy (see *KCNQ2*-Related Disorders and *KCNQ3*-Related Disorders)	*KCNQ2*, *KCNQ3*	AD	Seizures	Earlier age of onset
Benign (familial) neonatal infantile epilepsy (OMIM: 607745)	*SCN2A*	AD	Seizures	Earlier age of onset

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; PED = paroxysmal exertion-induced dyskinesia

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *PRRT2*-associated paroxysmal movement disorder *(PRRT2*-PxMD), the following evaluations are recommended if they have not already been completed:

- Consultation with a neurologist who is a specialist in epilepsy and/or movement disorders
- Patients with PKD. Consider MRI to evaluate for other causes (e.g., hemorrhage, stroke, focal cortical dysplasia).
- Patients with atypical or ambiguous paroxysmal movements. Consider EEG to evaluate for possible seizures.
- Patients with seizures. Consider:
  - Basic laboratory tests to evaluate for other causes of seizures;
  - EEG to confirm normal background for age (capturing seizures on EEG may not be necessary if events are clinically consistent with seizures).
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

PKD

Attack frequency is reduced or prevented by treatment with low doses of antiepileptic drugs (AEDs).

- Carbamazepine is often effective. Note that doses lower than those used to treat epilepsy are usually sufficient.
- Other AEDs including phenytoin, valproate, oxcarbazepine, lamotrigine, levetiracetam, or topiramate may also be effective.

Avoiding stress, sleep deprivation, anxiety, and other triggers that increase the likelihood for PKD episodes can help prevent attacks and can lower attack frequency.

No other pharmacotherapies or non-pharmacologic treatments have been investigated systematically.

BFIE

Seizure frequency is decreased by therapeutic doses of AEDs. Although response to carbamazepine or oxcarbazepine has not been well studied, these tend to be the preferred AEDs given the known favorable response in PKD and anecdotal response in HM.

During seizures lasting longer than five minutes or seizure clusters, benzodiazepines including lorazepam, diazepam, or midazolam can be used. Anecdotally, however, the response to benzodiazepines in *PRRT2*-associated seizures is less robust.

In patients with BFIE, no specific interventions are known to decrease the risk of later developing PKD.

Prevention of Secondary Complications

PKD. Falls and interference with activities such as driving are potential secondary complications. Counseling is needed to prevent these potential secondary complications.

Surveillance

PKD. Individuals with PKD or PKD/IC can be monitored clinically every one to two years, particularly with respect to evaluating medication needs and dosing. More frequent visits may be necessary in individuals who have not achieved sufficient control of attacks or children who need weight-based adjustment of medication doses.

BFIE. Patients are monitored clinically for seizures and AEDs are adjusted accordingly. Depending on the agent used, medication serum levels – as well as liver enzymes, complete blood count, electrolytes, and vitamin D levels – should be monitored periodically. Repeat EEGs are only recommended when there is concern for subclinical seizures.

While heterozygous *PRRT2* pathogenic variants are not known to be associated with an increased risk for developmental abnormalities, any seizure disorder carries the theoretic increased risk of developmental delay; thus, early developmental surveillance is recommended.

Agents/Circumstances to Avoid

PKD. Stress, sleep deprivation, and anxiety are consistently reported as factors that increase the likelihood for PKD episodes; avoiding these or other triggers can help prevent attacks and can lower attack frequency.

BFIE. Treat fevers promptly.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Prenatal exposure to AEDs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Discussion of the risks and benefits of using a given AED during pregnancy should ideally take place prior to conception. Because of the fetal risk related to anticonvulsant therapy, women with mild manifestations of PKD may consider discontinuing anticonvulsant

therapy prior to or during pregnancy. Alternatively, transitioning to a lower-risk AED prior to pregnancy may be considered [Sarma et al 2016].

See MotherToBaby for more information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PRRT2-associated paroxysmal movement disorders (*PRRT2*-PxMD) caused by a heterozygous *PRRT2* pathogenic variant or, in rare cases, 16p11.2 recurrent deletion (that includes *PRRT2*), are inherited in an autosomal dominant manner. (See 16p11.2 Recurrent Deletion for genetic counseling information specific to the 16p11.2 recurrent deletion.)

In rare cases (typically associated with a more severe phenotype), *PRRT2*-PxMD may be associated with biallelic *PRRT2* pathogenic variants and inherited in an autosomal recessive manner [Ebrahimi-Fakhari et al 2015].

Autosomal Dominant Inheritance, *PRRT2* Pathogenic Variant – Risk to Family Members

Parents of a proband

- About 90% of individuals diagnosed with a *PRRT2*-PxMD have an affected parent or other family member [Ebrahimi-Fakhari et al 2015]. Reduced penetrance and variable expressivity lead to clinical variability within families.
- About 10% of individuals diagnosed with a *PRRT2*-PxMD have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *PRRT2 de novo* pathogenic variant.
- If the *PRRT2* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, to date no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with a *PRRT2*-PxMD may appear to be negative because of failure to recognize the disorder in family members particularly given that symptoms tend to become less frequent in adulthood. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to be heterozygous for the *PRRT2* pathogenic variant, the risk to the sibs is 50%. Reduced penetrance and variable expressivity are commonly observed, leading to phenotypic variability within families.
- If the *PRRT2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the empiric recurrence risk to sibs is approximately 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- The sibs of a proband with clinically unaffected parents are still at increased risk for *PRRT2*-PxMD because of the possibility of reduced penetrance in a parent and the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *PRRT2*-PxMD has a 50% chance of inheriting the *PRRT2* pathogenic variant. Reduced penetrance and variable expressivity are commonly observed, leading to phenotypic variability within families.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *PRRT2* pathogenic variant, his or her family members may be at risk.

Autosomal Recessive Inheritance, Biallelic *PRRT2* Pathogenic Variants – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry a single copy of a *PRRT2* pathogenic variant (a *de novo* pathogenic variant has not yet been documented to cause autosomal recessive *PRRT2*-PXMD).
- Heterozygotes may be affected with a *PRRT2*-PxMD or may be asymptomatic given reduced penetrance and clinical variability.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being a heterozygous carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes may be affected with a *PRRT2*-PxMD or may be asymptomatic given reduced penetrance and clinical variability.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous.

Carrier (Heterozygote) Detection

Testing for at-risk relatives requires prior identification of the *PRRT2* pathogenic variants in the family.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRRT2* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Bachmann-Strauss Dystonia & Parkinson Foundation**
  michaeljfox.org
- **Child Neurology Foundation**
  Phone: 888-417-3435
  Email: programs@childneurologyfoundation.org
  childneurologyfoundation.org
- **Dystonia Europe**
  Belgium
  Phone: 46 739 98 49 61
  Email: sec@dystonia-europe.org
  www.dystonia-europe.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PRRT2-Associated Paroxysmal Movement Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PRRT2	16p11.2	Proline-rich transmembrane protein 2	PRRT2 @ LOVD Movement Disorder Society Genetic mutation database (PRRT2)	PRRT2	PRRT2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PRRT2-Associated Paroxysmal Movement Disorders (View All in OMIM)

128200	EPISODIC KINESIGENIC DYSKINESIA 1; EKD1
602066	CONVULSIONS, FAMILIAL INFANTILE, WITH PAROXYSMAL CHOREOATHETOSIS; ICCA
605751	SEIZURES, BENIGN FAMILIAL INFANTILE, 2; BFIS2
611913	CHROMOSOME 16p11.2 DELETION SYNDROME, 593-KB
614386	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2

Gene structure. *PRRT2* consists of four exons encoding a 340-amino acid protein. Alternative splicing at the 3' terminus leads to six splice variants. Three different isoforms exist; nearly all known pathogenic variants in *PRRT2* locate to a conserved region present in all isoforms. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. The majority of affected individuals (~80%) have the same frameshift pathogenic variant, c.649dupC [Ebrahimi-Fakhari et al 2015].

A summary of reported pathogenic variants [Ebrahimi-Fakhari et al 2015] is available through the Movement Disorder Society Genetic Mutation Database (see Table A).

Table 3. *PRRT2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.649dupC	p.Arg217ProfsTer8	NM_145239.2 NP_660282.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. PRRT2 is predicted to contain a proline-rich domain within its N-terminal extracellular region and two putative transmembrane domains at the C-terminal end. PRRT2 is thus predicted to be a membrane-bound protein.

Abnormal gene product. Most reported pathogenic variants in *PRRT2*, including the common c.649dupC variant, lead to unstable messenger RNA or a truncated protein product that undergoes rapid degradation [Ebrahimi-Fakhari et al 2015]. The mechanism is thus consistent with a loss of function of PRRT2.

Available evidence in cell culture models suggests that PRRT2 is involved in regulating synaptic vesicle release [Valente et al 2016]. Loss of *PRRT2* in cultured cells and transgenic mice leads to aberrant synaptic transmission [Valente et al 2016, Michetti et al 2017, Tan et al 2018].

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Suggested Reading (Historical References)

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Chapter Notes

Author Notes

The Movement Disorder Society Genetic mutation database (MDSGene) provides a comprehensive, systematic overview of published data on movement disorder patients including patients with PKD. Please refer to www.mdsgene.org.

Recommendations on the Nomenclature of Genetic Movement Disorders are provided by the Task Force on the Nomenclature of Genetic Movement Disorders from the International Parkinson and Movement Disorders Society. Current recommendations are provided in Marras et al [2016].

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