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NLM Citation: Yang K, Quiroz V, Ebrahimi-Fakhari D. *PRRT2*-Related Disorder. 2018 Jan 11 [Updated 2024 Jul 4]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

PRRT2-Related Disorder

Kathryn Yang, MD, FRCPC,[1] Vincente Quiroz, MD,[1] and Darius Ebrahimi-Fakhari, MD, PhD[1]

Created: January 11, 2018; Updated: July 4, 2024.

Summary

Clinical characteristics

PRRT2-related disorder, caused by heterozygous pathogenic variants in the gene *PRRT2* (associated with aberrant synaptic transmission), is characterized by three core episodic neurologic phenotypes: epilepsy, movement disorder, and migraine. Age at onset and phenotypes range from neonatal/infantile (self-limited [familial] infantile epilepsy), to childhood (childhood absence epilepsy), to adolescence to adulthood (paroxysmal kinesigenic dyskinesia [PKD] or migraine). As individuals with *PRRT2*-related disorder age, they may exhibit one of more of these core phenotypes in various combinations, either concurrently or sequentially. Additionally, family members with the same pathogenic *PRRT2* variant may display different core phenotypes.

Diagnosis/testing

The diagnosis of *PRRT2*-related disorder is established in a proband with suggestive findings and a heterozygous *PRRT2* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Neurologists experienced in epilepsy and movement disorders can tailor treatment based on the primary neurologic manifestations or movement disorder phenomenology, taking into consideration degree of functional impairment, potential comorbidities, and potential medication interactions, if applicable.

Surveillance: Monitoring existing manifestations, the individual's response to supportive care, and the emergence of new manifestations requires regularly scheduled follow up with the treating neurologist as well as educators and social services.

Agents/circumstances to avoid: For self-limited (familial) infantile epilepsy, treat fevers promptly. For PKD, avoid known triggers (stress, sleep deprivation, and anxiety) or other triggers to help prevent attacks and lower attack

Author Affiliation: 1 Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; Email: kathryn.yang@childrens.harvard.edu; Email: vicente.quiroz@childrens.harvard.edu; Email: darius.ebrahimi-fakhari@childrens.harvard.edu.

frequency. For migraine, use triptans and dihydroergotamine with caution due to the increased risk of ischemic vascular events.

Pregnancy management: Because prenatal exposure to anti-seizure medications (ASMs) 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 ASM during pregnancy should ideally take place prior to conception.

Genetic counseling

PRRT2-related disorder is typically caused by a heterozygous pathogenic variant and inherited in an autosomal dominant manner. (Biallelic *PRRT2* pathogenic variants, observed in <1% of individuals with *PRRT2* pathogenic variants, are most commonly associated with a more severe phenotype.) About 90% of individuals diagnosed with *PRRT2*-related disorder have an affected parent or other family member. Reduced penetrance and variable expressivity are commonly observed, leading to considerable phenotypic variability among heterozygous family members. Each child of an individual with a heterozygous *PRRT2* pathogenic variant has a 50% chance of inheriting the pathogenic variant. Once the *PRRT2* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

PRRT2-related disorder (*PRRT2*-RD) **should be considered** in individuals with any one of the following core phenotypes and/or in individuals with a paroxysmal movement disorder and a positive family history of any of the core phenotypes.

Self-Limited (Familial) Infantile Epilepsy (SeLIE)

SeLIE is characterized by the following clinical and supportive findings [Millevert et al 2023].

- **Clinical findings.** Most often focal-onset motor seizures ± impaired awareness & focal to bilateral tonic-clonic seizures with the following:
  - Onset in first year of life (usually age 4-7 months)
  - Spontaneous or in context of fever
  - Occurring in clusters of multiple brief seizures per day: on average up to eight to ten seizures per day every two to three hours
  - Excellent response to anti-seizure medications
  - Resolution by age two years
- **Supportive findings**
  - Normal development & developmental outcome
  - Normal neurologic exam
  - Normal interictal EEG (with sporadic focal epileptiform activity)
  - Normal brain MRI

Paroxysmal Kinesigenic Dyskinesia (PKD)

PKD is characterized by the following clinical and supportive findings [Bruno et al 2004]:

- **Clinical findings.** Sudden attacks of unilateral or bilateral involuntary movements (i.e., dyskinesias that can include a combination of dystonia, chorea, ballism, or athetosis) and the following:
  - Onset between ages 1-18 years

- A kinesigenic trigger (e.g., sudden voluntary movements, intention to move, or acceleration of movement)
- An aura preceding attacks (10% of persons)
- Short duration (typically <1 min)
- High frequency (can be as many as 100 times per day)
- No loss of consciousness or pain
- Prevention or control w/carbamazepine

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

Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions (PKD/IC)

PKD/IC is characterized by symptoms fulfilling the below criteria:

- In first year of life: seizures meeting criteria for SeLIE
- In childhood or adolescence: paroxysmal movements meeting criteria for PKD

Hemiplegic Migraine (HM)

HM, as defined by the International Classification of Headache Disorders, 3rd edition [Headache Classification Committee of the International Headache Society (IHS) 2018] (full text), is characterized by the following clinical and supportive findings:

- **Clinical findings.** Transient motor weakness or hemiparesis associated with the following:
  - Average age of onset 12-17 years
  - Migraine during or after motor aura
  - Presence of other manifestations incl visual, sensory, and/or speech impairment
  - Triggered by stress, anxiety, light, and/or heat
  - Frequency from a few per week to one per month
  - Duration can be prolonged >72 hours
- **Supportive findings**
  - Normal neurologic exam between attacks
  - Normal brain MRI

Family history is consistent with autosomal dominant inheritance (e.g., males and females in multiple generations with the same or different *PRRT2*-related features). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *PRRT2*-related disorder is established in a proband with suggestive findings and a heterozygous *PRRT2* pathogenic variant (or likely pathogenic variant) identified by molecular genetic testing [Chen et al 2011, Wang et al 2011, Ebrahimi-Fakhari et al 2015] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *PRRT2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

An epilepsy, movement disorder (i.e., dystonia or ataxia), or hemiplegic migraine multigene panel that includes *PRRT2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *PRRT2* pathogenic variants reported (i.e., nonsense, missense, or deletions) are within the coding regions of the gene and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *PRRT2*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PRRT2	Sequence analysis [3]	99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from Ebrahimi-Fakhari et al [2015] and the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

PRRT2-related disorder encompasses a spectrum of three core phenotypes: epilepsy, paroxysmal movement disorders, and migraine (see Table 2). As individuals with *PRRT2*-related disorder age, they may exhibit one of more of these core phenotypes in various combinations, either concurrently or sequentially. For instance, an individual initially presenting with self-limiting infantile epilepsy may later develop paroxysmal kinesigenic dyskinesia. Intrafamilial variability is also common, meaning that different combinations of the core phenotypes may appear among family members who are heterozygous for the same *PRRT2* pathogenic variant.

To date, more than 1,500 individuals have been identified with a heterozygous *PRRT2* pathogenic variant [Ebrahimi-Fakhari et al 2015]. The following description of the phenotypic features associated with *PRRT2*-related disorder is based on this report (see Table 3).

Table 2. *PRRT2*-Related Disorder: Frequency of Select Features

Clinical Category	Typical Age of Presentation	Phenotype [1]	Frequency of Phenotype
Epilepsy	Neonatal/infantile	**Self-limited (familial) infantile epilepsy** [2]	+++
	Childhood	Childhood absence epilepsy [3]	+
Movement disorder	Adolescence to adulthood	**Paroxysmal kinesigenic dyskinesia** [2]	+++
		Paroxysmal kinesigenic dyskinesia w/infantile convulsions [2]	+++
		Episodic ataxia [4]	+
		Paroxysmal torticollis [5]	+
		Paroxysmal hypnogenic dyskinesia [6]	+
		Paroxysmal non-kinesigenic dyskinesia	+
		Paroxysmal exercise-induced dyskinesia	+
Migraine		**Hemiplegic migraine** [7]	++
		Migraine w/ or w/o aura	+

+ = rare; ++ = infrequent; +++ = frequent

1. The core phenotypes of self-limited (familial) infantile epilepsy, paroxysmal kinesigenic dyskinesia (PKD), PKD with infantile convulsions, and hemiplegic migraine (which are more commonly seen in *PRRT2*-related disorder than the other phenotypes listed here) are in bold type.

2. Ebrahimi-Fakhari et al [2015]

3. Méneret et al [2013]

4. Gardiner et al [2012]

5. Dale et al [2012]

6. Liu et al [2016]

7. Riant et al [2022]

Epilepsy

Self-limited (familial) infantile epilepsy (SeLIE). Seizures are primarily focal-onset motor seizures with or without impaired awareness and focal to bilateral tonic-clonic seizures that occur independent of a fever. These

seizures are brief and frequently occur in clusters, with multiple clusters per day. Ictal EEGs often report onset originating in temporal, central, parietal, or occipital areas, with or without secondary generalization [Caraballo et al 2002].

Less common seizure semiologies include motor arrest, decreased responsiveness, and automatisms [Watanabe et al 1987].

Seizures rarely progress to status epilepticus. While respiratory depression can occur either during seizures or from medications such as benzodiazepines, sudden unexpected death in epilepsy (SUDEP) and long-term sequelae have not been reported.

The interictal EEG for most individuals is unremarkable. Nevertheless, in rare instances interictal focal epileptiform discharges may be detected, including bilateral centrotemporal spikes [Seo & You 2016], bilateral parietotemporal spikes [Torisu et al 2014], and unilateral frontocentral spikes [El Achkar et al 2017].

Prognosis is favorable. Seizures generally show a complete response to first-line anti-seizure medications (ASMs). In most children seizures remit by age two years and developmental outcomes are normal.

Movement Disorders

Paroxysmal kinesigenic dyskinesia (PKD). To date, the primary paroxysmal movement disorder seen in *PRRT2*-related disorders is PKD. Paroxysmal attacks are often characterized by dystonia, choreoathetosis, and/or ballism. These episodes are stereotyped, i.e., typically bilateral, most commonly involving the arms, followed in decreasing order by the legs, trunk, face, and neck.

Onset of *PRRT2*-related PKD is in childhood or adolescence (mean age: 10.3±4.9 years; range: age 1-20 years). It appears to be about 1.5-fold more common in males than females [Ebrahimi-Fakhari et al 2015].

Dyskinesias in *PRRT2*-related PKD are often provoked by kinesigenic triggers such as sudden voluntary movements, intention to move, and/or accelerations in movement. However, up to 40% of individuals can experience non-kinesigenic triggers, such as anxiety, startle, sleep deprivation, and/or sustained exercise, suggesting an overlap with other subtypes of paroxysmal dyskinesias, including a small number of individuals who meet clinical criteria for paroxysmal non-kinesigenic dyskinesia [Liu et al 2012, Becker et al 2013, Liu et al 2013, Wang et al 2013, Delcourt et al 2015], paroxysmal exercise-induced dyskinesia [Liu et al 2012], paroxysmal torticollis [Dale et al 2012], paroxysmal hypnogenic dyskinesia [Liu et al 2016],and episodic ataxia [Gardiner et al 2012, Labate et al 2012, Delcourt et al 2015]. Caffeine and alcohol are also reported precipitating factors.

In about 10% of affected individuals, PKD attacks are preceded by a nonspecific aura including a crawling sensation in the affected limb, paresthesias, or nonspecific epigastric discomfort.

Attacks are usually brief – in the range of a few seconds – but can last five or more minutes in some individuals. Episodes often respond well to ASMs, most commonly carbamazepine (see Management, Treatment of Manifestations).

The frequency of attacks, which can range from 100 per day to one per week, tends to decrease with age and may resolve completely in mid- or late adulthood [Ebrahimi-Fakhari et al 2015]. Improvement during pregnancy has also been observed [Bruno et al 2004].

Paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC). Approximately 30% of individuals with PKD have a history of SeLIE leading to the diagnosis of PKD/IC. In some individuals seizures can also be seen in other contexts such as childhood febrile seizures or generalized seizures in adulthood. While it is unknown to date how frequently SeLIE evolves into PKD/IC, paroxysmal movement disorders in these individuals typically begin in early childhood.

Migraine

Hemiplegic migraine (HM) falls within the classification of migraines with aura subtype related to cortical spreading depression. Episodes are characterized by a transient motor manifestation, typically some degree of hemiparesis.

Migraine with or without aura. Other types of auras comprise the following (in order of frequency):

- Visual symptoms or disturbance (e.g., scotoma, photopsia, or diplopia)
- Sensory loss (e.g., numbness or paresthesia)
- Speech symptoms (e.g., dysarthria)

Less commonly, pathogenic *PRRT2* variants are associated with migraine with or without aura.

Intrafamilial and Interfamilial Variability

Considerable variability in phenotype is seen both within and between families with the same *PRRT2* pathogenic variant.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified in *PRRT2*-related disorder [Ebrahimi-Fakhari et al 2015].

Penetrance

The penetrance of *PRRT2*-related disorder ranges from 50% to 90% [van Vliet et al 2012]; thus, individuals heterozygous for a known *PRRT2* pathogenic variant may be clinically unaffected.

Among the core phenotypes, penetrance is estimated to be 75%-95% for *PRRT2*-related SeLIE, 50%-61% for *PRRT2*-related PKD, and up to 87% for *PRRT2*-related HM [Riant et al 2022].

Nomenclature

Self-limited (familial) infantile epilepsy (SeLIE) was formerly known as benign familial infantile epilepsy (BFIE) or benign familial infantile seizures (BFIS). In the 2017 International League Against Epilepsy (ILAE) classification, the term "benign" was updated to "self-limited", emphasizing the notion that seizures typically resolved during early infancy and were associated with favorable developmental outcome [Scheffer et al 2017].

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

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

In the International Parkinson and Movement Disorder Society Task Force Recommendations for Nomenclature of Genetic Movement Disorders, paroxysmal (Px) movement disorders (MD) associated with *PRRT2* pathogenic variants are designated *PRRT2*-PxMD [Marras et al 2016, Lange et al 2022].

Prevalence

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

To date, more than 600 individuals with *PRRT2*-related SeLIE, more than 550 individuals with *PRRT2*-related PKD, and more than 200 individuals with *PRRT2*-related PKD/IC have been reported [Ebrahimi-Fakhari et al 2015].

Genetically Related (Allelic) Disorders

The **16p11.2 recurrent deletion** is a contiguous gene deletion involving *PRRT2* and adjacent genes including *KCTD13* and *TBX6*, with most deletions occurring *de novo*. The 16p11.2 recurrent deletion phenotype is characterized by developmental delay, often affecting motor and speech domains. Intellectual disability, autistic features, motor coordination difficulties, and obesity are common. Other manifestations may include sleep disorders, the presence of vertebral anomalies, hearing impairment, cardiac malformations, and congenital anomalies of the kidneys and urinary tract. Some individuals with a 16p11.2 deletion have epilepsy. Paroxysmal dyskinesia is uncommon, reported in a small subset only [Moufawad El Achkar et al 2022, Chung et al 2024, Vos et al 2024].

Biallelic *PRRT2* pathogenic variants, observed in <1% of individuals with *PRRT2* pathogenic variants, are typically associated with a more severe phenotype. Neurodevelopmental manifestations span a spectrum from normal development to intellectual disability, learning disabilities, autism spectrum disorder, attention-deficit disorder, and seizures. From a movement disorders standpoint, individuals with biallelic pathogenic *PRRT2* variants often present with longer episodes of ataxia (hours to months) or severe paroxysmal kinesigenic and nonkinesigenic dyskinesia. Reported brain MRI findings include cerebellar atrophy in some [Labate et al 2012, Delcourt et al 2015, Ebrahimi-Fakhari et al 2015, Martorell et al 2022].

Differential Diagnosis

PRRT2 pathogenic variants are found in the majority of individuals with paroxysmal kinesigenic dyskinesia (PKD), up to 70% of individuals with self-limited (familial) infantile epilepsy (SeLIE), and almost all individuals with PKD with infantile convulsions (PKD/IC) [Ebrahimi-Fakhari et al 2015]. It is proposed to be the fourth most common gene associated with familial hemiplegic migraines [Riant et al 2022]. *PRRT2* pathogenic variants are rarely identified in individuals with childhood absence epilepsy [Méneret et al 2013], episodic ataxia [Gardiner et al 2012], and paroxysmal torticollis [Dale et al 2012]. *PRRT2*-related paroxysmal hypnogenic dyskinesia has been reported in only two individuals to date [Liu et al 2016].

Other genes known to be associated with these phenotypes are listed in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of *PRRT2*-Related Disorder

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/ *PRRT2*-related disorder	Distinguishing from *PRRT2*-related disorder
ADCY5	*ADCY5*-related dyskinesia	AD (AR) [1]	Paroxysmal dyskinesias	Attacks: • Involve limbs, neck, &/or face • Often w/perioral dyskinesia ("facial twitches") • Dyskinesias often persist during sleep (nocturnal dyskinesias) Hypotonia & DD may be present.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/ *PRRT2*-related disorder	Distinguishing from *PRRT2*-related disorder
ATP1A2	Alternating hemiplegia of childhood (OMIM 104290)	AD	Paroxysmal hemiplegia & dystonia	• Attacks last longer • Recurrent hemiplegia • Onset age <18 mos • Variable other transient neurologic findings • Progressive cognitive deficits
	Familial hemiplegic migraine	AD	Paroxysmal hemiplegia	
ATP1A3	Alternating hemiplegia of childhood (See *ATP1A3*-Related Neurologic Disorders.)	AD	Paroxysmal hemiplegia & dystonia	• Attacks last longer • Recurrent hemiplegia • Onset age <18 mos • Variable other transient neurologic findings • Progressive cognitive deficits
CACNA1A	Episodic ataxia type 2 (See Hereditary Ataxia Overview.)	AD	Paroxysmal ataxia	• Brief intermittent episodes of ataxia of variable duration • Paroxysmal tonic upgaze or nystagmus may be present.
	Familial hemiplegic migraine	AD	Paroxysmal hemiplegia	
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency	AR	Paroxysmal dystonia	• Onset of attacks before age 10 yrs • Attacks triggered by high metabolic demand • Most individuals have associated DD & acute episodes of encephalopathy. • Isolated presentations of paroxysmal exercise-induced dyskinesias are rare.
GCH1	GTP cyclohydrolase 1-deficient dopa-responsive dystonia	AD	Paroxysmal dystonia	• Initially dystonia may be paroxysmal before becoming permanent. • Exhibit diurnal variation (dystonia worse in evening) • Characterized by focal dystonia w/ascending pattern of progression • Favorable response to levodopa
KCNA1	Episodic ataxia type 1	AD	Paroxysmal ataxia	Attacks: • Onset before age 20 yrs • Brief intermittent episodes of ataxia, myokymia, & dysarthria of variable duration • Can be assoc w/comorbidities such as hyperthermia & seizures
KCNMA1	Paroxysmal non-kinesigenic dyskinesia (OMIM 609446)	AD	Paroxysmal dyskinesias	Attacks: • Triggered by alcohol, fatigue, or stress • Assoc w/DD & generalized epilepsy
KCNQ2	*KCNQ2*-related SeLNE (See *KCNQ2*-Related Disorders.)	AD	Seizures	Earlier age of onset

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/ *PRRT2*-related disorder	Distinguishing from *PRRT2*-related disorder
KCNQ3	*KCNQ3*-related SeLNE & *KCNQ3*-related SeLIE (See *KCNQ3*-Related Disorders.)	AD	Seizures	Earlier age of onset
PNKD	Familial paroxysmal non-kinesigenic dyskinesia	AD	Paroxysmal dyskinesias	Attacks: • Occur at rest, in absence of kinesigenic trigger • Are often precipitated by caffeine or alcohol • Last longer (usually mins to hrs) & tend to occur less frequently (a few per day)
SCN1A	Familial hemiplegic migraine	AD	Paroxysmal hemiplegia	
SCN1A *SCN1B* & others	Simple febrile seizures, complex febrile seizures, generalized epilepsy w/febrile seizures plus (GEFS+) (See *SCN1A* Seizure Disorders.)	AD	Seizures	• Seizures in setting of fever • Often later onset of seizures
SCN2A	*SCN2A*-related SeLNE & *SCN2A*-related SeLIE (OMIM 607745)	AD	Seizures	Earlier age of onset
SCN8A	*SCN8A*-related epilepsy &/or neurodevelopmental disorders	AD	Paroxysmal dyskinesia	• Can be assoc w/ID, comorbid ASD or ADHD, ataxia, hypotonia, or history of seizures • Attacks are characterized by orobuccolingual dyskinesia, choreiform movements, tremors, or action-induced myoclonus.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/ *PRRT2*-related disorder	Distinguishing from *PRRT2*-related disorder
SLC2A1	Paroxysmal exercise-induced dyskinesia & epilepsy (See Glucose Transporter Type 1 Deficiency Syndrome.)	AD	Paroxysmal dyskinesias	Attacks: • Triggered by prolonged exertion or exercise for usually 5-15 min • Duration often in range of mins (often up to 30 min)
	Classic glucose transporter type 1 deficiency syndrome	AD (AR) [2]	Paroxysmal dyskinesias	• Attacks are assoc w/gait abnormalities, incl ataxia, spastic, ataxic-spastic, & dystonic gait, also known as "criss-cross gait." • Includes a spectrum of manifestations, e.g., paroxysmal exercise-induced dyskinesia, classic phenotype w/infantile-onset epileptic encephalopathy, & atypical phenotypes w/o epilepsy incl mixed movement disorders & ID or adult onset w/minimal manifestations • Of note, the ketogenic diet is highly effective in controlling seizures & improving gait disturbance.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; SeLNE = self-limited (familial) neonatal epilepsy; SeLIE = self-limited (familial) infantile epilepsy
1. ADCY5-related dyskinesia is typically inherited in an autosomal dominant manner. Autosomal recessive inheritance has been reported in two families.
2. Glucose transporter type 1 deficiency syndrome is most commonly inherited in an autosomal dominant manner; two families have demonstrated autosomal recessive inheritance (one of the families was consanguineous).

Management

No clinical practice guidelines for *PRRT2*-related disorder have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PRRT2*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *PRRT2*-Related Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	History & physical exam by neurologist experienced in epilepsy & movement disorders	Assess for: • Leading phenomenology of movement disorder (e.g., dystonia, chorea). Obtain videos of episodes where possible. • Time course & fluctuations in manifestations • Triggers for episodic manifestations • Baseline assessment of tone (e.g., hypotonia, spasticity, rigidity) • Functional impairment incl speech & swallowing
	Ancillary testing	Consider the following based on leading symptomatology: • EEG if concern for seizures • Brain MRI if atypical exam findings • Treatment trial w/carbamazepine
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *PRRT2*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support

MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *PRRT2*-related disorder. Therapeutic options are tailored depending on the primary neurologic manifestations or movement disorder phenomenology (see Table 5). Decisions regarding treatment should take into consideration degree of functional impairment, potential comorbidities, and potential medication interactions, if applicable.

Table 5. *PRRT2*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Seizures	Sodium channel blockers (carbamazepine or oxcarbazepine)	• Seizures in SeLIE most often also respond to other first-line ASMs (incl levetiracetam). ASMs should be chosen based on best risk vs benefit profile. • A seizure rescue plan for prolonged seizures is recommended.
Paroxysmal dyskinesias	Sodium channel blockers (carbamazepine or oxcarbazepine)	Doses of 100 mg/day or less have been effective in most persons w/ *PRRT2*-related PKD.
Hemiplegic events	Sodium channel blockers (carbamazepine or oxcarbazepine)	• Anecdotal evidence only • Acetazolamide or medications for typical migraine w/aura can be considered.

ASMs = anti-seizure medications; PKD = paroxysmal kinesigenic dyskinesia; SeLIE = self-limited (familial) infantile epilepsy

Self-limited (familial) infantile epilepsy (SeLIE). In most individuals, seizures respond well to conventional anti-seizure medications (ASMs) at therapeutic doses [Ebrahimi-Fakhari et al 2015]. While the efficacy of carbamazepine or oxcarbazepine specifically lacks extensive study, these tend to be the preferred ASMs given their effectiveness for the core phenotypes of *PRRT2*-related paroxysmal kinesigenic dyskinesia (PKD) and, anecdotally, *PRRT2*-related hemiplegic migraine. Clinical experience of the authors suggests that seizures in SeLIE respond to first-line ASMs, including medications that reach a therapeutic level quickly, such as

phenobarbital in neonates and levetiracetam or lacosamide in infants [D Ebrahimi-Fakhari, personal observations].

Rescue medications (commonly benzodiazepines including lorazepam, diazepam, or midazolam) are crucial during seizures that last more than five minutes or seizure clusters.

Currently, no proven interventions reduce the risk of individuals with SeLIE to develop PKD later in life. Management strategies primarily focus on seizure control and monitoring developmental progress.

Paroxysmal kinesigenic dyskinesia (PKD). Management involves low-dose ASMs that reduce attack frequency and minimize secondary complications such as falls and disruptions to activities such as driving.

Sodium channel blockers including carbamazepine or oxcarbazepine remain the first-line treatment, unless contraindicated. Notably, the required doses are generally lower than those used to treat epilepsy, with reported control at doses around 100 mg/day in most individuals.

Other ASMs including levetiracetam, lacosamide, phenytoin, valproate, lamotrigine, or topiramate may also be effective and offer alternatives when first-line options are unsuitable.

Lifestyle modifications, including avoiding known triggers such as stress, sleep deprivation, or anxiety, can reduce the frequency of PKD episodes.

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

Hemiplegic migraine (HM). Anecdotal evidence suggests that low doses of sodium channel blockers, such as carbamazepine, are effective in preventing attacks. Otherwise, there are no specific treatments for HM, and the use of medications for typical migraines with aura can be considered [Suzuki-Muromoto et al 2020].

Surveillance

Monitoring existing manifestations, the individual's response to supportive care, and the emergence of new manifestations requires regularly scheduled follow up with the treating neurologist as well as educators and social services. The evaluations summarized in Table 6 are recommended.

Table 6. *PRRT2*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Seizures	• Neurologic exam & baseline EEG • Imaging & further workup per treating neurologist	Per treating neurologist
Paroxysmal dyskinesias	• Neurologic exam • Imaging & further workup per treating neurologist	Once every 1-2 yrs
Hemiplegic events		On 1st occurrence & then 1x/yr
Development (young children)	Monitor developmental progress & educational needs.	At each visit
Cognition (older children/adults)		
Family/Community	Assess family need for social work support or follow-up genetic counseling if new questions arise (e.g., family planning).	

SeLIE. Individuals are monitored clinically for seizures; ASMs are adjusted accordingly. The following are recommended depending on the ASM used: regular assessments of blood concentrations of medications, electrolytes, and vitamin D as well as liver enzymes and complete blood counts. Repeat EEGs are advised when subclinical seizures are suspected.

The response to ASMs can inform decisions on medication weaning. Notably, seizures in SeLIE typically subside by age two years, thus reducing the need for prolonged ASM use beyond this age.

Although heterozygous *PRRT2* pathogenic variants are not known to be associated with an increased risk for developmental abnormalities, seizure disorders in general have a theoretic increased risk of developmental delay. Thus, monitoring early developmental progress is strongly advised.

Paroxysmal dyskinesias. Individuals with PKD or PKD with infantile convulsions (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 whose medication doses are weight based.

Hemiplegic events. Individuals should be monitored clinically once a year. More frequent assessments may be needed for individuals who have not achieved sufficient control of attacks and/or whose medication doses are weight based.

Agents/Circumstances to Avoid

SeLIE. Treat fevers promptly.

PKD. Avoid stress, sleep deprivation, and anxiety (consistently reported as factors that increase the likelihood for PKD episodes) and other triggers to help prevent attacks and lower attack frequency.

HM. Use triptans and dihydroergotamine with caution due to their associated increased risk of ischemic vascular events.

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 anti-seizure medications (ASMs) 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 ASM during pregnancy should ideally take place prior to conception. Because of the fetal risk related to use of ASMs, women with mild manifestations of *PRRT2*-related disorder may consider discontinuing ASMs prior to or during pregnancy. Alternatively, transitioning to a lower-risk ASM 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-related disorder is typically caused by a heterozygous pathogenic variant and inherited in an autosomal dominant manner.

Note: Biallelic *PRRT2* pathogenic variants, observed in <1% of individuals with *PRRT2* pathogenic variants, are typically associated with a more severe phenotype (see Genetically Related Disorders). Risk to family members of a proband with biallelic *PRRT2* pathogenic variants is not discussed in this section.

Risk to Family Members

Parents of a proband

- About 90% of individuals diagnosed with *PRRT2*-related disorder 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 *PRRT2*-related disorder have the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with a *PRRT2*-related disorder may appear to be negative because of reduced penetrance, variable expressivity, or 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 demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/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 considerable phenotypic variability among heterozygous family members (see Penetrance).
- If the *PRRT2* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is approximately 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PRRT2* pathogenic variant but are clinically unaffected, sibs of the proband are still presumed to be at increased risk for *PRRT2* because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband. Each child of an individual with a heterozygous *PRRT2* pathogenic variant has a 50% chance of inheriting the pathogenic variant.

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, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- 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.

Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic 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 and preimplantation genetic 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.

- **National Organization for Rare Disorders (NORD)**
  PRRT2-Associated Paroxysmal Movement Disorders
- **Child Neurology Foundation**
  Phone: 888-417-3435
  Email: programs@childneurologyfoundation.org
  childneurologyfoundation.org
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  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-Related Disorder: 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-Related Disorder (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
614386	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2

Molecular Pathogenesis

PRRT2 encodes proline-rich transmembrane protein 2 (PRRT2), a membrane-bound protein that interacts with SNARE complexes that are integral to neurotransmitter release and help modulate the availability and activity of voltage-dependent sodium channels. Loss of PRRT2 function in cultured cells and transgenic mice leads to aberrant synaptic transmission, underscoring the essential role of PRRT2 in synaptic dynamics [Valente et al 2016, Michetti et al 2017, Tan et al 2018, Lu et al 2021]. Disruptions in this function can potentially trigger episodic neurologic disorders [Valente et al 2016, Lu et al 2021].

Studies have demonstrated that PRRT2 deficiency sensitizes the cerebellar cortex to spreading depolarization, thereby increasing the excitability of cerebellar neurons. This heightened excitability can disrupt normal neuronal firing patterns in deep cerebellar nuclei crucial for motor control. In mice lacking *Prrt2*, these disruptions are tightly linked to the onset and persistence of dyskinetic movements characteristic of conditions such as *PRRT2*-related paroxysmal kinesigenic dyskinesia [Lu et al 2021].

Mechanism of disease causation. Most reported *PRRT2* pathogenic variants, 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 (via haploinsufficiency).

***PRRT2*-specific laboratory technical considerations.** The majority (70%-80%) of affected individuals have the frameshift variant c.649dupC [Ebrahimi-Fakhari et al 2015].

Table 7. *PRRT2* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_145239.2 NP_660282.2	c.649dupC	p.Arg217ProfsTer8	The majority (70%-80%) of affected persons have this frameshift variant [Ebrahimi-Fakhari et al 2015].

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.

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 paroxysmal kinesigenic dyskinesia.

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] and Lange et al [2022].

Acknowledgments

The authors are grateful to the many patients and families who support research on *PRRT2*. The authors also thank Dr Christelle Moufawad El Achkar and Dr Christine Klein for contributions to an earlier version of this chapter.

Author History

Darius Ebrahimi-Fakhari, MD, PhD (2018-present)
Christine Klein, MD; University of Lübeck (2018-2024)
Christelle Moufawad El Achkar, MD; Harvard Medical School (2018-2024)
Vincente Quiroz, MD (2024-present)
Kathryn Yang, MD, FRCPC (2024-present)

Revision History

- 4 July 2024 (bp) Comprehensive update posted live
- 11 January 2018 (bp) Review posted live
- 16 August 2017 (def) Original submission

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