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NLM Citation: Spacey S, Adams P. Familial Paroxysmal Kinesigenic Dyskinesia – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2005 Jun 24 [Updated 2013 Jun 27]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Familial Paroxysmal Kinesigenic Dyskinesia – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Paroxysmal Kinesigenic Choreoathetosis, Paroxysmal Kinesigenic Dyskinesia

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Created: June 24, 2005; Updated: June 27, 2013.

Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Familial paroxysmal kinesigenic dyskinesia (referred to as familial PKD in this entry) is characterized by unilateral or bilateral involuntary movements precipitated by other sudden movements such as standing up from a sitting position, being startled, or changes in velocity; attacks include combinations of dystonia, choreoathetosis, and ballism, are sometimes preceded by an aura, and do not involve loss of consciousness. Attacks can be as frequent as 100 per day to as few as one per month. Attacks are usually a few seconds to five minutes in duration but can last several hours. Age of onset, severity and combinations of symptoms vary. Age of onset, typically in childhood and adolescence, ranges from four months to 57 years. The phenotype of PKD can include benign familial infantile epilepsy (BFIE), infantile convulsions and choreoathetosis (ICCA), hemiplegic migraine, migraine with and without aura, and episodic ataxia. Familial PKD is predominantly seen in males.

Diagnosis/testing

The diagnosis of familial PKD is based on the clinical findings of attacks of dystonia, chorea, ballismus, or athetosis triggered by sudden movements that occur many times per day and can be prevented or reduced in frequency by phenytoin or carbamezepine. Heterozygous pathogenic variants in *PRRT2* have been reported as causative of a subset of cases of familial PKD. The other gene(s) associated with PKD have not been identified.

Management

Treatment of manifestations: Attack frequency is reduced or prevented by the anticonvulsants phenytoin or carbamezepine, typically given at lower doses than are used to treat epilepsy. Other effective anticonvulsants include oxcarbazepine, ethosuximide, and lamotrigine.

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Genetic counseling

Familial PKD is inherited in an autosomal dominant manner. More than 90% of individuals with familial PKD have an affected parent.

The proportion of cases caused by *de novo* pathogenic variants is unknown. Offspring of affected individuals with familial PKD have a 50% chance of inheriting the pathogenic variant. Because familial PKD demonstrates incomplete penetrance, a clinically unaffected parent may still have a pathogenic variant, placing the sibs of the proband at a 50% risk of inheriting the variant. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family has been identified.

Diagnosis

Clinical Diagnosis

The following findings support the clinical diagnosis of familial paroxysmal kinesigenic dyskinesia (PKD) [Bruno et al 2004]:

- Attacks of dystonia, chorea, ballismus, or athetosis triggered by sudden movement (e.g., having the individual stand up suddenly or walk briskly up and down the hall)
- Attack duration lasting seconds to minutes
- Attack frequency as high as 100 times/day
- No loss of consciousness during the attack
- Reduction in attack frequency or prevention by the anticonvulsants phenytoin or carbamazepine

  Note: The diagnosis of PKD can be further confirmed with a trial of low-dose phenytoin (100 mg) or carbamezepine (250 mg), which is usually sufficient to eliminate attacks.
- A normal interictal neurologic examination
- A normal ictal and interictal EEG
- A normal MRI
- A family history consistent with autosomal dominant inheritance

Molecular Genetic Testing

Gene. Heterozygous pathogenic variants in *PRRT2* have been reported as causative of familial PKD in a subset of cases [Chen et al 2011, Wang et al 2011, Cloarec et al 2012, Gardiner et al 2012, Li et al 2012, Liu et al 2012, Marini et al 2012, Riant et al 2012, Scheffer et al 2012]. The most common pathogenic variant is c.649_650dupC.

Evidence for locus heterogeneity. Other, as-yet unidentified loci are suspected, as not all families with familial PKD have linked to the *PRRT2* locus at 16q11.2-q12.1 [Zhou et al 2008, Cloarec et al 2012].

Table 1. Summary of Molecular Genetic Testing Used in Familial Paroxysmal Kinesigenic Dyskinesia

Gene [1]	Test Method	Variants Detected [2]	Variant Detection Frequency by Test Method [3]
PRRT2	Sequence analysis [4]	Sequence variants	Unknown
	Deletion/duplication analysis [5]	Partial and whole-gene deletions and/or duplications	Unknown

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Testing that identifies exon or whole-gene deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

Testing Strategy

To confirm/establish the diagnosis in a proband sequence analysis of *PRRT2* may be considered. If no pathogenic variant is found by sequence analysis, deletion/duplication analysis may be considered. However, the diagnosis of familial PKD is based on clinical findings; failure to identify a pathogenic variant in *PRRT2* does not exclude the diagnosis.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant in the family.

Clinical Characteristics

Clinical Description

Familial paroxysmal kinesigenic dyskinesia (PKD) is characterized by unilateral or bilateral involuntary movements precipitated by sudden movements, being startled, or changes in velocity [Demirkiran & Jankovic 1995, Houser et al 1999, Tomita et al 1999]. The attacks include combinations of dystonia, choreoathetosis, and ballism. Many individuals experience an "aura"-like sensation (stiffness, tension, paresthesia, or crawling sensation in the affected limb) preceding the attacks [Bhatia 1999, Bhatia 2001]. The attacks do not involve a loss of consciousness.

Attack frequency ranges from 100 per day to as few as one per month [Demirkiran & Jankovic 1995]. Most attacks last from a few seconds to five minutes [Houser et al 1999, Tomita et al 1999]; in a few instances, attacks can last several hours [Demirkiran & Jankovic 1995]. In most cases, the frequency of attacks decreases with age [Bhatia 1999, Tomita et al 1999, Bhatia 2001].

Familial PKD has been associated with infantile seizures [Hattori et al 2000, Swoboda et al 2000] but not adult-onset seizures [Spacey et al 2002].

Expressivity in familial PKD can be variable within as well as among families. Age of onset and severity of symptoms vary. Additionally, a variety of combinations of symptoms (i.e., with respect to movement type and location) are seen; for example, in one family member, an attack may manifest as mild dystonic symptoms on one half of the body, whereas another family member may experience severe bilateral chorea [Spacey et al 2002, Wang et al 2011].

Age of onset is typically in childhood or adolescence but ranges from four months to 57 years [Demirkiran & Jankovic 1995, Li et al 2005].

Familial PKD occurs more frequently in males than in females (~4:1 ratio) [Bhatia 1999].

While initially described as different conditions, benign familial infantile epilepsy (BFIE), infantile convulsions and choreoathetosis (ICCA), hemiplegic migraine, migraine with and without aura, and episodic ataxia may represent part of the clinical spectrum of PKD (see Genetically Related Disorders).

Precipitating factors. Attacks can be precipitated by sudden movement such as standing up from a seated position [Demirkiran & Jankovic 1995, Houser et al 1999, Tomita et al 1999]. Cold, hyperventilation, and mental tension have also been reported to trigger attacks in individuals who have classic features of familial PKD [Spacey et al 2002].

Neuroimaging. Resting state functional magnetic resonance imaging (fMRI) performed on seven individuals with PKD demonstrated significantly increased alteration of amplitude of low-frequency fluctuation bilaterally in the putamen when compared to controls, suggesting the possibility of an abnormality in the cortico-striato-pallido-thalamic loop in individuals with PKD [Zhou et al 2010b].

Diffusion tensor imaging, performed on seven individuals with PKD, demonstrated significantly higher fractional anisotropy in the right thalamus compared to controls. Persons with PKD also had lower mean diffusivity values in the left thalamus compared to controls, confirming ultrastructural abnormalities in the thalamus of those with PKD [Zhou et al 2010a].

Genotype-Phenotype Correlations

Considerable variation in phenotype is seen between families with the same pathogenic variant, suggesting a complex interaction between the mutated allele, genetic background, and non-genetic factors [Cloarec et al 2012, Gardiner et al 2012, Marini et al 2012, Riant et al 2012, Scheffer et al 2012]. No genotype-phenotype correlations are known [Heron & Dibbens 2013].

Penetrance

The penetrance for familial PKD has been reported to be between 80% and 90% in both males and females [Tomita et al 1999, Spacey et al 2002].

Anticipation

Anticipation has not been observed.

Nomenclature

Familial PKD is classified as a paroxysmal dyskinesia. All of the disorders included in the dyskinesia category are characterized by intermittent occurrence of dystonia, chorea, and ballism of varying duration. The nomenclature used to classify the paroxysmal dyskinesias has been evolving over the past 60 years.

Recent classification. The classification of the paroxysmal dyskinesias is based on the duration of attacks and whether the attacks are precipitated by movement. Demirkiran & Jankovic [1995] studied 46 individuals identified with paroxysmal movement disorders and devised the following classification system:

- **Paroxysmal kinesigenic dyskinesia (PKD).** Defined as attacks of dyskinesia precipitated primarily by sudden movement and typically lasting less than five minutes

- **Paroxysmal nonkinesigenic dyskinesia (PNKD).** Defined as attacks of dyskinesia precipitated by stress, fatigue, menses, and heat, but not precipitated by exercise or movement, typically lasting minutes to hours

  A recent study by Bruno et al [2007] suggested further modifications to the classification system to identify PNKD with *PNKD* pathogenic variants:

  - Hyperkinetic involuntary movement attacks, with dystonia, chorea, or a combination of these, typically lasting ten minutes to one hour, but potentially up to four hours
  - Normal neurologic examination results between attacks and exclusion of secondary causes
  - Onset of attack in infancy or early childhood
  - Precipitation of attacks by caffeine and alcohol consumption
  - Family history of movement disorder meeting all four preceding criteria

- **Paroxysmal exertion-induced dyskinesia** (now referred to as **paroxysmal exercise-induced dyskinesia**) **(PED).** Includes attacks of dyskinesia precipitated by five to 15 minutes of physical exertion, such as walking and running, typically lasting for 15 to 30 minutes

- **Paroxysmal hypnogenic dyskinesia.** Characterized by attacks of dyskinesia occurring primarily during sleep; now recognized to be autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a form of epilepsy

Historical classification/nomenclature. Initial classification of "familial paroxysmal choreoathetosis" was made by Mount and Reback in 1940. They described an individual with attacks of chorea occurring three times per day and lasting five minutes to hours. The precipitating factors included coffee, tea, alcohol, smoking, and fatigue [Mount & Reback 1940].

Kertesz [1967] suggested the term paroxysmal kinesigenic choreoathetosis for disorders characterized by attacks precipitated by sudden movement.

Richards & Barnett [1968] introduced the term paroxysmal dystonic choreoathetosis for disorders characterized by long-lasting attacks that were not provoked by sudden movement.

Lance [1977] classified the paroxysmal dyskinesias into three groups based primarily on the duration of attacks and whether movement induced the attacks:

- Paroxysmal dystonic choreoathetosis (PDC) included prolonged attacks (2 minutes to 4 hours) not precipitated by sudden movement or prolonged exertion.
- Paroxysmal kinesigenic choreoathetosis (PKC) included short attacks (seconds to 5 minutes) induced by sudden movement.
- An intermediate form included attacks (5-30 minutes in duration) precipitated by continued exertion rather than sudden movement.

Prevalence

PKD is rare; prevalence is estimated at 1:150,000. The autosomal dominantly inherited form (familial form) is more common than the simplex form (i.e., the occurrence of a single affected individual in a family).

Genetically Related (Allelic) Disorders

While initially described as different conditions, the following phenotypes may actually represent the clinical spectrum of PKD, as opposed to separate, allelic conditions (see Clinical Description, **Expressivity**).

Infantile convulsions and choreoathetosis syndrome (ICCA syndrome). ICCA is characterized by afebrile convulsions at age three to 12 months and variable paroxysmal choreoathetosis. Pathogenic variants in *PRRT2* have been identified in families with ICCA [Cloarec et al 2012, Heron et al 2012, Liu et al 2012]. The familial

form of ICCA is an autosomal dominant disorder with 80% penetrance. (Note: an individual with ICCA and infantile non-convulsive seizures has been reported to have compound heterozygous variants [c.510dupT and c.647C>G] inherited from her asymptomatic father and mother, respectively [Liu et al 2013]).

Benign familial infantile epilepsy (BFIE) is an autosomal dominant self-limiting seizure disorder of infancy with typical onset of symptoms at a mean of six months and remission by age two years. Seizures can be focal or generalized and interictal EEG and MRI are usually normal. Pathogenic variants in *PRRT2* have been identified in 54.5%-78% of families with BFIE [Marini et al 2012, Scheffer et al 2012].

Some individuals with febrile seizures (FS) and febrile seizures plus (FS+) have been found to have *PRRT2* pathogenic variants. These individuals are typically members of families with documented *PRRT2* pathogenic variants and BFIE or ICCA phenotypes [Scheffer et al 2012].

Other individuals from families with *PRRT2* pathogenic variants who have the PKD or ICCA phenotype have hemiplegic migraine, migraine with aura, or migraine without aura [Cloarec et al 2012, Gardiner et al 2012]. A *PRRT2* pathogenic variant has also been identified in a sporadic case of migraine with aura with an abnormal MRI [Cloarec et al 2012]. Episodic ataxia has also been reported as part of the diverse PKD *PRRT2*-related phenotype [Gardiner et al 2012].

Differential Diagnosis

Paroxysmal dyskinesias can occur sporadically or as a feature of a number of hereditary disorders.

Sporadic Causes

Sporadic causes of paroxysmal dyskinesias include lesions of the basal ganglia caused by multiple sclerosis [Roos et al 1991], tumors, and vascular lesions including Moyamoya disease [Demirkiran & Jankovic 1995, Gonzalez-Alegre et al 2003]. Lesions outside of the basal ganglia have been reported to cause symptoms resembling paroxysmal kinesigenic dyskinesia (PKD). An individual who sustained a right frontal penetrating injury with contusion and hemorrhage manifested PKD-like symptoms [Richardson et al 1987]. Central pontine myelinolysis has resulted in symptoms consistent with PKD [Baba et al 2003]. Neuroimaging (preferably MRI) is important to rule out these etiologies.

Focal seizures can present with paroxysms of dystonia; EEG is an essential part of the investigation.

Dyskinesias seen in association with rheumatic fever (Sydenham's chorea) are associated with a raised anti-streptolysin O (ASO) titer and normal cerebrospinal fluid.

Chorea gravidarum can present with paroxysms of chorea in the first trimester of pregnancy and usually resolves after delivery.

Paroxysmal chorea can also be seen with systemic lupus erythematosus, diabetes mellitus, hypoparathyroidism, pseudohypoparathyroidism, and thyrotoxicosis. The relevant blood work should be done if these etiologies are being considered [Clark et al 1995, Yen et al 1998, Puri & Chaudhry 2004, Mahmud et al 2005, Thomas et al 2010].

Autosomal Recessive Cause

Wilson disease is a disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, or a combination of these, in individuals ranging in age from three years to older than 50 years. Neurologic presentations include movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement). Treatment with copper-chelating agents or zinc can prevent the development of hepatic,

neurologic, and psychiatric findings in asymptomatic affected individuals and can reduce findings in many symptomatic individuals. Diagnosis depends in part on the detection of low serum copper and ceruloplasmin concentrations and increased urinary copper excretion. Wilson disease is caused by pathogenic variants in *ATP7B*.

Autosomal Dominant Causes

Most of the hereditary causes of paroxysmal dyskinesias need to be considered:

- **Paroxysmal exercise-induced dyskinesia (PED)** is characterized by attacks of dystonia, chorea, and athetosis lasting five to 30 minutes. Attacks are triggered by prolonged exertion (e.g., walking or running) for five to 15 minutes. The body part involved in the exercise is usually the one that experiences the attacks [Bhatia et al 1997].
  - PED with epilepsy is observed in glucose transporter type 1 deficiency syndrome, caused by pathogenic variants in *SLC2A1*, encoding the glucose transporter GLUT1 on chromosome 1 [Suls et al 2008, Schneider et al 2009]. Inheritance is autosomal dominant; however, *de novo* pathogenic variants account for the majority of affected individuals.
  - A single family with PED has been linked to the pericentric region of chromosome 16 [Münchau et al 2000].
  - The locus for autosomal recessive rolandic epilepsy with PED and writer's cramp has been mapped to 16p12-11.2.
- **Paroxysmal hypnogenic dyskinesia (PHD),** now considered to be **autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).** Attacks associated with PHD/ADNFLE range dramatically, but include dystonia, chorea, and ballism. The episodes generally occur during non-REM sleep. The attacks often evoke arousal followed by sleep. Individuals are able to recall the episodes in the morning. Precipitating factors include increased activity, stress, and menses. Pathogenic variants in *CHRNA4* [Rozycka et al 2003] and *CHRNB2* [Duga et al 2002] have been found in some families with PHD/ADNFLE.
- **Glucose transporter type 1 deficiency syndrome (Glut1-DS).** The phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1-DS) is described as a continuum that includes the classic phenotype as well as dystonia 9, dystonia 18, atypical childhood absence epilepsy, myoclonic astatic epilepsy, and paroxysmal non-epileptic findings such as intermittent ataxia, choreoathetosis, dystonia, and alternating hemiplegia.

Other hereditary causes of dyskinesias that may be considered include the following:

- **Benign hereditary chorea** is a rare autosomal dominant disorder characterized by non-progressive choreiform movements appearing in childhood without intellectual impairment. It does not shorten the life span of affected individuals, but severely affected individuals can be disabled by the chorea.
- **Huntington disease (HD)** is an autosomal dominant progressive disorder of motor, cognitive, and psychiatric disturbances. The mean age of onset is 35 to 44 years; the median survival time is 15 to 18 years after onset. The diagnosis of HD rests on positive family history, characteristic clinical findings, and the detection of an expansion in *HTT* of 36 or more CAG trinucleotide repeats.
- **X-linked paroxysmal dyskinesia and severe global retardation** has been described in two unrelated boys with severe global retardation, an uncommon pattern of thyroid hormone abnormalities, and paroxysmal dyskinesia provoked by stimuli including changing of their clothes or diapers. These two boys have pathogenic variants in the thyroid hormone transporter gene, *MCT8*. Thyroid dysfunction has previously been identified as a cause of PKD [Yen et al 1998, Puri & Chaudhry 2004]. See MCT8 (SLC16A2)-Specific Thyroid Hormone Cell Transporter Deficiency.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial paroxysmal kinesigenic dyskinesia (PKD), the following evaluations are recommended:

- MRI to rule out secondary causes of PKD
- EEG to rule out seizures as a cause of the dyskinesias
- Clinical genetics consultation and testing for pathogenic variants in *PRRT2*

Treatment of Manifestations

Attack frequency is reduced or prevented by the anticonvulsants phenytoin or carbamezepine, typically at lower doses than are used to treat epilepsy [Demirkiran & Jankovic 1995, McGrath & Dure 2003].

Other anticonvulsants proven to be effective include oxcarbazepine [Tsao 2004], ethosuximide [Guerrini et al 2002], lamotrigine [Pereira et al 2000], and gabapentin [Chudnow et al 1997].

Surveillance

Individuals with PKD can be monitored every one to two years, particularly with respect to medication needs and doses.

Evaluation of Relatives at Risk

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

Pregnancy Management

Pregnant women who are on anticonvulsants therapy for PKD are recommended to take folic acid 5 mg/day. Because of the risk of teratogenic effects related to anticonvulsants, women with mild symptoms related to PKD may wish to consider discontinuing anticonvulsant therapy during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov 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

Familial paroxysmal kinesigenic dyskinesia (PKD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- More than 90% of individuals with familial PKD have an affected parent.
- A proband with familial PKD may have the disorder as the result of a *de novo* pathogenic variant in *PRRT2*. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of an individual with an apparent *de novo* pathogenic variant include a thorough history and neurologic examination, and molecular genetic testing if the *PRRT2* pathogenic variant has been identified in the proband.

Sibs of a proband. The risk to the sibs of a proband depends on the status of the parents:

- If a parent of a proband is affected or has a *PRRT2* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Because familial PKD demonstrates incomplete penetrance, a clinically unaffected parent may still have a pathogenic variant in *PRRT2*, in which case the sibs of the proband are at a 50% risk of inheriting the variant.

Offspring of a proband. Offspring of affected individuals with familial PKD have 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 is affected, his or her family members are at risk.

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 clinical evidence of the disorder, it is possible that the proband has a *de novo* pathogenic variant or the disease is sporadic (see Differential Diagnosis). However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

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 Diagnosis

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

Requests for prenatal testing for conditions which (like familial PKD) do not affect intellect and have some treatment available are not common. 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. Although decisions about prenatal testing are the choice of the parents, discussion of these issues is appropriate.

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.

- **Dystonia Medical Research Foundation**
  One East Wacker Drive
  Suite 1730
  Chicago IL 60601-1905
  Phone: 800-377-3978 (toll-free); 312-755-0198
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  Paroxysmal Dyskinesias

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. Familial Paroxysmal Kinesigenic Dyskinesia: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EKD1	*PRRT2*	16p11.2	Proline-rich transmembrane protein 2	PRRT2 @ LOVD Movement Disorder Society Genetic mutation database (MDSGene)	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 Familial Paroxysmal Kinesigenic Dyskinesia (View All in OMIM)

128200	EPISODIC KINESIGENIC DYSKINESIA 1; EKD1
614386	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2

Gene structure. The *PRRT2* transcript variant NM_145239.2 represents the predominant transcript and has four exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than ten different *PRRT2* variants associated with familial PKD have been described [Chen et al 2011, Wang et al 2011, Li et al 2012, Liu et al 2012]. The most common pathogenic variant is c.649_650dupC (p.Arg217ProfsTer8); the duplication of a cytosine results in a frameshift and a premature stop [Chen et al 2011, Wang et al 2011, Li et al 2012, Liu et al 2012].

Table 2. *PRRT2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.510dupT	p.Leu171SerfsTer3	NM_145239.2 NP_660282.2
c.647C>G	p.Pro216Arg	
c.649_650dupC (649_650insC)	p.Arg217ProfsTer8 (P217fs*7)	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. The protein encoded by *PRRT2* (NP_660282.2) has 340 amino acids and is predicted to have two transmembrane segments. The function is unknown; however, yeast two-hybrid studies suggest that PRRT2 interacts with synaptosomal-associated protein 25kd (SNAP25) [Stelzl et al 2005]. RT-PCR of mouse tissues detected high PRRT2 expression in brain and spinal cord with negligible expression in all other tissues [Chen et al 2011]. Temporal expression patterns of *PRRT2* mRNA in developing mouse brain were found to be relatively low before embryonic day 16, substantially increased in postnatal stages, peaking at postnatal day 14, and decreasing to low levels in adulthood [Chen et al 2011]. RT-PCR and in situ hybridization of postnatal day 14 mouse brain revealed high PRRT2 expression in cerebral cortex, hippocampus, and cerebellum with enrichment in cortical layers of the cerebrum as well as in granule cells and Purkinje cell layers of the cerebellum [Chen et al 2011].

Abnormal gene product. The truncated PRRT2 protein results in altered subcellular localization [Chen et al 2011].

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Chapter Notes

Revision History

- 11 January 2018 (ma) Chapter retired: covered in *PRRT2*-Associated Paroxysmal Movement Disorders
- 27 June 2013 (me) Comprehensive update posted live
- 15 March 2012 (cd) Revision: prenatal testing available clinically for *PRRT2* mutations
- 16 February 2012 (cd) Revision: mutations in *PRRT2* identified as causative of a subset of cases of familial PKD
- 31 March 2011 (me) Comprehensive update posted live
- 26 August 2008 (cg) Comprehensive update posted live

- 24 June 2005 (ca) Review posted to live Web site
- 2 December 2004 (ss) Original submission

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