



## Familial Paroxysmal Nonkinesigenic Dyskinesia

Synonyms: Paroxysmal Dystonic Choreoathetosis, Paroxysmal Nonkinesigenic Dyskinesia, PNKD

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### Summary

#### Clinical characteristics

Familial paroxysmal nonkinesigenic dyskinesia (PNKD) is characterized by unilateral or bilateral involuntary movements. Attacks are typically precipitated by coffee, tea, or alcohol; they can also be triggered by excitement, stress, or fatigue, or can be spontaneous. Attacks involve dystonic posturing with choreic and ballistic movements, may be accompanied by a preceding aura, occur while the individual is awake, and are not associated with seizures. Attacks last minutes to hours and rarely occur more than once per day. Attack frequency, duration, severity, and combinations of symptoms vary within and among families. Age of onset is typically in childhood or early teens but can be as late as age 50 years.

#### Diagnosis/testing

The clinical diagnosis of familial PNKD is suspected in a proband who presents with attacks of dystonia, chorea, and/or ballismus typically provoked by alcohol or caffeine. Identification of a heterozygous pathogenic variant in *PNKD* by molecular genetic testing confirms the diagnosis.

#### Management

*Treatment of manifestations:* Avoid triggers (e.g., caffeine, alcohol, excitement, stress, fatigue). Response to pharmacologic treatment is poor; clonazepam or diazepam can be effective in some individuals. Some individuals have responded to gabapentin, levetiracetam, or acetazolamide.

*Surveillance:* Monitor medication requirements and dosage.

#### Genetic counseling

Familial PNKD is inherited in an autosomal dominant manner. To date, all reported individuals with familial PNKD have inherited PNKD from an affected parent. Offspring of an affected individual have a 50% chance of

inheriting the *PNKD* pathogenic variant. Once the *PNKD* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

## Diagnosis

### Suggestive Findings

Familial paroxysmal nonkinesigenic dyskinesia (PNKD) **should be suspected** in individuals with the following features:

- Attacks:
  - Of dystonia, chorea, and/or ballismus, with onset during infancy
  - That can be provoked by alcohol or caffeine
  - Not typically triggered by sudden movement or sustained exercise
  - Lasting several minutes to hours
  - Rarely occurring more than once per day
- No loss of consciousness during an attack
- Poor response to pharmacologic treatment (although clonazepam or diazepam can be effective)
- Normal:
  - Interictal neurologic examination
  - Brain MRI
  - EEG
- Family history consistent with autosomal dominant inheritance

### Establishing the Diagnosis

The diagnosis of familial PNKD is **established** in an individual with the above Suggestive Findings by identification of a heterozygous pathogenic variant in *PNKD* (formerly named *MR-1*) by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of PNKD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of PNKD has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

#### Option 1

When the phenotypic and laboratory findings suggest the diagnosis of PNKD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PNKD* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants.

Note: The usefulness of deletion/duplication analysis is unknown as no deletions or duplications involving *PNKD* as a cause of familial PNKD have been reported.

- **A multigene panel** that includes *PNKD* 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

When the diagnosis of PNKD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Familial Paroxysmal Nonkinesigenic Dyskinesia

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
PNKD	Sequence analysis <sup>3</sup>	~15 families <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	Unknown, none reported <sup>6</sup>

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. 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](#).

4. The most common PNKD pathogenic variants reported to date are p.Ala7Val and p.Ala9Val (see Molecular Genetics) [Rainier et al 2004, Stefanova et al 2006, Bruno et al 2007, Pons et al 2012, Yeh et al 2012].

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may 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.

6. No multiexon or whole-gene deletions or duplications have been reported in families with PNKD (see Genetically Related Disorders).

## Clinical Characteristics

### Clinical Description

Familial paroxysmal nonkinesigenic dyskinesia (PNKD) is characterized by unilateral or bilateral involuntary movements. Attacks are often precipitated by caffeinated beverages but can also be spontaneous or triggered by excitement, stress, fatigue, and very rarely by sudden movements or prolonged exercise [Erro et al 2014].

The clinical description of this disorder is based on the following citations, unless otherwise noted: Demirkiran & Jankovic [1995], Bhatia [1999], Bhatia [2001], Bruno et al [2007], Erro et al [2014], Gardiner et al [2015].

Age of onset is typically in infancy or childhood but can in rare cases be as late as age 50 years.

The attacks predominantly involve dystonic posturing with some choreic and ballistic movements. Individuals often experience an aura-like sensation preceding the attacks. Attacks are never associated with a loss of consciousness and never occur during sleep.

Attacks can occur as frequently as once or twice per day or as infrequently as once or twice per year. Although attacks can rarely be as short as 30 seconds, more frequently they last five minutes to six hours. In 50%-60% of individuals with familial PNKD, the frequency of attacks diminishes with age.

Expressivity is variable within and among families. Varying degrees of severity in symptoms occur; attacks involving respiratory muscles are potentially life threatening [Djarmati et al 2005, Bruno et al 2007, Zittel et al 2015].

Unlike familial paroxysmal kinesigenic dyskinesia (PKD), familial PNKD is not typically associated with seizures. When PNKD co-occurs with epilepsy, other genetic disorders should be considered (see Differential Diagnosis).

## Genotype-Phenotype Correlations

There are currently no known genotype-phenotype correlations.

## Penetrance

Bruno et al [2007] calculated the penetrance of familial PNKD in individuals with *PNKD* pathogenic variants to be 98%; the asymptomatic individual in the study was too young to be considered unaffected.

## Nomenclature

Familial PNKD is classified as paroxysmal dyskinesia [Erro & Bhatia 2019]. 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.

**Classification of the paroxysmal dyskinesias** is based on the duration of attacks and whether the attacks are precipitated by movement, sustained exercise, or nonkinesigenic triggers. Before the discovery of the genes responsible for the paroxysmal dyskinesias, Demirkiran and Jankovic [1995] studied 46 individuals identified with both "idiopathic" and symptomatic 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 coffee, alcohol, stress, fatigue, menses, and heat, but not precipitated by exercise or movement, typically lasting minutes to hours

A study by Bruno et al [2007] suggested further modifications to the clinical criteria to identify individuals 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 attacks in infancy or early childhood
- Precipitation of attacks by caffeine and alcohol consumption
- Family history of movement disorder meeting all 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 15 to 30 minutes.
- **Paroxysmal hypnogenic dyskinesia** is characterized by attacks of dyskinesia occurring primarily during sleep. This has been recognized in most cases to be a form of epilepsy: **autosomal dominant nocturnal frontal lobe epilepsy** (ADNFLE). However, pathogenic variants in *PRRT2* and *ADCY5* have recently been associated with non-epileptic paroxysmal dyskinesias occurring during sleep.

### Outdated terms for PNKD

- Familial paroxysmal choreoathetosis
- Paroxysmal dystonic choreoathetosis
- DYT8
- DYT-*MR-1*

## Prevalence

Familial PNKD is extremely rare; exact prevalence is unknown.

## Genetically Related (Allelic) Disorders

Affected individuals from one family with isolated hemiplegic migraine were reported to have *PNKD* pathogenic variant c.1022delC [Gardiner et al 2015].

## Differential Diagnosis

Paroxysmal dyskinesias have been reported in individuals with the following disorders (brain MRI examination is important to rule out these etiologies):

- Basal ganglia lesions caused by multiple sclerosis
- Tumors
- Vascular lesions including moyamoya disease
- Penetrating brain injury (e.g., right frontal)
- Central pontine myelinolysis

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

**Autoimmune disorders.** Dyskinesias seen in association with rheumatic fever (Sydenham's chorea) are associated with a raised anti-streptolysin O (ASO) titer and normal cerebrospinal fluid. PNKD has also been reported as a manifestation of antiphospholipid antibody syndrome [Engelen & Tijssen 2005].

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

**Other.** Paroxysmal chorea can also be seen with systemic lupus erythematosus, diabetes mellitus, hypoparathyroidism, pseudohypoparathyroidism, and thyrotoxicosis. The relevant laboratory testing should be done if these etiologies are being considered [Mahmud et al 2005].

## Inherited Causes of Paroxysmal Dyskinesia

**Table 2.** Disorders to Consider in the Differential Diagnosis of Familial PNKD

MOI / Category	Disorder	Gene(s)	Age of Onset	Neurologic Presentation
AD / Paroxysmal dyskinesias	Familial paroxysmal kinesigenic dyskinesia (See <a href="#">PRRT2-Associated Paroxysmal Movement Disorders</a> .)	<i>PRRT2</i> <sup>1</sup>	Typically childhood & adolescence	<p>Attacks of dyskinesia:</p> <ul style="list-style-type: none"> <li>• Are triggered by sudden movement;</li> <li>• Last secs to mins;</li> <li>• May occur 100x/day;</li> <li>• Do not cause loss of consciousness, &amp; persons have normal ictal EEG.</li> </ul> <p>Clinical spectrum can incl:</p> <ul style="list-style-type: none"> <li>• Episodic ataxia;</li> <li>• Hemiplegic migraine.</li> </ul> <p>Some persons have personal or family history of afebrile convulsions.</p>
	Glucose transporter type 1 deficiency syndrome	<i>SLC2A1</i>	Infancy	<p>PED:</p> <ul style="list-style-type: none"> <li>• Lasts 5-30 mins;</li> <li>• Can be part of a complex neurologic syndrome incl epilepsy, DD, ataxia, &amp; spasticity.</li> </ul>
	Autosomal dominant nocturnal frontal lobe epilepsy	Many	Infancy to adulthood	<ul style="list-style-type: none"> <li>• Incl dystonia, chorea, &amp; ballism</li> <li>• Episodes generally occur during non-REM sleep, often evoking arousal followed again by sleep.</li> <li>• Persons are able to recall the episodes in the morning.</li> </ul>
	<i>KCNMA1</i> -related paroxysmal dyskinesia (OMIM 609446)	<i>KCNMA1</i>	Childhood	<ul style="list-style-type: none"> <li>• Attacks of PNKD can be triggered by alcohol or coffee.</li> <li>• Persons also have epilepsy &amp;/or DD.</li> </ul>
	<i>ADCY5</i> -related dyskinesia	<i>ADCY5</i>	Childhood	Choreiform, myoclonic, &/or dystonic movements w/attacks of paroxysmal dyskinesia, exacerbated by anxiety, not precipitated by startle, caffeine, or alcohol
	Alternating hemiplegia of childhood (See <a href="#">ATP1A3-Related Neurologic Disorders</a> .)	<i>ATP1A3</i>	Childhood	Alternating (i.e., from one side of the body to the other) attacks of dystonia w/a typical rostrocaudal distribution that may be triggered by fever, trauma, or stress
AD / Dyskinesias	Benign hereditary chorea (See <a href="#">NKX2-1-Related Disorders</a> .)	<i>NKX2-1</i>	Childhood	<ul style="list-style-type: none"> <li>• Non-progressive choreiform movements</li> <li>• Severely affected persons can be disabled by the chorea.</li> </ul>

Table 2. continued from previous page.

MOI / Category	Disorder	Gene(s)	Age of Onset	Neurologic Presentation
XL & AR / Dyskinesias	Pyruvate dehydrogenase deficiency (See <a href="#">Primary Pyruvate Dehydrogenase Complex Deficiency Overview.</a> )	Many	Childhood	<ul style="list-style-type: none"> <li>• Paroxysmal attacks of dystonia &amp; chorea often in the form of PED</li> <li>• Attacks can be isolated or assoc w/signs &amp; symptoms of Leigh syndrome.</li> </ul>

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; PED = paroxysmal exercise-induced dyskinesia; XL = X-linked

1. Heterozygous pathogenic variants in *PRRT2* have been reported as causative of familial paroxysmal kinesigenic dyskinesia (PKD) in a subset of persons. The other gene(s) associated with PKD have not been identified.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial paroxysmal nonkinesigenic dyskinesia (PNKD), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Referral to a neurologist for discussion of treatment options
- Consultation with a clinical geneticist and/or genetic counselor

### Treatment of Manifestations

Avoid triggers (e.g., caffeine, alcohol).

Response to pharmacologic treatment is poor; however, clonazepam or diazepam can be effective in at least 50% of individuals with PNKD, although response may decrease over time.

- A child age four years with familial PNKD responded to gabapentin [Chudnow et al 1997].
- Szczałuba et al [2009] reported individuals from a family with PNKD who responded favorably to levetiracetam.
- Zittel et al [2015] reported individuals with severe PNKD who responded to acetazolamide.

### Surveillance

Monitor medication requirements and dosage.

### 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 anticonvulsant therapy for familial PNKD are advised to take folic acid (5 mg/day). Because of the risk of teratogenic effects related to anticonvulsants, women with mild symptoms related to familial PNKD may consider discontinuing anticonvulsant therapy during pregnancy.

See [MotherToBaby](#) for access further information on medication use during pregnancy.

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

Familial paroxysmal nonkinesigenic dyskinesia (PNKD) is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- To date, all reported individuals with PNKD have an affected parent.
- To date, no individuals diagnosed with PNKD have the disorder as the result of a *de novo* PNKD pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Neurologic assessment and molecular genetic testing are recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* variant in the proband or germline mosaicism in a parent (though theoretically possible, no instances of germline mosaicism have been reported).
- Note: Although to date all individuals diagnosed with familial PNKD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

**Sibs of a proband.** The risk to the sibs of a proband depends on the genetic status of the proband's parents:

- If the parents have been tested for the *PNKD* pathogenic variant identified in the proband and:
  - A parent of the proband has the *PNKD* pathogenic variant, the risk to the sibs of inheriting the variant is 50%; intrafamilial clinical variability has been observed (see Clinical Description).
  - The *PNKD* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PNKD* pathogenic variant but are clinically unaffected, the risk to sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for PNKD because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with PNKD has a 50% chance of inheriting the *PNKD* 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 *PNKD* pathogenic variant, his or her family members may be at risk.



## Related Genetic Counseling Issues

**Predictive testing** for at-risk asymptomatic adult family members requires prior identification of the *PNKD* pathogenic variant in the family.

**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

- 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 *PNKD* pathogenic variant has 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 testing. 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](#).*

- **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](mailto:dystonia@dystonia-foundation.org)  
[Paroxysmal Dyskinesias](#)
- **National Library of Medicine Genetics Home Reference**  
[Familial paroxysmal nonkinesigenic dyskinesia](#)

## 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 Nonkinesigenic Dyskinesia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

<a href="#">PNKD</a>	<a href="#">2q35</a>	<a href="#">Probable hydrolase PNKD</a>	<a href="#">PNKD database</a>	<a href="#">PNKD</a>	<a href="#">PNKD</a>
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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 Nonkinesigenic Dyskinesia ([View All in OMIM](#))

<a href="#">118800</a>	<a href="#">PAROXYSMAL NONKINESIGENIC DYSKINESIA 1; PNKD1</a>
<a href="#">609023</a>	<a href="#">PNKD METALLO-BETA-LACTAMASE DOMAIN-CONTAINING PROTEIN; PNKD</a>

**Gene structure.** *PNKD* (previously known as *MR-1*) exists in three alternatively spliced forms of three, nine, and ten exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

**Pathogenic variants.** In two studies including 62 affected individuals from ten families, one of the two pathogenic variants in Table 3 was found in all 62 individuals [Lee et al 2004, Rainier et al 2004]. An additional pathogenic variant (p.Ala33Pro) was reported in one affected individual.

**Table 3.** *PNKD* Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change	Reference Sequences
c.20C>T (66C>T)	p.Ala7Val	<a href="#">NM_015488.4</a> <a href="#">NP_056303.3</a>
c.26C>T (72C>T)	p.Ala9Val	
c.97G>C	p.Ala33Pro	

Variants listed in the table have been provided by the author. *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.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** *PNKD* encodes probable hydrolase PNKD. PNKD function has not been fully characterized; however, based on approximately 40% homology between *PNKD* and *HAGH*, the gene encoding hydroxyacylglycine hydrolase, which functions in detoxification of methylglyoxal, a compound produced during oxidative stress and found in alcoholic beverages and coffee, it was thought that PNKD was also implicated in this detoxification pathway [Lee et al 2004]. However, in cultured cells and transgenic animals PNKD did not effectively restore absent HAGH activity, suggesting that it does not intervene in this pathway at appreciable levels in vivo [Shen et al 2011].

*PNKD* binds to Rab3-interacting molecules (RIMs), a group of proteins playing a role in vesicle priming and calcium-dependent neurotransmitter release, suggesting a possible role in synaptic regulation [Shen et al 2015, Erro et al 2017]. Given that caffeine stimulates calcium efflux from the endoplasmic reticulum at presynaptic terminals, the hypothesis would be that neurons might be more vulnerable to high concentration of calcium and hence could become hyperexcitable when challenged with caffeine [Shen et al 2015].

Two reported *PNKD* transcripts are identical in their last eight exons but differ in the first two exons. [NM\\_015488.4](#) is the larger of the two and codes for a 385-amino acid protein; [NM\\_022572.4](#) encodes for a 361-amino acid protein. Expression detection by RT-PCR showed expression of *PNKD* [NM\\_015488.4](#) in brain and none in the liver, kidney, skeletal muscle, heart, or lung [Lee et al 2004, Rainier et al 2004].

**Abnormal gene product.** In three studies, all affected individuals studied had either an alanine-to-valine substitution at codon 7 or an alanine-to-valine substitution at codon 9 (Table 3) [Lee et al 2004, Rainier et al

2004, Bruno et al 2007]. Both of these amino acid substitutions are in a predicted amino-terminal alpha helix domain of the paroxysmal nonkinesigenic dyskinesia protein. The substitutions are predicted to disrupt the alpha helix structure [Rainier et al 2004].

## References

### Literature Cited

- Bhatia KP. The paroxysmal dyskinesias. *J Neurol*. 1999;246:149–55. PubMed PMID: 10323309.
- Bhatia KP. Familial (idiopathic) paroxysmal dyskinesias: an update. *Semin Neurol*. 2001;21:69–74. PubMed PMID: 11346027.
- Bruno MK, Lee HY, Auburger GW, Friedman A, Nielsen JE, Lang AE, Bertini E, Van Bogaert P, Averyanov Y, Hallett M, Gwinn-Hardy K, Sorenson B, Pandolfo M, Kwiecinski H, Servidei S, Fu YH, Ptáček L. Genotype-phenotype correlation of paroxysmal nonkinesigenic dyskinesia. *Neurology*. 2007;68:1782–9. PubMed PMID: 17515540.
- Chudnow RS, Mimbela RA, Owen DB, Roach ES. Gabapentin for familial paroxysmal dystonic choreoathetosis. *Neurology*. 1997;49:1441–2. PubMed PMID: 9371936.
- Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol*. 1995;38:571–9. PubMed PMID: 7574453.
- Djarmati A, Svetel M, Momcilovic D, Kostic V, Klein C. Significance of recurrent mutations in the myofibrillogenesis regulator 1 gene. *Arch Neurol*. 2005;62:1641. PubMed PMID: 16216955.
- Engelen M, Tijssen MA. Paroxysmal non-kinesigenic dyskinesia in antiphospholipid syndrome. *Mov Disord*. 2005;20:111–3. PubMed PMID: 15390045.
- Erro R, Bhatia KP. Unravelling of the paroxysmal dyskinesias. *J Neurol Neurosurg Psychiatry*. 2019;90:227–34. PubMed PMID: 30242089.
- Erro R, Bhatia KP, Espay AJ, Striano P. The epileptic and nonepileptic spectrum of paroxysmal dyskinesias: channelopathies, synaptopathies, and transportopathies. *Mov Disord*. 2017;32:310–8. PubMed PMID: 28090678.
- Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. *Mov Disord*. 2014;29:1108–16. PubMed PMID: 24963779.
- Gardiner AR, Jaffer F, Dale RC, Labrum R, Erro R, Meyer E, Xiromerisiou G, Stamelou M, Walker M, Kullmann D, Warner T, Jarman P, Hanna M, Kurian MA, Bhatia KP, Houlden H. The clinical and genetic heterogeneity of paroxysmal dyskinesias. *Brain*. 2015;138:3567–80. PubMed PMID: 26598494.
- Lee HY, Xu Y, Huang Y, Ahn AH, Auburger GW, Pandolfo M, Kwiecinski H, Grimes DA, Lang AE, Nielsen JE, Averyanov Y, Servidei S, Friedman A, Van Bogaert P, Abramowicz MJ, Bruno MK, Sorensen BF, Tang L, Fu YH, Ptáček LJ. The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. *Hum Mol Genet*. 2004;13:3161–70. PubMed PMID: 15496428.
- Mahmud FH, Linglart A, Bastepe M, Juppner H, Lteif AN. Molecular diagnosis of pseudohypoparathyroidism type Ib in a family with presumed paroxysmal dyskinesia. *Pediatrics*. 2005;115:e242–4. PubMed PMID: 15629959.
- Pons R, Cuenca-Leon E, Miravet E, et al. Paroxysmal non-kinesigenic dyskinesia due to a PNKD recurrent mutation: report of two Southern European families. *Eur J Paediatr Neurol*. 2012;16:86–89. PubMed PMID: 21962874.

- Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet.* 2016;48:126–33. PubMed PMID: 26656846.
- Rainier S, Thomas D, Tokarz D, Ming L, Bui M, Plein E, Zhao X, Lemons R, Albin R, Delaney C, Alvarado D, Fink JK. Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis. *Arch Neurol.* 2004;61:1025–9. PubMed PMID: 15262732.
- Shen Y, Ge WP, Li Y, Hirano A, Lee HY, Rohlmann A, Missler M, Tsien RW, Jan LY, Fu YH, Ptáček LJ. Protein mutated in paroxysmal dyskinesia interacts with the active zone protein RIM and suppresses synaptic vesicle exocytosis. *Proc Natl Acad Sci U S A.* 2015;112:2935–41. PubMed PMID: 25730884.
- Shen Y, Lee HY, Rawson J, Ojha S, Babbitt P, Fu YH, Ptacek LJ. Mutations in PNKD causing paroxysmal dyskinesia alters protein cleavage and stability. *Hum Mol Genet.* 2011;20:2322–32. PubMed PMID: 21487022.
- Stefanova E, Djarmati A, Momcilovic D, et al. Clinical characteristics of paroxysmal nonkinesigenic dyskinesia in Serbian family with myofibrillogenesis regulator 1 gene mutation. *Mov Disord.* 2006;21:2010–2015. PubMed PMID: 16972263.
- Szczałuba K, Jurek M, Szczepanik E, Friedman A, Milewski M, Bal J, Mazurczak T. A family with paroxysmal nonkinesigenic dyskinesia: genetic and treatment issues. *Pediatr Neurol.* 2009;41:135–8. PubMed PMID: 19589464.
- Yeh TH, Lin J, Lai S, Wu-chou Y, Chen A. Familial paroxysmal nonkinesigenic dyskinesia: clinical and genetic analysis of a Taiwanese family. *J Neurol Sci.* 2012;323:80–4. PubMed PMID: 22967746.
- Zittel S, Ganos C, Münchau A. Fatal paroxysmal non-kinesigenic dyskinesia. *Eur J Neurol.* 2015;22:e30–1. PubMed PMID: 25572910.

## Chapter Notes

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