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Pantothenate Kinase-Associated Neurodegeneration

Synonym: PKAN

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Summary

Clinical characteristics

Pantothenate kinase-associated neurodegeneration (PKAN) is a type of neurodegeneration with brain iron accumulation (NBIA). The phenotypic spectrum of PKAN includes classic PKAN and atypical PKAN. Classic PKAN is characterized by early-childhood onset of progressive dystonia, dysarthria, rigidity, and choreoathetosis. Pigmentary retinal degeneration is common. Atypical PKAN is characterized by later onset (age >10 years), prominent speech defects, psychiatric disturbances, and more gradual progression of disease.

Diagnosis/testing

The diagnosis of PKAN is established in a proband with the characteristic clinical features and the "eye of the tiger" sign identified on brain MRI (a central region of hyperintensity surrounded by a rim of hypointensity on coronal or transverse T_2-weighted images of the globus pallidus). Identification of biallelic *PANK2* pathogenic variants on molecular genetic testing confirms the diagnosis.

Management

Treatment of manifestations: Intramuscular botulinum toxin, ablative pallidotomy or thalmotomy, intrathecal or oral baclofen, oral trihexyphenidyl, deep brain stimulation, physical therapy and occupational therapy to maintain joint mobility, referral for adaptive aids (walker, wheelchair) for gait abnormalities, speech therapy and/or assistive communication devices, treatment for retinopathy by ophthalmology, referral to community resources: financial services, services for the blind, and educational programs.

Prevention of secondary complications: Full-mouth dental extraction when severe orobuccolingual dystonia results in recurrent tongue biting; gastrostomy tube feeding as needed.

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Surveillance: Evaluation for treatable causes of pain during episodes of extreme distress; monitoring of height and weight; routine ophthalmologic assessment; oral assessment for trauma, assessment of ambulation and speech abilities, feeding and nutrition assessment.

Genetic counseling

PKAN is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at risk, and preimplantation genetic testing are possible if both pathogenic variants have been identified in an affected family member.

GeneReview Scope

Pantothenate Kinase-Associated Neurodegeneration: Included Phenotypes [1]
• Classic PKAN • Atypical PKAN

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

Diagnosis

Suggestive Findings

Pantothenate kinase-associated neurodegeneration (PKAN) **should be suspected** in individuals with the following clinical, radiographic, and laboratory features and family history.

Clinical features

- Dystonia
- Dysarthria
- Spasticity
- Choreoathetosis
- Parkinsonism
- Hyperreflexia
- Extensor toe signs
- Onset in first to third decade of life
- Gait change / loss of ambulation
- Pigmentary retinopathy
- Intellectual and developmental disabilities, mainly in children with very young onset

Radiographic features. "Eye of the tiger" sign on T_2-weighted brain MRI (≥1.5 Tesla): a central region of hyperintensity surrounded by a rim of hypointensity on coronal or transverse T_2-weighted images of the globus pallidus. See Figure 1.

Laboratory features

- **Acanthocytosis.** Acanthocytes have been reported in a subset of individuals with PKAN [Schiessl-Weyer et al 2015]. Rigorous analysis for acanthocytes is technically difficult and rarely used now that molecular genetic diagnosis has been available for several years.
- **Low** or **absent plasma pre-beta lipoprotein fraction.** See Clinical Description.

Family history consistent with autosomal recessive inheritance, including consanguinity

Exclusionary findings

- Abnormalities of plasma ceruloplasmin concentration or copper metabolism (See Wilson Disease.)
- Evidence of neuronal ceroid-lipofuscinosis by electron microscopy, enzymatic assay, or the presence of a pathogenic variant in any of the genes associated with this condition
- Beta-hexosaminidase A deficiency or GM1 galactosidase deficiency
- Pathologic evidence of spheroid bodies in the peripheral nervous system, indicative of *PLA2G6*-associated neurodegeneration (PLAN) or mitochondrial membrane protein-associated neurodegeneration (MPAN)

Establishing the Diagnosis

The diagnosis of PKAN **is established** in a proband with the following hallmark features. The diagnostic criteria continue to evolve to reflect the distinctions between PKAN and other forms of neurodegeneration with brain iron accumulation (NBIA). Identification of biallelic pathogenic (or likely pathogenic) variants in *PANK2* by molecular genetic testing confirms the diagnosis if clinical features are inconclusive (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *PANK2* variants of uncertain significance (or of one known *PANK2* pathogenic variant and one *PANK2* variant of uncertain significance) does not establish or rule out the diagnosis.

Hallmark features of classic and atypical PKAN (See Figure 1.)

- **Extrapyramidal dysfunction,** including one or more of the following:
  - Dystonia
  - Spasticity
  - Choreoathetosis
- **Onset**
  - **Classic form.** Usually in first decade of life
  - **Atypical form.** More commonly in the second or third decade of life
- **Loss of ambulation**
  - **Classic form.** Often occurring within ten to 15 years of onset
  - **Atypical form.** May occur within 15 to 40 years of onset
- **"Eye of the tiger" sign** on T_2-weighted brain MRI (≥1.5 Tesla): a central region of hyperintensity surrounded by a rim of hypointensity on coronal or transverse T_2-weighted images of the globus pallidus (Figure 1)

Note: (1) The sign may be absent in the early stages of disease [Chiapparini et al 2011]. (2) The hyperintense region is replaced by iron, becoming more uniformly hypointense over time [Delgado et al 2012]. (3) Some affected individuals in the Dominican Republic lacked the "eye of the tiger" sign [Delgado et al 2012]. (4) Some individuals with a purported "eye of the tiger" sign have a diagnosis of MPAN.

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *PANK2* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.

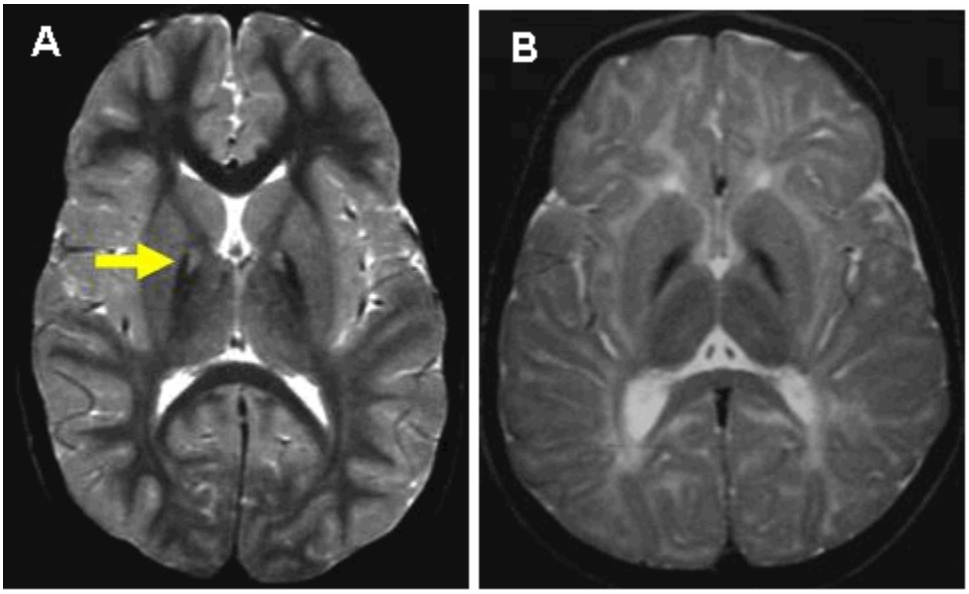

Figure 1. T_2-weighted brain MRI of PKAN (A) and non-PKAN NBIA (B)

A. Arrow indicates the "eye of the tiger" change characteristic of PKAN.

B. MRI shows globus pallidus hypointensities only, consistent with iron deposition and supporting a diagnosis of non-PKAN NBIA.

- **A multigene panel** that includes *PANK2* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 PKAN and NBIA

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
PANK2	Sequence analysis [3]	>99% of individuals with NBIA with "eye of the tiger" sign on MRI [4, 5] ~50% of individuals with clinical diagnosis of NBIA
	Gene-targeted deletion/duplication analysis [6]	~3%-5% [7]

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. NBIA International Mutation Database, Oregon Health & Science University, unpublished data
5. Sequence analysis of the coding region and splice sites of *PANK2* identifies at least one pathogenic variant in all individuals with the "eye of the tiger" sign on MRI. Preliminary data indicate that approximately 5% of individuals with clinical and radiographic evidence of PKAN demonstrate only one pathogenic variant by sequence analysis. Approximately 23% of families with PKAN have known or suspected consanguinity and 33% of families with PKAN demonstrate homozygous *PANK2* pathogenic variants.
6. 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.
7. Exon and multiexon deletions in *PANK2* may not be detected by sequence analysis; several such alleles have been reported (see Table A).

Pathologic diagnosis. The majority of pathology is found in the globus pallidus and variably in adjacent structures [Kruer et al 2011]. In the index case reported by Kruer et al, the "eye of the tiger" sign identified on MRI images correlated to a region of rarefaction in the center of the globus pallidus interna, which was depleted of viable neurons. Iron, mainly as coarse granular hemosiderin deposits, was distributed in a perivascular pattern. In PKAN, axonal spheroids have been observed in the pallidonigral system as well as in the white and gray matter of the cerebrum [Swaiman 2001]. The spheroids are not limited to those portions of the brain in which iron accumulates. A recent study identified apolipoprotein E enrichment in previously described, ubiquinated proteinaceous aggregates in the globus pallidus in individuals with PKAN, similar to lesions seen in individuals with infarcts involving this same region. This new finding suggests that tissue or cellular hypoxic/ischemic injury in the globus pallidus may underlie the pathogenesis of PKAN [Woltjer et al 2015].

Clinical Characteristics

Clinical Description

Classic Pantothenate Kinase-Associated Neurodegeneration (PKAN)

The clinical features of classic PKAN are remarkably homogeneous. It presents in early childhood, usually before age six years (mean age: 3.4 years). The most common presenting symptom is impaired gait resulting from a combination of lower-extremity dystonia and spasticity, as well as restricted visual fields in those children with retinopathy. Some children have developmental delay, which is primarily motor but occasionally global. Early histories of ADHD or toe-walking are also common. Visual symptoms may bring children with PKAN to medical attention.

Neurologic signs and symptoms of classic PKAN are primarily extrapyramidal and include dystonia and dysarthria. Dystonia is always present and usually an early manifestation. Cranial dystonia and limb dystonia are frequent and may lead, respectively, to recurrent trauma to the tongue and to atraumatic long bone fracture

from the combination of extreme bone stress and osteopenia. The resulting pain and distress can contribute to development of status dystonicus in a cycle that can be difficult to break.

Corticospinal tract involvement is common and includes spasticity, hyperreflexia, and extensor toe signs.

Seizures are rare.

Intellectual impairment is a feature of PKAN, particularly in children with young onset. A study of 16 children and adults with PKAN showed varied cognitive expression as measured by standardized evaluation tools, with skills ranging from high average to markedly below average. Age of onset had a strong inverse correlation with intellectual impairment (i.e., earlier onset was associated with greater impairment) [Freeman et al 2007]. However, children with classic disease retain cognitive abilities achieved and do not lose these skills in tandem with later motor function loss.

Retinal degeneration. Pigmentary retinal degeneration occurs in two thirds of affected individuals with classic PKAN. Retinopathy occurs early in the disease, although it is not often recognized until a full diagnostic evaluation including electroretinogram (ERG) and visual field testing is performed. The retinal degeneration follows a typical clinical course, with nyctalopia (night blindness) followed by progressive loss of peripheral visual fields and sometimes eventual blindness. Funduscopic changes initially include a flecked retina and later progress to bone spicule formation, conspicuous choroidal vasculature, and "bull's-eye" annular maculopathy. Individuals with a normal ophthalmologic examination at the time of diagnosis generally do not develop retinopathy later.

Abnormal eye movements, including vertical saccades and saccadic pursuits, are common. In one study, eight of ten individuals with PKAN had sectoral iris paralysis and partial loss of the pupillary ruff consistent with bilateral Adie's pupil [Egan et al 2005]. Optic atrophy is rarely seen in PKAN.

Prognosis. PKAN is a progressive disorder. Lost skills are usually not regained. The rate of progression correlates with age at onset: those with early symptoms decline more rapidly. As the disease advances, dystonia and spasticity compromise the child's ability to ambulate; most of those with early-onset disease are wheelchair bound by the mid-teens, and some much earlier. PKAN progresses at a non-uniform rate. Affected individuals experience episodes of rapid deterioration, often lasting one to two months, interspersed with longer periods of stability. Common causes of stress and catabolism do not appear to correlate with periods of decline, a phenomenon for which no cause has been found.

Premature death does occur. However, with improvements in medical care, a greater number of affected individuals are living into adulthood. Orofacial dystonia can result in the secondary effects of swallowing difficulty and poor nutrition. Premature death is more likely related to these secondary effects (e.g., nutrition-related immunodeficiency, aspiration pneumonia) than to the primary neurodegenerative process. In rare cases death occurs during status dystonicus.

Atypical PKAN

The clinical features of atypical PKAN are more varied than those of classic PKAN. Onset is in the first three decades (mean age: 13.6 years). Progression of the atypical form is slower, and presenting features are distinct, usually involving speech as either the sole presenting feature or part of the constellation of findings. The speech defects include palilalia (repetition of words or phrases), tachylalia/tachylogia (rapid speech of words and/or phrases), and dysarthria (poor articulation, slurring).

Psychiatric symptoms including personality changes with impulsivity and violent outbursts, depression, and emotional lability are common in atypical PKAN. Affected individuals may also exhibit motor and verbal tics, obsessive-compulsive behavior, and, rarely, psychotic symptoms [del Valle-López et al 2011].

As with classic PKAN, cognitive impairment may occur in individuals with atypical PKAN, but additional investigations are needed. Freeman et al [2007] found that later age of onset is correlated with less intellectual and adaptive behavior impairment.

Motor involvement is usually a later feature, although individuals with motor involvement often have been described as clumsy in childhood and adolescence. Spasticity, hyperreflexia, and other signs of corticospinal tract involvement are common and eventually limit ambulation. Conspicuously reminiscent of Parkinson disease, "freezing" during ambulation (especially when turning corners or encountering surface variations) is observed [Guimarães & Santos 1999].

An essential tremor-like syndrome has also been reported [Yamashita et al 2004].

Retinopathy is rare in atypical PKAN, and optic atrophy has not been associated with atypical PKAN.

HARP syndrome (*h*ypoprebetalipoproteinemia, *a*canthocytosis, *r*etinitis pigmentosa, and *p*allidal degeneration). Initially described as having a separate clinical entity, the two families described with HARP syndrome are now known to fall within the phenotypic spectrum of PKAN.

Genotype-Phenotype Correlations

A clear genotype-phenotype correlation for PKAN has not been observed.

However, individuals with two null variants (which predict no protein production) consistently have classic PKAN. Other combinations of pathogenic variants (i.e., null/missense, homozygous missense, or compound heterozygous missense) yield either classic or atypical phenotypes in no predictable pattern.

Homozygosity for the pathogenic missense variant p.Gly521Arg consistently presents as classic PKAN; however, the phenotype associated with homozygosity of other common alleles is unpredictable. Two thirds of individuals with PKAN are compound heterozygotes, with disease of unpredictable clinical course.

Within families, the phenotype is fairly consistent among affected individuals. Greater variance in age at onset, presenting features, and rate of progression is seen in families with atypical PKAN.

Nomenclature

The eponym Hallervorden-Spatz syndrome (HSS) is no longer favored in view of the unethical activities of these two German neuropathologists before and during World War II [Shevell 2003].

Prevalence

No reliable prevalence data on this rare disorder have been collected. An estimate of one to three in 1,000,000 has been suggested. This figure would imply a general population carrier frequency of 1:275-1:500.

A founder effect has been described in the Netherlands [Rump et al 2005]. A community in the southwest Dominican Republic also shares a common founder variant: c.680A>G (p.Tyr227Cys). The carrier frequency in this small, isolated population is significantly increased [Delgado et al 2012].

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with pathogenic variants in *PANK2*.

Differential Diagnosis

Pantothenate kinase-associated neurodegeneration (PKAN) is a form of **neurodegeneration with brain iron accumulation (NBIA).** NBIA is defined as the group of progressive extrapyramidal disorders with radiographic

evidence of focal iron accumulation in the brain, usually in the basal ganglia. Types of NBIA are included in Table 2.

Neurodegeneration with brain iron accumulation multigene panels may include testing for a number of the genes associated with disorders discussed in this section. Note: The genes included and the methods used in multigene panels vary by laboratory and are likely to change over time; a panel may not include a specific gene of interest.

Table 2. Types of NBIA: Molecular Genetics

Gene	Disease Name	MOI	Progression
ATP13A2	Kufor-Rakeb syndrome [1]	AR	Later-onset, slowly progressive NBIA w/onset after 1st decade
C19orf12	MPAN	AR	Early-onset (during 1st decade) or later-onset (after 1st decade), slowly progressive NBIA
CP	Aceruloplasminemia	AR	Later-onset, slowly progressive NBIA w/onset after 1st decade
CoASY	CoPAN	AR	Early-onset, slowly progressive NBIA w/onset during 1st decade
DCAF17	Woodhouse-Sakati syndrome	AR	Early-onset, slowly progressive NBIA w/onset during 1st decade
FA2H	FAHN	AR	Early-onset, slowly progressive NBIA w/onset during 1st decade
FTL	Neuroferritinopathy	AD	Later-onset, slowly progressive NBIA w/onset after 1st decade
PANK2	Atypical PKAN	AR	Later-onset, slowly progressive NBIA w/onset after 1st decade
	Classic PKAN		Early-onset rapidly progressive NBIA w/onset during 1st decade
PLA2G6	Atypical neuroaxonal dystrophy	AR	Early-onset, slowly progressive NBIA w/onset during 1st decade
	Infantile neuroaxonal dystrophy		Early-onset, rapidly progressive NBIA w/onset during 1st decade
	PLA2G6-associated dystonia-parkinsonism		Later-onset, slowly progressive NBIA w/onset after 1st decade
WDR45	BPAN	XL	Early-onset, slowly progressive NBIA w/onset during 1st decade
Unknown	Idiopathic NBIA		Later-onset, slowly progressive NBIA w/onset after 1st decade

AD = autosomal dominant; AR = autosomal recessive; BPAN = beta-propeller protein-associated neurodegeneration; CoPAN = COASY protein-associated neurodegeneration; FAHN = fatty acid hydroxylase-associated neurodegeneration; MOI = mode of inheritance; MPAN = mitochondrial membrane protein-associated neurodegeneration; PKAN = pantothenate kinase-associated neurodegeneration; XL = X-linked

1. Some individuals with Kufor-Rakeb syndrome have high brain iron [Schneider et al 2010].

PKAN can be distinguished from other forms of NBIA by the following findings:

- Brain MRI

- In most individuals with non-PKAN NBIA, the globus pallidus is uniformly hypointense on T_2-weighted images (see Figure 1), indicating high iron content. This change is distinct from the "eye of the tiger" sign and is not seen in association with pathogenic variants in *PANK2*. It should be noted that in MPAN, hyperintense streaking of the medial medullary lamina between the globus pallidus interna and externa can resemble an "eye of the tiger" sign [Hogarth et al 2013].
- Iron deposition in the red nucleus and dentate nucleus is seen in neuroferritinopathy and aceruloplasminemia. Cerebellar atrophy is common in PLAN.
- Bilateral calcification of the globus pallidus, detected by CT scan, has been reported in both PKAN and BPAN [Wu et al 2013, Fasano et al 2017].

- Absence of seizures in PKAN; prominence of seizures in some forms of non-PKAN NBIA

Classic PKAN. Four disorders may show early clinical changes similar to those seen in classic PKAN:

- **X-linked intellectual disability with Dandy-Walker malformation.** Unlike PKAN, affected children have severe intellectual disability. MRI of the brain, recommended for suspected PKAN, would rule out this diagnosis.
- **Alpha-L fucosidosis** (OMIM 230000). Affected children have coarse facial features and visceromegaly consistent with a lysosomal storage disease. Although a hyperintense signal in the globus pallidus has been documented by T_2-weighted MRI in some individuals, the "eye of the tiger" sign has not been observed. Alpha-L fucosidosis is caused by pathogenic variants in *FUCA1* and inherited in an autosomal recessive manner.
- **Leigh syndrome.** Symmetric hyperintense signal in the globus pallidus on T_2-weighted MRI can resemble an "eye-of-the-tiger" sign but lacks the surrounding hypointensity caused by iron accumulation. Unlike PKAN, symmetric hyperintensities occur frequently in other regions of the basal ganglia (see Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview and Mitochondrial DNA-Associated Leigh Syndrome and NARP).
- **Infantile neuroaxonal dystrophy (INAD).** A portion of individuals show hypointense signal in the globus pallidus and substantia nigra, but the "eye of the tiger" sign is absent and cerebellar atrophy is common. In INAD, axonal spheroids are present in the peripheral nervous system and in PKAN they are only located in the central nervous system.

Atypical PKAN. Differential diagnoses include the following:

- **Early-onset Parkinson disease** including parkin type of juvenile Parkinson disease and *PLA2G6*-associated dystonia-parkinsonism may initially present similarly to atypical PKAN, with onset between age 20 and 40 years and lower-limb dystonia. Bradykinesia and rest tremor are also common features.
- **Primary familial brain calcification (PFBC).** Affected individuals have abnormal calcium deposits in the basal ganglia, including deposits in the globus pallidus that can resemble an "eye of the tiger" sign. Features common to PKAN include parkinsonism, dysarthria, dystonia, and spasticity. Calcium deposits accumulate over time in the basal ganglia and cerebral cortex, helping to distinguish it from PKAN. Pathogenic variants in *PDGFB*, *PDGFRB*, and *SLC20A2* have been reported to cause PFBC; inheritance is autosomal dominant.
- **Aceruloplasminemia.** Affected individuals also have iron accumulation in the viscera and develop diabetes mellitus relatively early in the disease progression. They have retinal degeneration with characteristic yellow opacities in the retinal pigment epithelium.
- **Neuroferritinopathy** typically presents with involuntary movements in the fourth to fifth decade of life and does not exhibit the marked dysarthria observed in PKAN.
- **Steele-Richardson-Olzewski syndrome** (also known as progressive supranuclear palsy) (OMIM 260540). Average age of onset is 66 years and other common features include vertical gaze palsy, diplopia, and

photophobia, which are not features of PKAN. Steele-Richardson-Olzewski syndrome is caused by pathogenic variants in *MAPT*; inheritance is autosomal recessive.

- **Primary psychiatric illnesses.** The presence of impulsivity and other behavioral changes without dysarthria could indicate a primary psychiatric illness. For all of the disorders in this category, T_2-weighted brain MRI would distinguish PKAN based on the presence of the "eye of the tiger" sign.

Other disorders to consider:

- Neuronal ceroid-lipofuscinosis
- Childhood-onset hereditary ataxias (especially SCA3 and SCA7)
- Dystonias such as DYT1
- Juvenile Huntington disease
- Chorea-acanthocytosis
- Lesch-Nyhan syndrome
- Wilson disease
- Recessive hereditary spastic paraplegia
- Tourette disorder [Scarano et al 2002]

Neuroacanthocytosis syndromes. Neurologic disorders associated with RBC acanthocytosis are called neuroacanthocytosis syndromes.

One group of neuroacanthocytosis syndromes is associated with lipid malabsorption and primarily affects the spinal cord, cerebellum, and peripheral nervous system. The neurologic findings include the following:

- A progressive spinocerebellar degeneration with ataxia of gait, dysmetria, and dysarthria
- A demyelinating sensorimotor and axonal peripheral neuropathy with hyporeflexia and diminished vibration and position sense
- Pyramidal tract signs (rare)
- Cranial nerve involvement (rare)

These disorders include the following:

- Hypobetalipoproteinemia type 1 (FHBL1; OMIM 615558)
- Hypobetalipoproteinemia type 2 (FHBL2; OMIM 605019)
- Abetalipoproteinemia (ABL, Bassen-Kornzweig disease)

FHBL1, FHBL2, and ABL share the findings of acanthocytosis, dysarthria, neuropathy, and areflexia, but differ in that ABL, FHBL1, and FHBL2 have pigmentary retinopathy and do not have basal ganglia involvement. ABL, FHBL1, and FHBL2 are caused by pathogenic variants affecting the microsomal triglyceride transfer protein causing vitamin E deficiency. ABL is inherited in an autosomal recessive manner. FHBL1 and FHBL2 have clinical manifestations in both the homozygous and heterozygous states.

A second group of neuroacanthocytosis syndromes predominantly affects the central nervous system, in particular the basal ganglia, resulting in a chorea syndrome resembling Huntington disease. These disorders include the following:

- **McLeod neuroacanthocytosis syndrome (MLS)** is a multisystem disorder with hematologic, neuromuscular, and central nervous system (CNS) manifestations. Affected males have the McLeod blood group phenotype and RBC acanthocytosis. Neuromuscular manifestations of MLS comprise subclinical or mild sensorimotor axonopathy, myopathy, and cardiomyopathy. CNS manifestations of MLS resemble Huntington disease and consist of a choreiform movement disorder, "subcortical" cognitive deficits, psychiatric manifestations, and in some individuals, epileptic seizures. *XK* is the only gene in which pathogenic variants are known to cause MLS; inheritance is X-linked.

- **Chorea-acanthocytosis (ChAc)** is characterized by chorea, myopathy, progressive cognitive and behavioral changes, and seizures. Mean age of onset is approximately 35 years, although ChAc can develop as early as the first decade or as late as the seventh decade. *VPS13A* is the only gene in which mutation is currently known to cause ChAc; inheritance is autosomal recessive.
- **Huntington disease-like 2 (HDL2)** manifests in the third to fourth decade and has a progressive course over ten to 15 years. Dystonia is a frequent finding; chorea or parkinsonism may change with evolution of the disease. Almost all affected individuals reported to date have been of African ancestry. RBC acanthocytosis is variable. *JPH3* is the only gene in which mutation is known to cause HDL2; inheritance is autosomal dominant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with pantothenate kinase-associated neurodegeneration (PKAN), the following are recommended if they have not already been completed:

- Neurologic examination for dystonia, rigidity, choreoathetosis, and spasticity, including evaluation of ambulation and speech
- Ophthalmologic assessment for evidence of retinopathy
- Screening developmental assessment, with referral for more formal testing if delay is indicated
- Assessment for physical therapy, occupational therapy, and/or speech therapy
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A consensus clinical management guideline for PKAN is available to provide management information at a detailed level [Hogarth et al 2017]. Pharmacologic and surgical interventions have focused on palliation of symptoms.

Symptomatic treatment is aimed primarily at the **dystonia**, which can be profoundly debilitating and distressing to the affected individual and caregivers. Therapies to manage dystonia in affected individuals that have been used with varying success include the following:

- Intramuscular botulinum toxin
- Oral baclofen, trihexyphenidyl, and clonazepam: the first-line drugs most commonly effective in PKAN
- Second-line drugs including clonidine, gabapentin, tetrabenazine, and pregabalin
- Intrathecal and intraventricular baclofen
- Deep brain stimulation, used clinically with increasing frequency and some evidence for initial benefit, although it may not be sustained as disease progresses [Lim et al 2012, Garcia-Ruiz et al 2015, Hogarth et al 2017]
- Ablative pallidotomy or thalmotomy. These ablative procedures have mainly been replaced by DBS, but in certain individuals may still be useful [Dwarakanath et al 2014].
- Urgent medical treatment (often hospitalization) for status dystonicus (dystonic storm), which is a common occurrence. The PKAN consensus guideline provides detailed information about approach and management of dystonic storms [Hogarth et al 2017].
- Physical and occupational therapy as indicated, particularly for those who are only mildly symptomatic. Therapies to maintain normal joint mobility for as long as possible may be useful.
- Referral for adaptive aids as needed (e.g., a walker or wheelchair for gait abnormalities)
- Speech therapy and/or assistive communication devices for PKAN-related dysarthria and speech delay

Other manifestations

- Treatment and interventions for retinopathy as per ophthalmology
- Referral to appropriate community resources for financial services, services for the blind (if retinopathy is present), and special education

Prevention of Secondary Complications

Recurrent tongue biting from severe orobuccolingual dystonia is a specific challenge that is difficult to manage in PKAN. Customized bite-lock orthodontic appliances can be made and cemented in place to prevent tongue lacerations. Every effort should be made to avoid full dental extraction.

Once the individual can no longer maintain an adequate diet orally due to dysphagia or respiratory complications, gastrostomy tube placement is indicated.

In later stages of classic disease, tracheostomy may also be indicated.

Surveillance

As the disease progresses, episodes of extreme distress may last for days or weeks. It is especially important during these episodes to evaluate for treatable causes of pain. These may include occult GI bleeding, urinary tract infections, mouth lacerations, and occult bone fractures. The combination of osteopenia in a nonambulatory individual with marked stress on long bones from dystonia places individuals with PKAN at especially high risk for fractures without apparent trauma.

The following should be performed on a regular basis:

- Monitoring of height and weight using appropriate growth curves to screen children for worsening nutritional status
- Ophthalmologic assessment
- Oral assessment for consequences of trauma
- Assessment of ambulation, environmental adaptations, speech abilities, and communication needs to help affected individuals to maintain independence
- Swallowing evaluation and regular dietary assessments to assure adequate nutrition

Agents/Circumstances to Avoid

Anecdotal reports of three sibs with atypical PKAN treated with alpha-tocopherol and idebenone indicated worsening of symptoms, with subsequent improvement once these compounds were stopped [JP Harpey, personal communication].

Evaluation of Relatives at Risk

See Related Genetic Counseling Issues.

Therapies Under Investigation

Iron chelation. Interest in iron chelation has reemerged as data on deferiprone (Ferriprox®) have accumulated in several populations of affected individuals. Unlike earlier drugs, deferiprone crosses the blood-brain barrier and removes intracellular iron. One small Phase II pilot trial has been performed to assess deferiprone in the PKAN population. Deferiprone was tolerated well in the nine affected individuals who completed the study, and there was a statistically significant reduction of iron in the pallida by MRI evaluation. However, there was no change in their clinical status. The authors suggested that a longer trial period may be necessary to produce

clinical amelioration [Zorzi et al 2011]. An international randomized, double-blind, placebo-controlled trial of deferiprone was recently completed and the data are currently being analyzed (ClinicalTrials.gov).

Additional therapies. Multiple compounds are currently in development for PKAN and anticipated to go to clinical trial. Clinicians should check ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe regularly and maintain contact with PKAN investigators.

Other

Pantothenate. The existence of residual enzyme activity in some individuals with PKAN raises the possibility of treatment using high-dose pantothenate, the *PANK2* enzyme substrate. Pantothenate has no known toxicity in humans; high oral doses of pantothenic acid or calcium pantothenate (≤10 g/day for several weeks) do not appear to be toxic to humans. The efficacy of pantothenate supplementation in ameliorating symptoms is currently unknown; some individuals with an atypical disease course have anecdotally reported improvement in their symptoms (dysarthria, gait imbalance, sense of well-being) when taking pantothenate.

Docosahexanoic acid (DHA). Based on the role of coenzyme A in the synthesis and degradation of fatty acids, the importance of DHA as a major component of rod photoreceptor disc membranes, and the observation of retinal degeneration in a large portion of individuals with PKAN, DHA may have a role in preventing this complication, although no studies have yet been performed. The compound may be provided as an oral nutritional supplement in the form of omega-3 fats (fish oil) and is without known toxicity.

Other treatments

- Therapies that may have a role in other forms of NBIA but generally do not help individuals with PKAN include levodopa/carbidopa and bromocriptine.
- Treatment of PKAN with phosphopantothenate, the product of pantothenate kinase, is complicated by the lack of available compound as well as any information about its safety or toxicity in humans or animals. Furthermore, it is unlikely that phosphopantothenate would be readily transported across cell membranes, making the success of this hypothetical treatment doubtful.

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

Pantothenate kinase-associated neurodegeneration (PKAN) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are expected to be obligate heterozygotes (i.e., carriers of one *PANK2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with PKAN rarely reproduce.
- The offspring of an individual with PKAN are obligate heterozygotes (carriers).
- The offspring are at risk of being affected only if the proband's reproductive partner is heterozygous for a *PANK2* pathogenic variant.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PANK2* pathogenic variants in the family.

Related Genetic Counseling Issues

Testing of asymptomatic at-risk sibs, especially those younger than the proband. Neurologic evaluation (including brain MRI) and genetic testing may be considered for the seemingly healthy sibs of probands, especially when they are younger than the proband. Although evaluation and testing of asymptomatic individuals younger than age 18 years has not been encouraged in the past, it may be more commonly considered in light of therapeutics under development and data analysis under way from the deferiprone clinical trial.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of 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, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PANK2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for PKAN are possible.

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 Library of Medicine Genetics Home Reference**
  Pantothenate kinase-associated neurodegeneration
- **NBIA Alliance**
  Email: Info@NBIAalliance.org

www.nbiaalliance.org

- **NBIA Disorders Association**
  www.nbiadisorders.org
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/
- **NBIAcure**
  Center of Excellence for NBIA Clinical Care and Research
  International Registry for NBIA and Related Disorders
  Oregon Health & Science University
  Email: info@nbiacure.org
  www.nbiacure.org
- **Treat Iron-Related Childhood Onset Neurodegeneration (TIRCON)**
  Germany
  Email: TIRCON@med.uni-muenchen.de
  www.TIRCON.eu

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. Pantothenate Kinase-Associated Neurodegeneration: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PANK2	20p13	Pantothenate kinase 2, mitochondrial	PANK2 database	PANK2	PANK2

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 Pantothenate Kinase-Associated Neurodegeneration (View All in OMIM)

234200	NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 1; NBIA1
606157	PANTOTHENATE KINASE 2; PANK2
607236	none found

Molecular Pathogenesis

Pantothenate kinase-associated neurodegeneration (PKAN) is attributed to a deficiency or complete absence of pantothenate kinase 2, which is encoded by *PANK2*, one of four human pantothenate kinase genes. Pantothenate kinase deficiency is thought to cause accumulation of N-pantothenoyl-cysteine and pantetheine, which may cause cell toxicity directly or via free radical damage as chelators of iron [Yang et al 2000, Yoon et al 2000]. Deficient pantothenate kinase 2 is also predicted to result in coenzyme A (CoA) depletion and defective membrane biosynthesis in those tissues in which this is the major pantothenate kinase or in tissues with the greatest CoA demand.

Rod photoreceptors continually generate membranous discs; therefore, the retinopathy frequently observed in classic PKAN may be secondary to this deficit. The biochemical perturbations leading to clinical sequelae are still not completely understood and require further investigation.

Gene structure. *PANK2* encodes a 1.85-kb transcript that is derived from seven exons spanning just over 35 Mb of genomic DNA. Detailed sequence analysis reveals that *PANK2* is a member of a family of eukaryotic genes consisting of a group of six exons that encode homologous core proteins, preceded by a series of alternative initiating exons, some of which encode unique amino-terminal peptides. Alternative splicing, involving the use of alternate first exons, results in multiple transcripts encoding different isoforms. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Aside from the three common *PANK2* pathogenic variants described in Table 3, pathogenic variants are usually private to each family and vary in type.

Table 3. Selected *PANK2* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences [2]
c.680A>G	p.Tyr227Cys	NM_153638.2 NP_705902.2
c.1351C>T [3] (1021C>T)	p.Arg451Ter [3] (Arg341Ter)	
c.1561G>A (1231G>A) [3, 4]	p.Gly521Arg [3, 4] (Gly411Arg)	
c.1583C>T [3] (1253C>T)	p.Thr528Met [3] (Thr418Met)	
c.1413-1G>T [5] (IVS4-1G>T)	--	NM_153638.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Reference sequence is for the longest isoform, *PANK2* isoform 1 preproprotein.
3. Common pathogenic variants (allele frequency): p.Gly521Arg (25%); p.Thr528Met (8%); p.Arg451Ter (3%)
4. Homozygosity for this allele results in classic disease.
5. Pathogenic variant resulting in PKAN, originally seen in an individual diagnosed with HARP syndrome [Ching et al 2002]

Normal gene product. *PANK2* encodes a predicted 50.5-kd protein that is a functional pantothenate kinase [Zhou et al 2001]. Pantothenate kinase is an essential regulatory enzyme in CoA biosynthesis, catalyzing the phosphorylation of pantothenate (vitamin B_5), N-pantothenoyl-cysteine, and pantetheine. Pantothenate kinase is regulated by acyl-CoA levels in prokaryotes and by acetyl-CoA levels in eukaryotes.

Abnormal gene product. Pathogenic variants can generally be categorized into null or missense alleles. Individuals who are homozygous for null alleles usually have classic disease. It is currently unknown if individuals with atypical PKAN have partial enzyme function. Interallelic complementation has been postulated for those who are compound heterozygous for pathogenic missense variants. Interallelic complementation results when pathogenic variants in domains that interact between protein subunits are able to restore partial function. This is theorized to be variant specific, with some variants precluding complementation. Hence, some compound heterozygotes for missense variants may present with classic disease while others have a more atypical course. A recent study of *PANK2* pathogenic variants in affected individuals confirmed that the most frequent *PANK2* pathogenic variant, p.Gly521Arg, leads to a protein that is misfolded and devoid of activity

[Zhang et al 2006]. However, nine other pathogenic variants were found to result in proteins having normal catalytic activity and regulatory function. The authors suggested that PANK2 protein may have additional functions that are not yet appreciated.

Chapter Notes

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- 3 August 2017 (sw) Comprehensive update posted live
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