Clinical Features:
Pantothenate Kinase-Associated Neurodegeneration (PKAN) is one type of NBIA (neurodegeneration with brain iron accumulation) disorder. In 1922, PKAN was first described by two German neuropathologists, who termed the condition as “Hallervorden-Spatz” syndrome. Now that the PANK2 gene has been identified, the term “PKAN” is preferred. Mutations in PANK2 can manifest into two categories with wide clinical variability. Not all individuals will fall into one of these two categories (1, 2).

- **Classic PKAN**
  - Early age of onset – mean age is between 3 and 4 years
  - Rapid progression – most are wheelchair bound within 10 to 15 years after onset
  - Most common features: impaired gait, restricted visual fields, dystonia, dysarthria, rigidity, spasticity, hyperreflexia, extensor toe signs, pigmentary retinopathy, possible cognitive impairment
  - Other rare features: seizures, optic atrophy, toe-walking, red blood cell acanthocytosis

- **Atypical PKAN**
  - Late age of onset – mean age is between 13 and 14 years
  - Slow progression – most are wheelchair bound within 15 to 40 years after onset
  - Most common features: speech difficulties (palilalia, tachylalia, dysarthria, hypophonia), neurobehavioral changes (impulsivity, violent outbursts, depression, emotional lability), Parkinson-like symptoms, spasticity, hyperreflexia, extensor toe signs, possible cognitive impairment
  - Other rare features: motor/verbal tics, pigmentary retinopathy, red blood cell acanthocytosis

Individuals with Classic and Atypical PKAN experience phases of rapid deterioration followed by clinical stability.

Most individuals with PANK2 mutations show brain iron accumulation on a T2-weighted MRI scan. This accumulation is specific to the globus pallidus and substantia nigra and appears as the “eye of the tiger” sign (1). MRI should be performed at the initial diagnostic evaluation of PKAN as the “eye of the tiger” sign has been shown to regress over time (3).

Inheritance:
PKAN follows an autosomal recessive inheritance pattern. There have been no cases of germline mosaicism or de novo mutations reported. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%. Prevalence is estimated to be 1-3 in 1,000,000 (2).

Molecular Genetics:
The PANK2 gene, located at 20p13-p12.3, codes for one of four pantothenate kinase proteins (4). PANK2 is a key regulatory enzyme in several metabolic pathways of Coenzyme A biosynthesis. More specifically, it acts as a catalyst for the phosphorylation of pantothenate (vitamin B5), N-pantothenyl-cystine, and pantetheine. PKAN is caused by a deficiency or complete absence of PANK2, which has been hypothesized to lead to the accumulation of substrates and cell toxicity. More than 100 null and missense mutations have been identified in the PANK2 gene (2). Recently, deletions in PANK2 have also been identified in a minority of patients (5). Individuals who are homozygous for null alleles tend to present with classic PKAN. Compound heterozygotes for missense mutations may present with classic or atypical PKAN. It is unknown if individuals with atypical PKAN have partial PANK2 enzyme function (1). PANK2 sequence analysis will detect mutations in over 98% of individuals with NBIA and the “eye of the tiger sign”, but in only 50% of individuals with a clinical diagnosis of NBIA (2). Intragenic deletions of one or more exons of the PANK2 gene have been reported in approximately 4% of alleles in affected individuals (5).
**Additional Resources:**
NBIA Disorders Association  
Phone: 619-588-2315  
Email: info@NBIAdisorders.org  
www.nbiadisorders.org

**Test methods:**
We offer mutation analysis of all 7 coding exons and intron/exon boundaries of *PANK2* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *PANK2* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

**PANK2 sequencing analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube  
  - Cost: $900  
  - CPT codes: 81405  
  - Turn-around time: 4 – 6 weeks

**PANK2 deletion/duplication analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube  
  - Cost: $1000  
  - CPT codes: 81404  
  - Turn-around time: 4 weeks

**Testing for a known mutation in additional family members by sequence analysis**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube  
  - Cost: $390  
  - CPT codes: 81403  
  - Turn-around time: 3-4 weeks

**Prenatal testing for a known mutation by sequence analysis**
- Sample specifications: 2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid  
  - Cost: $540  
  - CPT codes: 81403  
  - Turn-around time: 1-2 weeks

**Results:**
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

**References:**