The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu dnatesting.uchicago.edu
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PANK2 Testing

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 wihtin 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 perfomed at the initial diagnotic 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 to10 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 to10 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 to10 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:

1. Hayflick SJ, Westaway SK, Levinson B et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med 2003: 348: 33-40.
2. Gregory A, Hayflick S. Pantothenate Kinase-Associated Neurodegeneration (PKAN). In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2002.
3. Baumeister FA, Auer DP, Hörtnagel K et al. The eye-of-the-tiger sign is not a reliable disease marker for Hallervorden-Spatz syndrome. Neuropediatrics 2005: 36: 221-222.
4. Zhou B, Westaway SK, Levinson B et al. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. Nat Genet 2001: 28: 345-349.
5. Hartig MB, Hörtnagel K, Garavaglia B et al. Genotypic and phenotypic spectrum of PANK2 mutations in patients with neurodegeneration with brain iron accumulation. Ann Neurol 2006: 59: 248-256.

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