

The University of Chicago Genetic Services Laboratories



5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

PANK2 Gene Sequencing

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 [2]. 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 [1].

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 [1]. 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 [2]. *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 [1].

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.

Mutation analysis (sequencing)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1325
CPT codes:	83891, 83898 x 4, 83904 x 5, 83912
Turn-around time:	4 – 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

Soma Das, Ph.D.
Director, Molecular Genetics Laboratory
ABMG Certified Molecular Geneticist

Stuart Schwartz, Ph.D.
Director, Cytogenetics Laboratory
ABMG Certified Cytogeneticist

William B. Dobyns, M.D. and Darrel J. Waggoner, M.D.
Clinical Advisors
ABMG Certified Clinical Geneticists

Melissa Dempsey, M.S.
Certified Genetic Counselor

References:

1. Coryell J, Gregory A, Hayflick SJ. Pantothenate Kinase-Associated Neurodegeneration [*PKAN*]. (2004) GeneReviews, www.geneclinics.org. Last update: 10/27/04.
2. Hayflick SJ, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. (2003) N Engl J Med 348(1): 33-40.
3. Baumeister FA et al. The eye-of-the-tiger sign is not a reliable disease marker for Hallervorden-Spatz syndrome. (2005) Neuropediatrics 36: 221-2.
4. Zhou B et al. A novel pantothenate kinase gene (*PANK2*) is defective in Hallervorden-Spatz syndrome. (2001) Nat Genet 28:345-9.
5. Hartig et al. Genotype and phenotype spectrum of *PANK2* mutation in patients with neurodegeneration with brain iron accumulation. (2006) Am Neurol 59: 248-256.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS