

The University of Chicago Genetic Services Laboratories



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PLA2G6 analysis for Infantile Neuroaxonal Dystrophy

Clinical Features:

Patients with Infantile Neuroaxonal Dystrophy (INAD) [OMIM #256600] have infantile onset of progressive neurodegeneration characterized by hypotonia, spasticity, hyperreflexia, visual disturbances and deterioration of motor skills. Another distinctive pathological finding includes axonal degeneration with distended spheroid bodies pervasive throughout the central nervous system. Signal hyperintensity in the cerebellar cortex can be visualized by T2-weighted MRI and is a characteristic feature of INAD. Cerebellar atrophy occurs with this disease as a result of neuronal loss, increased astrocyte formation and shrinkage of the cerebellar cortex. Some individuals develop high levels of iron accumulation in the globus pallidus. Late onset cases of INAD have been reported, and there is overlap between INAD and other types of Neurodegeneration with Brain Iron Accumulation (NBIA, OMIM #610217), such as panthokinase associated neurodegeneration (PKAN) and Karak syndrome. [1,2].

Molecular and Biochemical Genetics:

Mutations of the phospholipase A2 group IV gene (*PLA2G6*) [OMIM #603604] have been identified in patients with Karak syndrome, INAD and NBIA [2,3]. *PLA2G6* has 16 coding exons, and more than 45 different mutations have been identified. Mutations in *PLA2G6* have been found in 39/44 patients with a clinical and pathological diagnosis of INAD and in 4/24 patients diagnosed with NBIA [2]. Nonsense, missense, frameshift and splicing mutations have been detected in the *PLA2G6* gene.

The *PLA2G6* enzyme plays an important role in cell membrane homeostasis and phospholipid metabolism. Mutations in the *PLA2G6* gene may result in membrane structure abnormalities and phospholipase A2 dysfunction critical in brain iron regulation and normal axonal pathology [2].

Inheritance:

The frequency of INAD remains unknown, but the frequency of NBIA is estimated to be approximately 1-3/1,000,000 individuals. *PLA2G6* mutations are inherited in an autosomal recessive pattern. The recurrence risk for carrier parents is 25%.

Test methods:

We offer full gene sequencing of all 16 coding exons and intron/exon boundaries.

Mutation analysis (sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$2025
CPT codes:	83891, 83898x4, 83904x9, 83912
Turn-around time:	4 - 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to10 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:

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References:

1. Hayflick, S.J., Neurodegeneration with brain iron accumulation: from genes to pathogenesis. *Semin Pediatr Neurol*, 2006. **13**(3):182-185.
2. Morgan, N.V., *et al.*, *PLA2G6*, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat Genet*, 2006. **38**(7):752-754.
3. Khateeb, S., *et al.*, *PLA2G6* mutation underlies infantile neuroaxonal dystrophy. *Am J Hum Genet*, 2006. **79**(5):942-948.

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