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 mutation analysis of all 16 coding exons and intron/exon boundaries of *PLA2G6* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *PLA2G6* 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.

PLA2G6 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 - 6 weeks

PLA2G6 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
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. Neurodegeneration with brain iron accumulation: from genes to pathogenesis. Semin Pediatr Neurol 2006: 13: 182-185.
2. Morgan NV, Westaway SK, Morton JE et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Nat Genet 2006: 38: 752-754.
3. Khateeb S, Flusser H, Ofir R et al. PLA2G6 mutation underlies infantile neuroaxonal dystrophy. American journal of human genetics 2006: 79: 942-948.

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