OHSU Clinical Genetics Laboratories
Shipping Address: 2525 SW 3rd Avenue, Suite 350
Portland, OR 97201

Phone: (503) 494-5400
Fax: (503) 494-6922

Biochemical Genetics Laboratory *Cytogenetics Laboratory* *Molecular Diagnostic Center*

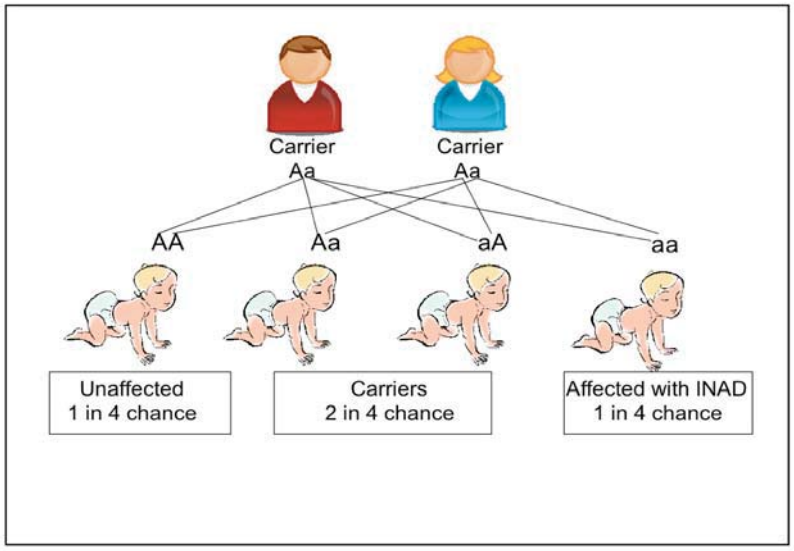
INFANTILE NEUROAXONAL DYSTROPHY
Information for Physicians

Clinical Diagnosis

Infantile neuroaxonal dystrophy (INAD) is a progressive neurodegenerative disorder that was diagnosed by clinical findings prior to discovery of the causative gene, *PLA2G6*, in 2006. For classic INAD, the most common clinical features are onset before 3 years of age, clinical evidence for CNS involvement, psychomotor regression, progression, and histopathologic evidence of dystrophic axons (spheroid bodies). The strongest corroborative features include cerebellar atrophy (seen in most cases), optic atrophy, and axial hypotonia leading to spasticity and rigidity. In about half of cases abnormal iron accumulation will be detected in the globus pallidus on T2-weighted MRI. An atypical form with later onset and slower progression also occurs in a minority of cases. For a complete review of INAD, please refer to the listing on www.genereviews.org.

Inheritance

INAD is inherited in an autosomal recessive fashion, meaning that both parents of an affected child are obligate carriers of mutations in the *PLA2G6* gene. The recurrence risk for a couple with an affected child is 1 in 4 (25%) for any future pregnancy, and each healthy sibling of an affected child has a 2 in 3 (66%) chance of being a carrier.



Molecular Genetic Testing

PLA2G6 is the only known gene associated with INAD. Clinical uses for testing include confirmation of the diagnosis, carrier testing for others such as parents or siblings, and prenatal diagnosis to determine whether a developing fetus is affected. Pre-implantation genetic diagnosis uses in vitro fertilization techniques with molecular genetic testing to predict which embryos will be affected before transfering them into the mother. PGD will be possible for families with identifiable mutations, and the OHSU Molecular Diagnostic Center can provide input to PGD centers as needed for these cases.

Testing is done by DNA sequencing of the coding region (17 exons) and splice sites to determine the presence

of disease-causing mutations and/or benign single nucleotide polymorphisms. Testing detects approximately 85% of mutations in individuals with a clinical diagnosis of INAD. For the entire population of individuals positive for *PLA2G6* mutations, approximately 10% have only one mutation identified. If the clinical findings are consistent with INAD, then it is assumed that a second mutation is present that cannot be detected by current testing methodologies.

Specimen Requirements:
Blood: ACD (solution A or B) tubes, 5 mL for adults and children, 2-3 mL for infants. Requisition form must accompany specimen, including ethnicity, clinical and family history information. Turnaround time is approximately 3 weeks.

CPT codes:
83891, 83898x17, 83904x17, 83912

Cost:
Full gene sequencing costs approximately $2050.00 (please contact lab for exact amount). Testing additional family members for known mutations is done for a reduced charge.

Testing Strategy for a Proband

Discovery of the *PLA2G6* gene has altered the testing strategy. When INAD is suspected, we recommend an ophthalmological examination and brain MRI because cerebellar atrophy and optic atrophy are strong corroborative features. If suspicion remains high, mutation scanning of *PLA2G6* is recommended as the next step instead of a nerve biopsy. If no mutations are found but the evolving phenotype remains most consistent with INAD, then a biopsy to assess for spheroid bodies could be considered.

Genetically Related (Allelic) Disorders

Mutations in *PLA2G6* have been found in individuals with Karak syndrome and neurodegeneration with brain iron accumulation (NBIA). These disorders represent the phenotypic spectrum of INAD and are no longer considered to be clinically distinct. Mutations in *PLA2G6* have also been found in 2 unrelated families with adult-onset dystonia-parkinsonism, but it is not yet clear how often this occurs or whether it should be considered part of the INAD spectrum.

Patient resources:

International INAD Research Registry
Oregon Health & Science University
Portland, OR
503-494-4344

NBIA Disorders Association
San Diego, CA
www.NBIADisorders.org
619-588-2315

International Dystrophie Neuro Axonale Infantile Association
Paris, France
http://asso.orpha.net/DNAI/

Funding for the development of this educational brochure was awarded by the Collaboration, Education and Test Translation Program for Rare Genetic Diseases, NIH Office of Rare Diseases. Updated 1/2010