PLA2G6-ASSOCIATED NEURODEGENERATION
Information for Genetics Professionals

Clinical Diagnosis

PLA2G6-associated neurodegeneration (PLAN) is an inherited group of diseases that includes three different phenotypes; classic infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (NAD), and PLA2G6-related dystonia–parkinsonism. Infantile neuroaxonal dystrophy (INAD) is an autosomal recessive 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. Another form, called atypical neuroaxonal dystrophy (NAD), has later onset and slower progression. NAD starts in early childhood to late adolescence. Features include speech delay, autistic features, abnormal gait, and dystonia. The third form, PLA2G6-related dystonia–parkinsonism, occurs most commonly in late adolescence to early adulthood. Symptoms include progressive parkinsonism, dystonia, and neuropsychiatric changes. For a complete review of PLAN, please refer to the listing on www.genereviews.org.

Molecular Genetic Testing

PLA2G6 is the only known gene associated with PLAN. Clinical uses for testing include diagnostic testing, confirmatory testing, carrier testing and prenatal diagnosis. Pre-implantation genetic diagnosis (PGD) will be possible for families with identifiable mutations, and Knight Diagnostic Laboratories can provide input to PGD centers as needed.

Testing is done by 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 PLAN. For the entire population of individuals positive for PLA2G6 mutations, approximately 10% have only one mutation identified. If the clinical findings are consistent with PLAN, 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 or atypical NAD are suspected, we recommend an ophthalmological examination and brain MRI because cerebellar atrophy and optic atrophy are strong corroborative features. If suspicion remains high, sequencing 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

Individuals with Karak syndrome, Schindler disease, and neurodegeneration with brain iron accumulation (NBIA) were found to be in the phenotypic spectrum of PLAN, and are no longer considered to be clinically distinct.

Patient resources:
International PLAN Research Registry
Oregon Health & Science University
Portland, OR
503-494-4344

NBIA Disorders Association
El Cajon, CA
www.NBIAdisorders.org
(619) 588-2315

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

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