GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Infantile Neuroaxonal Dystrophy

[*Seitelberger syndrome. Includes: Atypical Infantile Neuroaxonal Dystrophy, Classic Infantile Neuroaxonal Dystrophy*]

Allison Gregory , MS, CGC
Molecular & Medical Genetics
Oregon Health & Science University
gregorya@ohsu.edu

Susan J Hayflick , MD
Molecular & Medical Genetics, Pediatrics and Neurology
Oregon Health & Science University
hayflick@ohsu.edu

Initial Posting: June 19, 2008.

Summary

Disease characteristics. Infantile neuroaxonal dystrophy (INAD) comprises a classic form and an atypical form. Classic disease usually begins between ages six months and three years with hypotonia, progressive psychomotor delay, and symmetric pyramidal tract signs. Strabismus, nystagmus, and optic atrophy are common. Disease progression is rapid. Many affected children never learn to walk or lose the ability shortly after attaining it. Severe spasticity, progressive cognitive decline, and visual impairment typically result in death during the first decade. The atypical form is more varied than the classic form. In general, onset is in early childhood but can be as late as the late teens. The presenting signs may be gait instability or ataxia (as in the classic form) or speech delay and autistic features, which are sometimes the only evidence of disease for a year or more. The course is fairly stable during early childhood and resembles static encephalopathy but is followed by neurologic deterioration between ages seven and 12 years.

Diagnosis/testing. Before 2006, the diagnosis of INAD was established by clinical and pathologic findings alone. Since the discovery of *PLA2G6*, the only gene known to be associated with INAD, molecular genetic testing has been used to help confirm the diagnosis and, in many cases, eliminates the need for tissue biopsy.

Management. *Treatment of manifestations:* routine pharmacologic treatment of spasticity and seizures, trial of oral or intrathecal baclofen for dystonia associated with atypical INAD, control of secretions with transdermal scopolamine patch as needed, feeding modifications as needed to prevent aspiration pneumonia, treatment of neuropsychiatric symptoms by a psychiatrist. *Prevention of secondary complications:* early physical therapy and orthopedic management to prevent contractures as the disease progresses. *Surveillance:* periodic assessment of vision and hearing. *Other:* Current chelation therapies are not effective.

Genetic counseling. INAD is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the disease-causing mutations in the family are known.

Diagnosis

Clinical Diagnosis

Until 2006, when the *PLA2G6* gene was identified as causative [Morgan et al 2006], the diagnosis of infantile neuroaxonal dystrophy (INAD) was established by clinical and pathologic findings alone. Currently, molecular genetic testing helps confirm the diagnosis and in many cases eliminates the need for tissue biopsy.

Note: Assessment of a large cohort of individuals with INAD clarified the clinical findings of classic INAD. Screening of additional individuals with idiopathic neurodegeneration with brain iron accumulation (NBIA) for *PLA2G6* mutations identified individuals with atypical NAD [Kurian et al 2008; Gregory et al, in press].

Classic INAD

Predominant features

- Onset before age three years
- Psychomotor regression (most common presenting feature)
- Cerebellar atrophy (see Figure 1)
- Optic atrophy
- Characteristic pattern of early truncal hypotonia followed by development of tetraparesis (usually spastic but sometimes areflexic)
- Histopathologic evidence of dystrophic axons on biopsy from one or more of the following tissues: conjunctiva, skin, rectum, muscle, or other peripheral nerve (sural). Dystrophic axons viewed by electron microscopy (EM) exhibit:
  - Membranotubular profiles
  - Mitochondrial aggregates
  - Increased axonal diameter and thinned membrane

Other common features

- Symmetric pyramidal tract signs
- Nystagmus
- Strabismus
- Bulbar dysfunction
- Ataxia
- EMG (electromyogram): evidence of denervation
- EEG (electroencephalogram): fast rhythms
- VEP (visual evoked potential): delayed with reduced amplitudes
- NCV (nerve conduction velocity): decreased
- T2-weighted MRI of the brain: hypointense globus pallidus (indicating iron accumulation), cortical cerebellar hyperintensities, white matter abnormalities, thinning of corpus callosum (see Figure 1)

Atypical NAD

Predominant features

- Onset before age 20 years
- Psychomotor regression
- Disease progression slower than in classic disease
- Cerebellar atrophy
- Optic atrophy
- Progressive dystonia and dysarthria
- T2-weighted MRI of the brain: hypointense globus pallidus (indicating iron accumulation)
- Histopathologic evidence of dystrophic axons identical to that described for classic INAD

Other common features

- Psychiatric/behavioral abnormalities
- Spasticity (without preceding hypotonia)
- Joint contractures
- Seizures
- Nystagmus
- VEP: delayed with reduced amplitudes

Note: MRI of the brain and ophthalmologic examination are keys to establishing strong clinical features of INAD.

Testing

Tissue biopsy. Before the availability of molecular genetic testing, identification of dystrophic axons on electron microscopic examination of nerve ultrastructure in a tissue biopsy of conjunctiva, skin, muscle, sural nerve, or rectum was the finding necessary to establish the diagnosis of INAD. Because axonal spheroids accumulate with age and may not be evident in all tissues, individuals with INAD may require multiple biopsies over time before axonal spheroids are identified. Therefore, a negative biopsy cannot rule out INAD; a positive biopsy is considered diagnostic.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PLA2G6* is the only gene known to be associated with INAD and atypical NAD.

Other loci. Linkage data support the presence of at least one additional INAD locus [Morgan et al 2006].

Clinical testing

- **Sequence analysis**. Sequence analysis of the coding region and splice sites of *PLA2G6* is thought to identify approximately 85% of mutations. For the entire population of individuals positive for *PLA2G6* mutations, approximately 10% have only one allele identified [NBIA International Mutation Database, unpublished data].

Research testing

- **Deletion/duplication testing**. Large intragenic deletions may account for some of the mutations not detected by sequence analysis. This possibility is based on the presence of individuals in whom only one mutation is identifiable by mutation scanning.

Table1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Infantile Neuroaxonal Dystrophy

Gene Symbol	Proportion of INAD Attributed to Mutations in This Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
PLA2G6	~95%	Sequence analysis	Sequence variants	85%	Clinical Testing
		Deletion/ duplication testing [1]	Exonic or whole-gene deletions	Unknown	Research only

1. Testing that detects deletions/duplications not readily detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), and array CGH may be used.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

The steps to confirm the diagnosis in a proband have been altered by the advent of molecular genetic testing.

When the clinician suspects a diagnosis of INAD, an ophthalmologic examination and brain MRI are recommended first because optic atrophy and cerebellar atrophy are strong clinical features:

- If suspicion remains high, molecular genetic testing of *PLA2G6* is recommended as the next step instead of an invasive biopsy.
- If no *PLA2G6* mutations are found but the evolving phenotype remains most consistent with INAD, a biopsy to assess for axonal spheroids could be considered. Preferred tissues are, in order: conjunctiva, skin, rectum, other peripheral nerve.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

Though still only speculative, mutations in *PLA2G6* may underlie Schindler disease as well. This may explain the discordance between the clinical and biochemical phenotypes observed in Schindler disease, which is categorized as a neuroaxonal dystrophy. Schindler disease was

originally reported in sibs with early-onset, rapidly progressive psychomotor regression, evidence of axonal spheroids, and deficiency of α-N-acetylgalactosaminidase (α-NAGA) [Schindler et al 1989]. Alpha-NAGA deficiency underlies the oligosaccharidruria found in Schindler disease, but its causal role in the neurologic phenotype has been questioned because other persons with α-NAGA deficiency have a spectrum of clinical findings ranging from angiokeratoma to no abnormalities [Keulemans et al 1996, Bakker et al 2001].

The authors have proposed that mutations in *PLA2G6* account for the early-onset neurodegenerative phenotype that occurs in a subset of individuals with Schindler disease based on their common clinical and pathologic features, their interrelatedness, and the proximity of *PLA2G6* to *NAGA* on chromosome 22 [Westaway et al 2007]. Molecular genetic testing of samples from the original sibs diagnosed with Schindler disease should resolve this question; such samples have not been available.

Clinical Description

Natural History

Classic INAD. Onset of classic disease usually occurs between ages six months and three years. Disease presents with psychomotor delay, delayed walking, or gait disturbance. Eventually, psychomotor regression is evident with loss of previously acquired milestones.

Truncal hypotonia, observed early in disease course, is eventually replaced by spastic tetraparesis, a characteristic of progression specific to infantile neuroaxonal dystrophy (INAD). Symmetric pyramidal tract signs are also frequently seen.

Visual signs and symptoms are common. Strabismus and nystagmus are early features of the disease. Later optic atrophy occurs in most cases. Optic atrophy may be observed early as optic nerve pallor; thin optic chiasm and tracts have also been reported on brain MRI [Farina et al 1999].

Seizures occur in a minority of individuals as a later symptom [Nardocci et al 1999].

The progression of disease is usually rapid. Many affected children never learn to walk or lose this ability shortly after attaining it. During the end stages of disease, severe spasticity, progressive cognitive decline, and visual impairment result in a vegetative state. Death occurs as a result of secondary illnesses such as aspiration pneumonia, associated with bulbar dysfunction. Many affected children do not survive beyond their first decade, but some survive into their teens or later. Supportive care can contribute to a longer life span by reducing the risk of infection and other complications.

Atypical NAD. Whereas the features of classic INAD are relatively homogeneous, atypical disease is quite varied.

In general, onset in atypical cases is in early childhood but can be as late as the late teens. In a series of 13 individuals, four had onset by age three years but a fairly stable course during early childhood resembling static encephalopathy, followed by neurologic deterioration between ages seven and 12 years [Nardocci et al 1999].

The presenting signs and symptoms may be similar to classic INAD, including gait instability or ataxia. Others may present with speech delay and autistic features, which may remain as the only evidence of disease for a year or more given the slow progression of atypical disease compared to classic disease [Gregory et al, in press].

Although tetraparesis (i.e., spasticity) is present late in the disease, it is not necessarily preceded by early truncal hypotonia. In contrast to classic disease, extrapyramidal findings (i.e., dystonia and dysarthria) predominate in atypical cases. Eye findings are similar to classic INAD. Neuropsychiatric disturbances including impulsivity, poor attention span, hyperactivity, and emotional lability are also common [Gregory et al, in press].

Aypical cases are rare, and the life span is not known; however, it is expected to be longer than that observed in classic disease.

Genotype-Phenotype Correlations

Genotype correlates with phenotype to a limited extent:

- All individuals with two null alleles of *PLA2G6* had classic INAD.
- The less severe atypical NAD phenotype is caused exclusively by compound heterozygosity for missense mutations.

Nomenclature

Outdated terms. Seitelberger [1952] first described this condition, which was originally named Seitelberger disease.

Karak syndrome was described in two sibs with early-onset cerebellar ataxia, dystonia, spasticity, and intellectual decline. MRI findings included cerebellar atrophy and iron accumulation in the globus pallidus and substantia nigra [Mubaidin et al 2003]. Morgan et al (2006) identified mutations in *PLA2G6* in individuals with Karak syndrome, which is now included in the phenotypic spectrum of INAD and is no longer considered to be a clinically distinct entity.

Current nomenclature. In addition to INAD, later-onset variants have been called late infantile, juvenile, or atypical neuroaxonal dystrophy and neurodegeneration with brain iron accumulation (NBIA).

The authors propose the following usage:

- **Classic INAD** for early-onset, rapidly progressive disease
- **Atypical NAD** for later childhood-onset disease with slower progression and extrapyramidal findings (dystonia, dysarthria). The atypical NAD phenotype is expected to include a broad range of presentations.

Prevalence

Disease prevalence is not established; it is estimated at approximately 1:1,000,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Infantile Neuroaxonal Dystrophy (INAD)

Early diagnosis of infantile neuroaxonal dystrophy (INAD) is challenging because the initial symptoms of psychomotor regression and progression are also observed in other conditions.

The degree of weakness early in the disease course may initially direct the clinician toward a myopathy or spinal muscular atrophy.

Cerebellar atrophy can be detected by brain MRI before age two years in some children [Farina et al 1999]. The differential diagnosis for childhood cerebellar atrophy includes infantile neuronal ceroid-lipofuscinosis (Santavuori-Haltia), ataxia-telangectasia, and hereditary ataxia; however, cerebellar atrophy usually presents later for these disorders.

Forty to 50% of individuals with INAD have abnormal iron accumulation in the basal ganglia (primarily the globus pallidus), which is best detected on T2-weighted MRI. For this reason, conditions included in the NBIA category should also be considered in the differential diagnosis of INAD. Individuals with INAD have not been found to have an eye-of-the-tiger sign, which specifically correlates with pantothenate kinase-associated neurodegeneration (PKAN) [Hayflick et al 2003].

Since the identification of *PLA2G6* mutations as causative of INAD, the need for invasive nerve biopsy to aid in diagnosis has decreased. While the presence of axonal spheroids in peripheral tissues remains specific to INAD, spheroids are found in brain in a few other conditions, including PKAN, idiopathic NBIA, infantile GM2 gangliosidosis (see Hexosaminidase A Deficiency), Niemann-Pick disease type C, and Menkes disease (see ATP7A-Related Copper Transport Disorders).

Atypical Neuroaxonal Dystrophy (NAD)

Initial speech delay and limited social interaction may be consistent with autism (see Autism Overview).

Spasticity, dystonia, and dysarthria, findings similar to those of other forms of NBIA, eventually predominate; high brain iron in the globus pallidus and substantia nigra has been observed in nearly all cases, although ascertainment is likely to be biased [Gregory et al, in press]. Therefore, idiopathic NBIA should also be considered in the differential diagnosis of atypical NAD. PKAN may present with similar features.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with infantile neuroaxonal dystrophy (INAD), the following evaluations are recommended:

- Thorough ophthalmologic examination (if not performed during the diagnostic evaluation) to assess for optic atrophy
- EEG for the possibility of unrecognized seizure activity

Note: The extent of disease is often well-characterized by the time of diagnosis, since the diagnostic work-up frequently includes neurophysiologic studies (EEG, EMG, electroretinogram (ERG), and/or visual evoked potentials) and brain MRI.

Treatment of Manifestations

The following treatments for INAD are palliative:

- Pharmacologic treatment of spasticity and seizures
- Trial of oral or intrathecal baclofen for those with atypical INAD who have significant dystonia (see Dystonia Overview)
- Treatment by a psychiatrist for those with a later-onset, more protracted course accompanied by neuropsychiatric symptoms

- Over-the-counter fiber supplements and/or stool softeners to treat constipation that is likely caused by a combination of immobility, diet, and medications
- Transdermal scopolamine patch to reduce the volume of secretions in those with excessive drooling or difficulty controlling secretions
- Measures such as a gastric feeding tube or tracheostomy as needed to prevent aspiration pneumonia

Prevention of Secondary Complications

A rehabilitation program including physical therapy and orthopedic management should be initiated early in the disease course to prevent contractures when the individual is permanently nonambulatory.

Surveillance

Periodic assessment of vision and hearing of nonverbal children is indicated as needed to determine the level of sensory deficits.

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Because a portion of individuals with INAD have high brain iron and this disorder falls into the category of NBIA, the option of chelation therapy is sometimes raised. Anecdotal evidence suggests that current chelation therapies are unable to reduce brain iron levels, and this type of therapy is not currently recommended.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Infantile neuroaxonal dystrophy (INAD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and, therefore, carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Individuals with INAD have not been known to reproduce.

Other family members of a proband. Each sib of the proband's parents is at 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is possible if the disease-causing mutations in the family are known. The following situations may arise when carrier detection is pursued by at-risk individuals and their reproductive partners:

- Two disease-causing *PLA2G6* mutations are identified in the proband. In this case, the at-risk family member can be offered testing for the family-specific mutations to clarify his/her carrier status.
- Only one *PLA2G6* mutation is identified in the proband. Molecular genetic testing will be informative for relatives related to the parent with the identifiable mutation. Molecular genetic testing will not be informative for relatives related to the carrier parent in whom no mutation has been identified.
- Neither disease-causing mutation is identified in the proband. Molecular genetic testing of relatives will not be informative.
- The proband is deceased, and no DNA-based testing was performed. It is appropriate to attempt to obtain any available tissue samples for DNA extraction for *PLA2G6* molecular genetic testing. If DNA cannot be obtained, it is appropriate to test at-risk family members following genetic counseling in which the limitations of testing are explained. For those family members in whom a *PLA2G6* mutation is not identified, a revised carrier risk can be calculated.
- A person has a reproductive partner who is a known carrier or is at risk of being a carrier. The reproductive partners of carriers or those at risk of being carriers can be offered molecular genetic testing with the understanding that a negative result can reduce but does not eliminate their risk of being a carrier.

Related Genetic Counseling Issues

Testing at-risk sibs. The proband may have younger or similarly-aged sibs who could be affected. Although early diagnosis is not likely to significantly reduce morbidity or mortality, the family may desire testing of the at-risk sibs:

- If both *PLA2G6* mutations have been identified in the proband, the sibs may be tested to determine if they have inherited both *PLA2G6* disease-causing mutations.
- If the *PLA2G6* mutations have not been identified in the proband, a plan for assessing at-risk sibs should be designed based on the primary findings in the proband and the established clinical criteria for INAD. Evaluations are likely to include brain MRI, ophthalmologic assessment, and possibly biopsy for histologic examination of peripheral nerves (see Diagnosis).

  Note: Neither the absence of axonal spheroids nor a normal brain MRI rules out INAD, as these findings develop over time and spheroids vary by location. Diagnostic tests may need to be repeated at a later age for at-risk sibs in families without *PLA2G6* mutations. A normal MRI and absence of other symptoms (including regression) in a sib who is older than the affected sibling was when cerebellar atrophy and/or other symptoms were present is reassuring.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing for pregnancies at increased risk is possible by molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing mutations in the *PLA2G6* gene must be identified in the affected sib or both parents before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Infantile Neuroaxonal Dystrophy

Gene Symbol	Chromosomal Locus	Protein Name
PLA2G6	22q13.1	85 kDa calcium-independent phospholipase A2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Infantile Neuroaxonal Dystrophy

256600	NEUROAXONAL DYSTROPHY, INFANTILE; INAD1
603604	PHOSPHOLIPASE A2, GROUP VI; PLA2G6
610217	NEURODEGENERATION WITH BRAIN IRON ACCUMULATION, PLA2G6-RELATED

Table C. Genomic Databases for Infantile Neuroaxonal Dystrophy

Gene Symbol	Entrez Gene	HGMD
PLA2G6	8398 (MIM No. 603604)	PLA2G6

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The *PLA2G6* gene encodes iPLA$_2$-VIA, a calcium-independent phospholipase. This family of phospholipase A$_2$ enzymes catalyzes the hydrolysis of glycerophospholipids, generating a free fatty acid (usually arachidonic acid) and a lysophospholipid. The encoded protein has proposed roles in phospholipid remodeling, arachidonic acid release, leukotriene and prostaglandin synthesis, and apoptosis [Balsinde & Balboa 2005]. The iPLA$_2$ enzymes play a critical role in cell membrane homeostasis by helping to regulate levels of phospholipids [Baburina & Jackowski 1999]. Defects in iPLA$_2$-VIA could lead to a relative abundance of membrane phospholipids or skewing of the proportions of specific species and secondary structural abnormalities, which may contribute to the axonal pathology observed in INAD [Morgan et al 2006].

Normal allelic variants: The *PLA2G6* gene has 17 exons that are alternatively spliced to create transcripts encoding multiple protein isoforms [Larsson et al 1998]. No commonly occurring gene polymorphisms have been identified to date.

Pathologic allelic variants: The original report of disease-causing mutations in *PLA2G6* described 44 unique mutations, including 32 missense, five deletions leading to a frameshift, three nonsense, two leading to amino-acid deletions without a frameshift, one splice site, and one large deletion [Morgan et al 2006]. Some mutations have been identified in multiple families reported to be unrelated, although several share ethnic backgrounds [NBIA International Mutation Database, unpublished data].

Normal gene product: *PLA2G6* encodes iPLA$_2$-VIA, one of several calcium-independent phospholipases. The protein is active as a tetramer. *PLA2G6* transcript variants encode multiple isoforms [Larsson et al 1998].

Abnormal gene product: The two enzymatically active forms of the protein are predicted to be affected by all of the mutations reported to date [Morgan et al 2006]. A subset of mutations would also alter the shorter enzymatically inactive isoforms, which seem to act as dominant-negative inhibitors when incorporated in the tetramer [Larsson et al 1998, Balsinde & Balboa 2005].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Dystrophie Neuro Axonale Infantile
http://asso.orpha.net/DNAI

NBIA Disorders Association
2082 Monaco Court
El Cajon CA 92019-4235
Phone: 619-588-2315
Fax: 619-588-4093
Email: info@NBIAdisorders.org
www.nbiadisorders.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Baburina I, Jackowski S. Cellular responses to excess phospholipid. *J Biol Chem* 1999;274:9400–8. [PubMed: 10092620]

Bakker HD, de Sonnaville ML, Vreken P, Abeling NG, Groener JE, Keulemans JL, van Diggelen OP. Human alpha-N-acetylgalactosaminidase (alpha-NAGA) deficiency: no association with neuroaxonal dystrophy? *Eur J Hum Genet* 2001;9:91–6. [PubMed: 11313741]

Balsinde J, Balboa MA. Cellular regulation and proposed biological functions of group VIA calcium-independent phospholipase A2 in activated cells. *Cell Signal* 2005;17:1052–62. [PubMed: 15993747]

Farina L, Nardocci N, Bruzzone MG, D'Incerti L, Zorzi G, Verga L, Morbin M, Savoiardo M. Infantile neuroaxonal dystrophy: neuroradiological studies in 11 patients. *Neuroradiology* 1999;41:376–80. [PubMed: 10379598]

Gregory A, Westaway SK, Holm IE, Kotzbauer PT, Hogarth P, Sonek S, Coryell JC, Nguyen TM, Nardocci N, Zorzi G, Rodriguez D, Desguerre I, Bertini E, Simonati A, Levinson B, Dias C, Barbot C, Carrilho I, Santos M, Malik I, Gitschier J, Hayflick SJ. Neurodegeneration associated with genetic defects in phospholipase A2. *Neurology*.

Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003;348:33–40. [PubMed: 12510040]

Keulemans JL, Reuser AJ, Kroos MA, Willemsen R, Hermans MM, van den Ouweland AM, de Jong JG, Wevers RA, Renier WO, Schindler D, Coll MJ, Chabas A, Sakuraba H, Suzuki Y, van Diggelen OP. Human alpha-N-acetylgalactosaminidase (alpha-NAGA) deficiency: new mutations and the paradox between genotype and phenotype. *J Med Genet* 1996;33:458–64. [PubMed: 8782044]

Kurian MA, Morgan NV, MacPherson L, Foster K, Peake D, Gupta R, Philip SG, Hendriksz C, Morton JE, Kingston HM, Rosser EM, Wassmer E, Gissen P, Maher ER. Phenotypic spectrum of neurodegeneration associated with mutations in the PLA2G6 gene (PLAN). *Neurology* 2008;70:1623–9. [PubMed: 18443314]

Larsson PK, Claesson HE, Kennedy BP. Multiple splice variants of the human calcium-independent phospholipase A2 and their effect on enzyme activity. *J Biol Chem* 1998;273:207–14. [PubMed: 9417066]

Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, Cangul H, Coryell J, Canham N, Nardocci N, Zorzi G, Pasha S, Rodriguez D, Desguerre I, Mubaidin A, Bertini E, Trembath RC, Simonati A, Schanen C, Johnson CA, Levinson B, Woods CG, Wilmot B, Kramer P, Gitschier J, Maher ER, Hayflick SJ. PLA2G6, encoding a phospholipase A(2), is mutated in neurodegenerative disorders with high brain iron. *Nat Genet* 2006;38:752–4. [PubMed: 16783378]

Mubaidin A, Roberts E, Hampshire D, Dehyyat M, Shurbaji A, Mubaidien M, Jamil A, Al-Din A, Kurdi A, Woods CG. Karak syndrome: a novel degenerative disorder of the basal ganglia and cerebellum. *J Med Genet* 2003;40:543–6. [PubMed: 12843330]

Nardocci N, Zorzi G, Farina L, Binelli S, Scaioli W, Ciano C, Verga L, Angelini L, Savoiardo M, Bugiani O. Infantile neuroaxonal dystrophy: clinical spectrum and diagnostic criteria. *Neurology* 1999;52:1472–8. [PubMed: 10227637]

Schindler D, Bishop DF, Wolfe DE, Wang AM, Egge H, Lemieux RU, Desnick RJ. Neuroaxonal dystrophy due to lysosomal alpha-N-acetylgalactosaminidase deficiency. *N Engl J Med* 1989;320:1735–40. [PubMed: 2733734]

Seitelberger F (1952) Eine unbekannte Form von infantiler lipoid-Speicher Krankheit des Gehirns. Paper presented at Proc 1st Intl Cong of Neuropathology. Rome, 1952

Westaway SK, Gregory A, Hayflick SJ. Mutations in PLA2G6 and the riddle of Schindler disease. *J Med Genet* 2007;44:e64. [PubMed: 17209134]

Chapter Notes

Acknowledgments

This work was supported in part by grants from the National Institute of Child Health and Human Development, the National Eye Institute, L'Association Internationale De Dystrophie Neuro Axonale Infantile, and the NBIA Disorders Association. This work was made possible by support from the Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1 RR024140 01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

Revision History

- 19 June 2008 (me) Review posted live
- 14 June 2007 (ag) Original submission

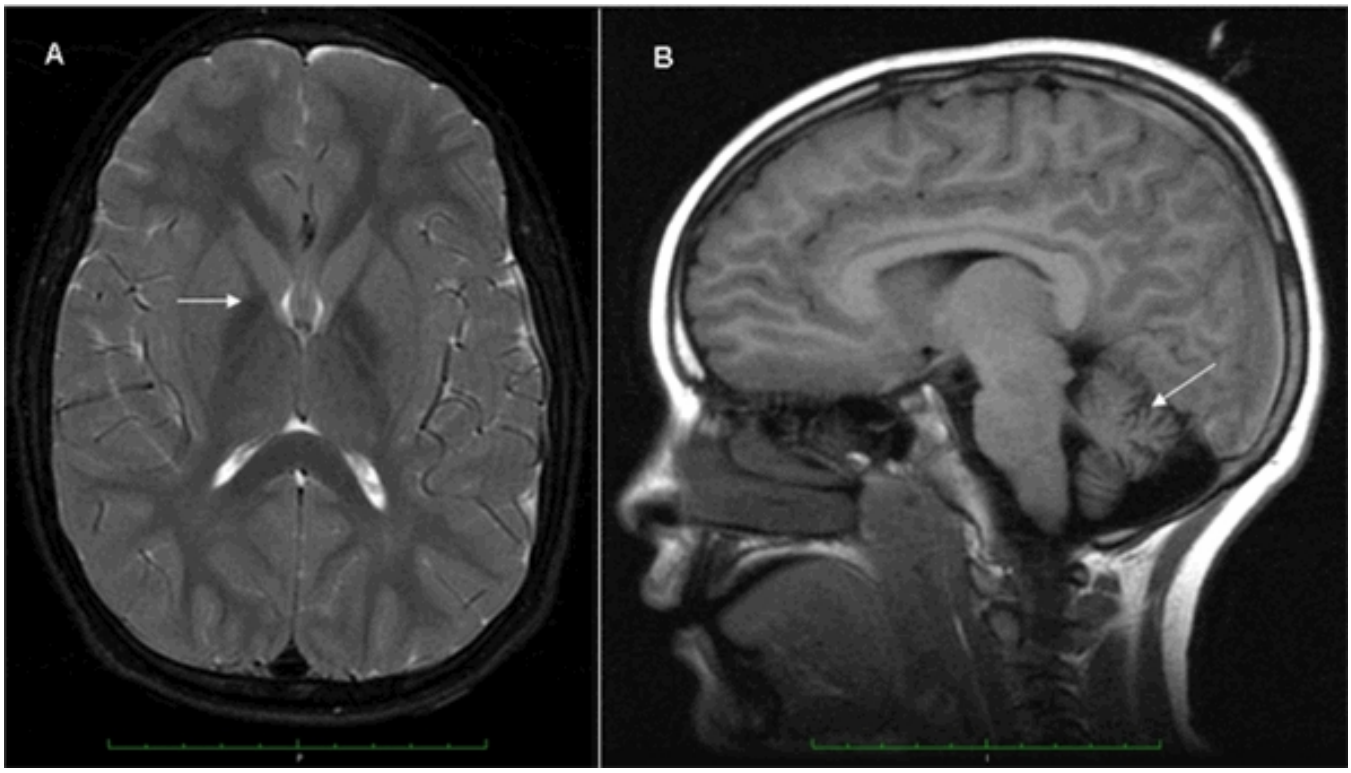

Figure 1. Panel A. Left axial image shows high brain iron in the globus pallidus (see arrow) on T2-weighted MRI. Panel B. Right sagittal image shows cerebellar atrophy (see arrow).