GENEReviews

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Childhood Ataxia with Central Nervous System Hypomyelination/ Vanishing White Matter

[*Leukoencephalopathy with Vanishing White Matter, CACH/VWM . Includes: EIF2B1-, EIF2B2-, EIF2B3-, EIF2B4-, and EIF2B5-Related Childhood Ataxia with Central Nervous System Hypomyelination/Vanishing White Matter*]

Raphael Schiffmann, MD
Clinical Investigations Section
Developmental and Metabolic Neurology Branch
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD

Anne Fogli, PhD
Faculty of Medicine
INSERM UMR 384
Clermont-Ferrand

Marjo S Van der Knaap, MD, PhD
Department of Child Neurology
VU University Medical Center
Amsterdam

Odile Boespflug-Tanguy, MD, PhD
Reference Center for Leukodystrophies
Department of Human Genetics
Clermont-Ferrand University Hospital and Faculty of Medicine
INSERM UMR 384
Clermont-Ferrand

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Summary

Disease characteristics. Childhood ataxia with central nervous system hypomyelination/ vanishing white matter disease (CACH/VWM) is characterized by ataxia, spasticity, and variable optic atrophy. The phenotypes range from a prenatal/congenital form to a subacute infantile form (onset age <1 year), an early childhood-onset form (onset age 1-5 years), a late childhood-/juvenile-onset form (onset age 5-15 years), and an adult-onset form. The prenatal/ congenital form is characterized by severe encephalopathy. In the later-onset forms initial motor and mental development is normal or mildly delayed followed by neurologic deterioration with a chronic progressive or subacute course. Chronic progressive decline can be exacerbated by rapid deterioration during febrile illnesses or following head trauma or major surgical procedures, or by acute psychological stresses such as extreme fright.

Diagnosis/testing. The diagnosis of CACH/VWM can be made with confidence in individuals with typical clinical findings, characteristic abnormalities on cranial MRI, and identifiable mutations in one of five causative genes *(EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) encoding the five subunits of the eucaryotic translation initiation factor, eIF2B. Mutations have been found in approximately 90% of individuals with CACH/VWM using sequence analysis or mutation scanning.

Management. *Treatment of manifestations:* physical therapy and rehabilitation for motor dysfunction (mainly spasticity and ataxia); antiepileptic drugs for seizures. *Prevention of secondary complications:* prevention of infections and fever when possible through the use of vaccinations, low-dose maintenance antibiotics during winter, antibiotics for minor infections, and antipyretics for fever. *Surveillance:* close monitoring of neurologic status for several days following head trauma or surgical procedures with anesthesia. *Agents/circumstances to avoid:* contact sports; head trauma; stressful situations, such as high body temperature.

Genetic counseling. CACH/VWM 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. Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutations in an affected relative have been identified.

Diagnosis

Clinical Diagnosis

The diagnosis of childhood ataxia with central nervous system hypomyelination/ leukoencephalopathy with vanishing white matter (CACH/VWM) can be made with confidence in individuals with typical clinical findings, characteristic abnormalities on cranial MRI [van der Knaap et al 1997], and identifiable mutations in one of the five causative genes *(EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) encoding the five subunits of the eucaryotic translation initiation factor, eIF2B [Leegwater et al 2001, van der Knaap et al 2002].

Clinical findings

- Antenatal/early-infantile forms are characterized by severe encephalopathy; oligohydramnios, intrauterine growth retardation, microcephaly, contractures, cataract, pancreatitis, hepatosplenomegaly, and renal hypoplasia may be present.
- In all later-onset forms initial motor and mental development is normal or mildly delayed.
- Neurologic deterioration has a chronic progressive or subacute course. Episodes of subacute deterioration may follow minor infection or minor head trauma and may lead to lethargy or coma.
- Clinical examination usually shows a combination of truncal and appendicular ataxia, pyramidal signs, and spasticity with increased tendon reflexes. The peripheral nervous system is usually not involved.
- Optic atrophy may develop.
- Epilepsy may occur but is not the predominant sign of the disease except in an acute situation.
- Mental abilities may be affected but not to the same degree as motor functions. Alteration in mental abilities associated with behavioral changes can be the initial symptom in adult-onset forms.
- Ovarian dysgenesis may be present as primary or secondary amenorrhea.

MRI findings

- The cerebral hemispheric white matter is symmetrically and diffusely abnormal.

- The abnormal white matter has a signal intensity close to or the same as cerebrospinal fluid (CSF) on T1-weighted (Figure 1), T2-weighted (Figure 2), and fluid-attenuated inversion recovery (FLAIR) (Figure 3) images.
- On T1-weighted and FLAIR images, a fine meshwork of remaining tissue strands is usually visible within the areas of CSF-like white matter, with a typical radiating appearance on sagittal and coronal images and a dot-like pattern in the centrum semiovale on the transverse images (Figure 4) [van der Knaap et al 1997,van der Knaap et al 2002].

The MRI abnormalities are present in all affected individuals regardless of age of onset and are even present in asymptomatic at-risk sibs of a proband. Over time, increasing amounts of white matter vanish and are replaced with CSF; cystic breakdown of the white matter is seen on proton density or FLAIR images [van der Knaap et al 1998]. Cerebellar atrophy varies from mild to severe and primarily involves the vermis.

Supratentorial cortico-subcortical atrophy can be observed in adult-onset forms with slow progression. Cranial CT scan is of limited use and usually shows diffuse and symmetric hypodensity of the hemispheric white matter with no calcifications.

Testing

Routine laboratory tests, including CSF analysis, are normal.

The asialotransferrin/total transferrin ratio was found to be low in persons with genetically confirmed CACH/VWM, a finding that can help identify those likely to have mutations in any of the five genes encoding the eIF2B1 subunits detected on sequence analysis. Such testing is available on a research basis only.

Neuropathologic findings in general are a "cavitating orthochromatic leukodystrophy with rarity of myelin breakdown and relative sparing of axons." Vacuolation and cavitation of the white matter are diffuse, giving a spongiform appearance. Cerebral and cerebellar myelin is markedly diminished, whereas the spinal cord is relatively spared.

Oligodendrocytes are increased in number [Rodriguez et al 1999, van Haren et al 2004], whereas astrocytes are decreased, especially in the severe infantile form [Francalanci et al 2001]. The hallmark is the presence of oligodendrocytes with "foamy" cytoplasm and markedly hypotrophic and sometimes atypical astrocytes [Wong et al 2000].

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—Genes. Mutations in the five genes *(EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) encoding the five subunits of the eukaryotic translation initiation factor eIF2B are known to be associated with CACH/VWM.

Other loci. Approximately 10% of families with CACH/VWM diagnosed by MRI and clinical criteria do not have an identifiable mutation on sequence analysis of *EIF2B1-5*, suggesting the possibility of causative mutations in other genes, such as the recently described apparently autosomal dominant disorder for which the gene is still unknown [Labauge et al 2005, van der Knaap & Scheper 2006a, van der Knaap & Scheper 2006b].

Clinical testing

- **Sequence analysis/mutation scanning.** Mutations in *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5* have been found in approximately 90% of individuals with clinical and MRI presentation of CACH/VWM by use of mutation scanning or sequence analysis of the coding regions and splice sites [Fogli, Schiffmann, Bertini et al 2004; Fogli & Boespflug-Tanguy et al 2006; Pronk et al 2006; van der Knaap, Pronk et al 2006].
  - Approximately 90% of mutations are missense [Fogli, Schiffmann, Bertini et al 2004].
  - Affected individuals are homozygotes or compound heterozygotes for mutations within the same gene.
  - Mutations have been found in affected individuals of all ethnic origins [Leegwater et al 2001; Fogli, Wong et al 2002; van der Knaap et al 2002; Fogli, Schiffmann, Bertini et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in CACH/VWM

Test Type	Mutations Detected	Proportion of CACH/VWM Attributed to Mutations in This Gene [1]	Mutation Detection Frequency [2]	Test Availability
Sequence analysis/ mutation scanning	*EIF2B1* sequence variants	4%	~90%	Clinical Testing
	EIF2B2 sequence variants	15%		Clinical Testing
	EIF2B3 sequence variants	7%		Clinical Testing
	EIF2B4 sequence variants	17%		Clinical Testing
	EIF2B5 sequence variants	57%		Clinical Testing

1. Leegwater et al 2001; van der Knaap et al 2002; van der Knaap et al 2003; Fogli, Schiffmann, Bertini et al 2004; Ohtake et al 2004, Fogli & Boespflug-Tanguy 2006; Scali et al 2006
2. In individuals with MRI-confirmed CACH/VWM

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

Testing Strategy

To confirm the diagnosis in a proband, molecular genetic testing (in order) of *EIF2B5*, *EIF2B4*, *EIF2B2*, *EIF2B3*, and *EIF2B1* is recommended.

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

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

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

Thus far, all individuals with eIF2B-related disease have a leukodystrophy; no other phenotypes have been observed.

Clinical Description

Natural History

Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM) phenotypes range from a congenital or early-infantile form to a subacute infantile form (onset age <1 year), an early childhood-onset form (onset age 1-5 years), a late childhood-/juvenile-onset form (onset age 5-15 years), and an adult-onset form [Fogli & Boespflug-Tanguy 2006]. Both the childhood and juvenile forms have been observed in sibs [Leegwater et al 2001]; the infantile and juvenile/adult forms have never been observed within the same family.

Neurology. The neurologic signs include ataxia, spasticity, and variable optic atrophy. In the early-onset forms, the encephalopathy is severe, seizures are often a predominant clinical feature and decline is rapid and followed quickly by death; in the later-onset forms, decline is usually slower and milder [van der Knaap et al 2002]. Chronic progressive decline can be exacerbated by rapid deterioration during febrile illness or following minor head trauma or fright [Vermeulen et al 2005, Kaczorowska et al 2006].

Ovarian failure. While the juvenile and adult forms are often associated with primary or secondary ovarian failure, a syndrome referred to as "ovarioleukodystrophy" [Schiffmann et al 1997, Fogli et al 2003], ovarian dysgenesis may occur in any of the forms regardless of age of onset [van der Knaap et al 2003]; it has been found at autopsy in infantile and childhood cases. Because the affected individuals were prepubertal, the ovarian dysgenesis was clinically not manifest.

Antenatal form. The antenatal-onset form presents in the third trimester of pregnancy with oligohydramnios and decreased fetal movement [van der Knaap et al 2003]. Clinical features that may be noted soon after birth include feeding difficulties, vomiting, hypotonia, mild contractures, and cataract (sometimes oil droplet cataract) and microcephaly. Apathy, intractable seizures, and finally apneic spells and coma follow. Other organ involvement can include hepatosplenomegaly, renal hypoplasia, pancreatitis, and ovarian dysgenesis.

The clinical course is rapidly and relentlessly downhill; the adverse effect of stress factors is less clear. So far, all infants with neonatal presentation have died within the first year of life [van der Knaap et al 2003].

Infantile form. A rapidly fatal severe form of CACH/VWM is characterized by onset in the first year of life and death a few months later [Francalanci et al 2001; Fogli, Dionisi-Vici et al 2002; Fogli, Wong et al 2002]. Two sisters described by Francalanci et al (2001) developed irritability, stupor, and rapid loss of motor abilities following an intercurrent infection at age ten to 11 months and died at age 21 months.

Another infantile-onset phenotype was described as "Cree leukoencephalopathy" because of its occurrence in the native North American Cree and Chippewayan indigenous population [Fogli, Wong et al 2002]. Infants typically have hypotonia followed by sudden onset of seizures (age 3-6 months), spasticity, rapid breathing, vomiting (often with fever), developmental regression, blindness, lethargy, and cessation of head growth, with death by age two years.

Early childhood-onset form. Initially most children develop normally; some have mild motor or speech delay. New-onset ataxia is the most common initial symptom between ages one and five years [Hanefeld et al 1993]. Some children develop dysmetric tremor or become comatose, spontaneously or acutely following mild head trauma or febrile illness [Schiffmann et al 1994, van der Knaap et al 1997].

Subsequently, generally progressive deterioration results in increasing difficulty in walking, tremor, spasticity with hyperreflexia, dysarthria, and seizures. Once a child becomes nonambulatory, the clinical course may remain stable for several years. Swallowing difficulties and optic atrophy develop late in the disease.

Head circumference is usually normal; however, severe progressive megalencephaly occurring after age two years has been reported [Passemard et al 2007], and microcephaly has also been observed. The peripheral nervous system is usually normal, although predominantly sensory nerve involvement has been reported in recent cases [Federico et al 2006, Huntsman et al 2007]. Mental abilities are relatively preserved.

The time course of disease progression varies from individual to individual even within the same family, ranging from rapid progression with death occurring one to five years after onset to very slow progression with death occurring many years after onset.

Late-childhood/juvenile-onset form. Children develop symptoms between ages five and 15 years. They often have a more slowly progressive spastic diplegia, relative sparing of cognitive ability, and likely long-term survival with long periods of stability and even improvement of motor function [Schiffmann et al 1994, van der Knaap et al 1998]. However, rapid progression and death after a few months have also been described [van der Knaap et al 1998].

Adult-onset form. Behavioral problems associated with cognitive decline are frequently reported before neurologic symptoms appear [Denier et al 2007]. Acute, transient neurologic symptoms (optic neuritis, hemiparesis) or severe headache, as well as primary or secondary amenorrhea in females, can be the presenting symptoms.

Asymptomatic and symptomatic adults with two mutations in one of the genes and a typically affected sibling have also been described [Leegwater et al 2001, Biancheri et al 2003, Ohtake et al 2004, van der Knaap et al 2004].

Genotype-Phenotype Correlations

Although intrafamilial variability exists, correlation between certain homozygous mutations and age of onset and disease severity has been described [Fogli, Schiffmann, Bertini et al 2004].

- In individuals homozygous for the 91T>A mutation in *EIF2B5*, the phenotype may vary from childhood onset to adults with no symptoms [Leegwater et al 2001].
- The neonatal-onset form is characterized by a more diffuse encephalopathy with failure of development and serious seizures [van der Knaap et al 2003].
- Certain *EIF2B5* homozygous mutations, such as p.Arg113His, never give rise to the infantile type [Fogli, Schiffmann, Bertini et al 2004].
- Certain *EIF2B5* mutations, such as p.Val309Leu, are predictably associated with severe disease [Fogli, Schiffmann, Bertini et al 2004].

Penetrance

Some adults who are homozygous or compound heterozygous for two disease-causing mutations in the same gene may be asymptomatic for prolonged periods of time [van der Knaap et al 2004].

Nomenclature

"Cree leukoencephalopathy," described in the native North American Cree and Chippewayan indigenous population, is now recognized to be the same as the infantile form of CACH/VWM [Fogli, Wong et al 2002].

Prevalence

The prevalence of CACH/VWM is not known; it is considered one of the most common leukodystrophies. In a study of unclassified leukodystrophies in childhood, CACH/VWM was the most common [van der Knaap et al 1999].

In some countries, the incidence of CACH/VWM is close to that of metachromatic leukodystrophy (see Arylsulfatase A Deficiency) [van der Knaap, personal communication].

Differential Diagnosis

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

Other disorders affecting the white matter diffusely during childhood to be considered, with their distinguishing MRI findings:

- **X-linked adrenoleukodystrophy, metachromatic leukodystrophy (see Arylsulfatase A Deficiency), Krabbe disease, and Canavan disease**. In the cerebral form of X-linked adrenoleukodystrophy and the other three disorders, MRI shows extensive or diffuse cerebral white matter changes but as a rule no cystic degeneration. Biochemical genetic testing and/or molecular genetic testing is available for diagnosis of each of these conditions.
- **Alexander disease**. In this condition white matter signal changes have a frontal predominance. The cystic degeneration may affect the subcortical or deep white matter. Basal ganglia and thalamic abnormalities are frequently present. Contrast enhancement of characteristic structures often facilitates the diagnosis. The diagnosis can be established with molecular genetic testing.
- **Megalencephalic leukoencephalopathy with subcortical cysts (MLC)** is characterized by diffusely abnormal and mildly swollen cerebral hemispheric white matter that does not show signs of diffuse rarefaction or cystic degeneration. Subcortical cysts are almost always present in the anterior temporal area and often in other regions. The cysts are best seen on proton density and FLAIR. The diagnosis can usually be established with molecular genetic testing.
- **Mitochondrial disorders** such as deficiencies of pyruvate dehydrogenase and pyruvate carboxylase. MRI abnormalities similar to those seen in CACH/VWM with prominent and diffuse white matter rarefaction and cystic degeneration may be seen in mitochondrial disorders [DeLonlay-Debeney et al 2000].
- ***PLP1*-related disorders (Pelizaeus Merzbacher disease and X-linked spastic paraplegia type 2).** Diffuse hyperintensity of the white matter on T2-weighted images is also observed in leukodystrophies with primary hypomyelination, such as the PLP1-related disorders; however, these disorders have a normal or nearly normal

white matter signal on T1-weighted images and CT scan. In addition, central nerve conduction evaluated with evoked potentials is always severely affected even at an early stage of the disease.

- **CADASIL, lamin B1 mutations, or acquired white matter disorders such as multiple sclerosis** need to be considered in individuals with adult-onset CACH/WM; however, the early, constant, diffuse, symmetric alteration of the white matter on MRI in eIF2B-related disorders is distinctive.

Further studies are needed to determine if white matter disorders described as orthochromatic leukodystrophies are related to CACH/VWM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM), the following evaluations are recommended:

- Brain MRI
- Ophthalmologic examination
- Neurologic examination
- Physical therapy/occupational therapy assessment as needed

Treatment of Manifestations

- Physical therapy and rehabilitation for motor dysfunction (mainly spasticity and ataxia)
- Ankle-foot orthotics in individuals with hypotonia and weakness of ankle dorsiflexors
- Antiepileptic drugs for treatment of seizures and abnormalities of behavior and mood

Prevention of Secondary Complications

Considering the known adverse effect of fever, it is important to prevent infections and fever as much as possible, (e.g., through the use of vaccinations, including anti-flu vaccination), low-dose maintenance antibiotics during winter time, antibiotics in minor infections, and antipyretics in fever.

Surveillance

Close surveillance for several days following head trauma or major surgical procedure with anesthesia is indicated because neurologic deterioration (presumably stress related) may follow.

Agents/Circumstances to Avoid

Avoid contact sports and other activities with a high risk of head trauma.

Avoid stressful emotional and physical situations such as extreme temperatures.

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

Corticosteriods and intravenous gamma globulin are not effective in the treatment of CACH/VWM. Corticosteriods have been used unsuccessfully in acute situations including intractable status epilepticus.

Genetics clinics, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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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

Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM) 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. No clinical or MRI abnormalities have been found in carriers for mutations in *EIF2B1-5*.

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.

- Age of onset of neurologic signs can differ from one individual to another within the same family. Therefore, a neurologically asymptomatic sib of an affected individual may be homozygous for the mutation and at high risk of developing the disease. The large majority (if not all) of apparently asymptomatic individuals seem to have the diffuse white matter abnormalities characteristic of the syndrome on head MRI, and may have very mild learning, cognitive, or behavioral disabilities.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic. No clinical or MRI abnormalities have been found in carriers for mutations in *EIF2B1-5*.

Offspring of a proband. The offspring of an individual with CACH/VWM are obligate heterozygotes (carriers) for a disease-causing mutation in *EIF2B1-5*.

Other family members of a proband. Sibs of the proband's parents are at increased risk of being carriers.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

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 parents of an affected individual and to young adults who are affected or at risk.

Testing of at-risk asymptomatic individuals. Testing of at-risk asymptomatic individuals for CACH/VWM is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for CACH/VWM, an affected family member should be tested first to confirm the molecular diagnosis in the family.

DNA banking. 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 DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified 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 in an affected family member. 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 Childhood Ataxia with Central Nervous System Hypomelination/Vanishing White Matter

Gene Symbol	Chromosomal Locus	Protein Name
EIF2B1	Chromosome 12	Translation initiation factor eIF-2B subunit alpha
EIF2B2	14q24	Translation initiation factor eIF-2B subunit beta
EIF2B3	1p34.1	Translation initiation factor eIF-2B subunit gamma
EIF2B4	2p23.3	Translation initiation factor eIF-2B subunit delta
EIF2B5	3q27	Translation initiation factor eIF-2B subunit epsilon

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 Childhood Ataxia with Central Nervous System Hypomelination/Vanishing White Matter

603896	LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER; VWM
603945	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 5; EIF2B5
606273	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 3; EIF2B3
606454	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 2; EIF2B2
606686	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 1; EIF2B1
606687	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 4; EIF2B4

Table C. Genomic Databases for Childhood Ataxia with Central Nervous System Hypomelination/Vanishing White Matter

Gene Symbol	Entrez Gene	HGMD
EIF2B1	1967 (MIM No. 606686)	EIF2B1
EIF2B2	8892 (MIM No. 606454)	EIF2B2
EIF2B3	8891 (MIM No. 606273)	EIF2B3
EIF2B4	8890 (MIM No. 606687)	EIF2B4
EIF2B5	8893 (MIM No. 603945)	EIF2B5

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The eukaryotic translation initiation factor eIF2B is composed of five subunits. Its function is to convert protein synthesis initiation factor 2 (eIF2) from an inactive GDP-bound form to an active eIF2-GTP complex, allowing the formation of the 43S complex, precursor of protein translation initiation. It is not yet understood why a defect in eIF2B, a ubiquitous protein complex, affects predominantly the brain white matter. The crucial role of eIF2B as regulator

of protein synthesis under mild stress conditions could explain the neurologic deterioration during or after head trauma and fever [Leegwater et al 2001].

Null mutations for the genes *EIF2B1-5* in yeast are not viable. Mutations that completely abolish eIF2B activity are probably lethal in the homozygous state in humans; this explains why nonsense mutations are rare and only observed in compound heterozygotes in association with a missense mutation [Leegwater et al 2001; Fogli, Wong et al 2002; van der Knaap et al 2002]. Mutations in *EIF2B1-5* were recently shown to decrease the guanine exchange factor (GEF) activity in vitro in yeast and mammalian cellular models. This reduction in activity results from aberrant protein folding leading to impaired ability to form functional eIF2B complexes that bind substrate normally [Li et al 2004, Richardson et al 2004, van Kollenburg et al 2006]. The decrease in GEF activity leads to enhanced translation of specific mRNA of proteins similar to the situation that occurs when a cell is under stress. Decreased GEF activity of 20%-60% of normal was also found in lymphoblasts of affected individuals but was normal in obligate heterozygotes [Fogli, Schiffmann, Hugendubler et al 2004].

Normal allelic variants: See Table 2. (pdf)

Pathologic allelic variants: See Table 3. (pdf)

Normal gene product: See Table 4. (pdf)

Abnormal gene product: See Molecular Genetic Pathogenesis.

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.

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

European Leukodystrophy Association (ELA)
Email: ela@ela-asso.com
http://www.ela-asso.com/

United Leukodystrophy Foundation (ULF)
2304 Highland Drive
Sycamore IL 60178
Phone: 800-728-5483; 815-895-3211
Fax: 815-895-2432
Email: office@ulf.org
www.ulf.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.

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Suggested Readings

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Chapter Notes

Revision History

- 30 July 2007 (me) Comprehensive update posted to live Web site
- 20 February 2003 (me) Review posted to live Web site
- 19 November 2002 (pb) Original submission

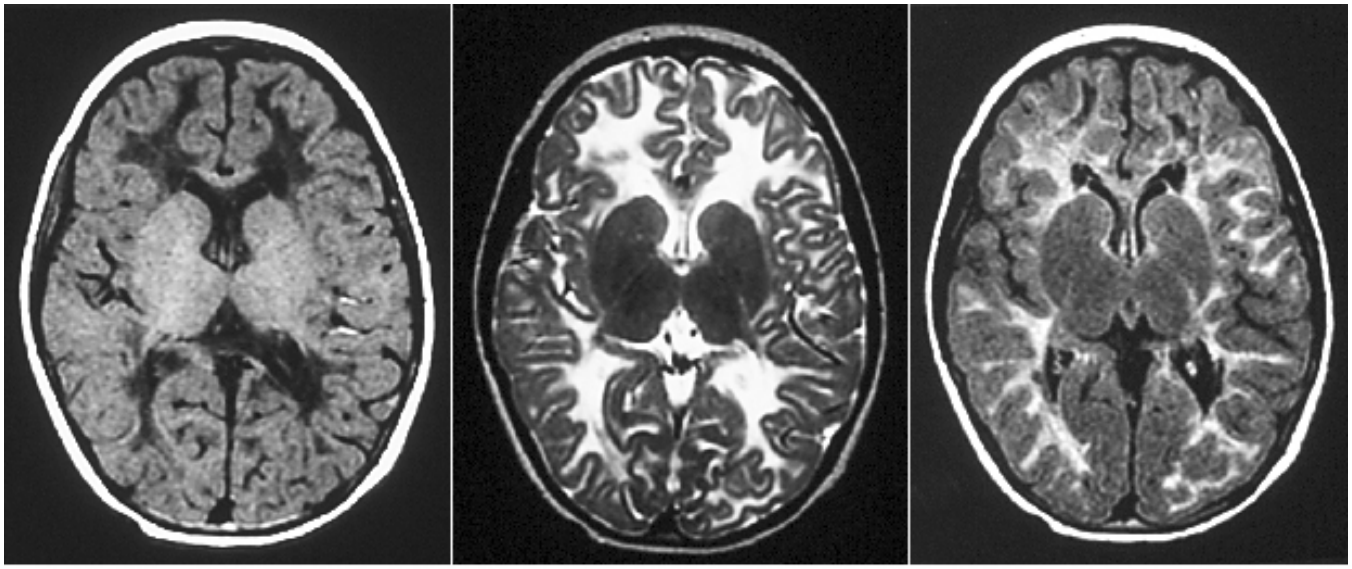

Figure 1. T1 Figure 2. T2 Figure 3. FLAIR

MRI of an individual with the classic form of CACH
Figure 1. Diffuse hypointensity of the white matter on T1-weighted images
Figure 2. Increased signal intensity in the same white matter area on T2-weighted images
Figure 1, Figure 3. Secondary cavitation in the abnormal white matter seen on both the T1-weighted and the FLAIR images. Note the absence of cortical atrophy and of dilation of the lateral ventricles.

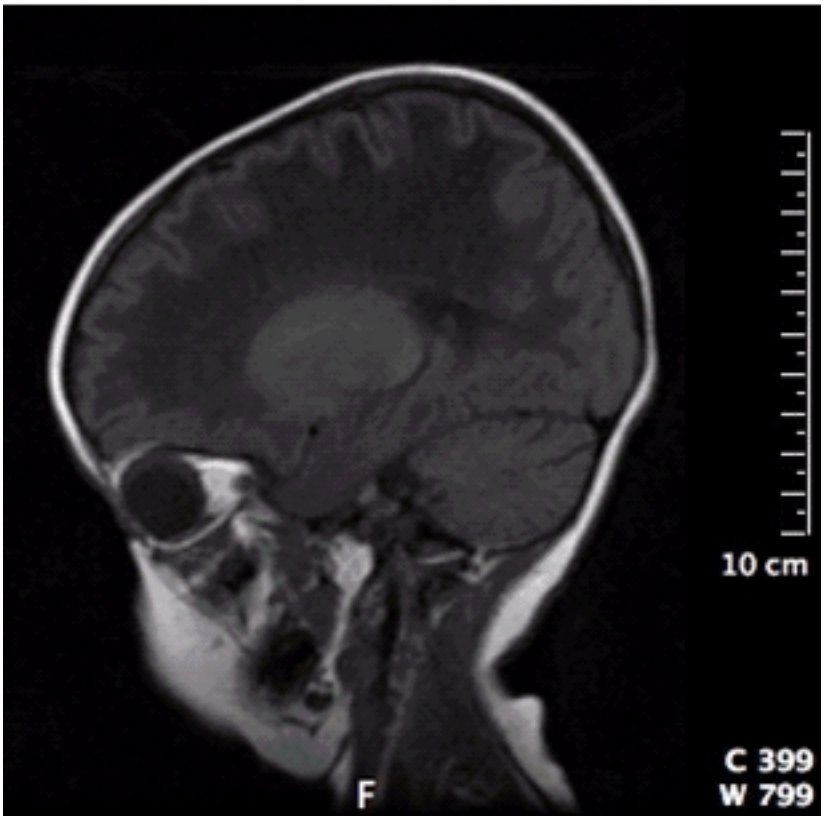

Figure 4. Parasagittal T1-weighted MRI image of an individual with CACH shows diffuse hypointensity of the white matter interrupted by a typical meshwork of remaining tissue strands radiating across the abnormal white matter.