GENEReviews

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X-Linked Adrenoleukodystrophy

[*X-ALD. Includes: Adrenomyeloneuropathy (AMN)*]

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Summary

Disease characteristics. X-ALD is a disorder that affects the nervous system white matter and the adrenal cortex. Three main phenotypes are seen in males. The childhood cerebral form manifests most commonly between ages four and eight years. It initially resembles attention deficit disorder or hyperactivity; progressive impairment of cognition, behavior, vision, hearing, and motor function follow the initial symptoms and often lead to total disability within two years. The second phenotype, adrenomyeloneuropathy (AMN), manifests most commonly in the late twenties as progressive paraparesis, sphincter disturbances, sexual dysfunction, and often, impaired adrenocortical function; all symptoms are progressive over decades. The third phenotype, "Addison disease only," presents with primary adrenocortical insufficiency between age two years and adulthood and most commonly by age 7.5 years, without evidence of neurologic abnormality; however, some degree of neurologic disability (most commonly AMN) usually develops later. Approximately 20% of females who are carriers develop neurologic manifestations that resemble adrenomyeloneuropathy, but have later onset (age 35 years or later) and milder disease than do affected males.

Diagnosis/testing. The diagnosis of X-ALD is based on clinical findings. MRI is always abnormal in males with neurologic symptoms and often provides the first diagnostic lead.

Testing for plasma concentration of very long chain fatty acids (VLCFA) reveals abnormal levels in 99% of males with X-ALD. Increased concentration of VLCFA in plasma and/or cultured skin fibroblasts is present in approximately 85% of affected females; 20% of known carriers have normal plasma concentration of VLCFA. Molecular genetic analysis of the *ABCD1* gene, the only gene associated with X-ALD, is clinically available; it is used primarily in the context of genetic counseling for determination of carrier status in at-risk female relatives and for prenatal diagnosis.

Management. Corticosteroid replacement therapy is essential for the treatment of individuals with X-ALD in whom adrenal insufficiency is identified. Affected boys benefit from the general supportive care of parents and psychological and educational support. Physical therapy, management of urologic complications, and family and vocational counseling are of value for men with adrenomyeloneuropathy. Surveillance for males with X-ALS should include periodic reevaluation of adrenal cortical function.

Genetic counseling. X-ALD is inherited in an X-linked recessive manner. About 93% of index cases have inherited the *ABCD1* mutation from one parent; at most, 7% of individuals with X-ALD have *de novo* mutations. Affected males transmit the *ABCD1* mutation to all of their daughters and none of their sons. Carrier females have a 50% chance of transmitting the *ABCD1* mutation in each pregnancy. Males who inherit the mutation will be affected; females who inherit the mutation are carriers and will usually not be seriously affected. The phenotypic expression and prognosis of an affected male is unpredictably variable. Carrier testing of at-risk female relatives is available. When the disease-causing mutation is known, prenatal testing is possible for pregnancies of women who are carriers.

Diagnosis

Clinical Diagnosis

The diagnosis of X-ALD should be considered in four clinical settings:

- **Boys** with symptoms of attention deficit disorder who also show signs of dementia, progressive behavioral disturbance, vision loss, difficulty in understanding spoken language, worsening handwriting, incoordination, or other neurologic disturbances
- **Young or middle-aged men** with progressive gait disorders, leg stiffness or weakness, abnormalities of sphincter control, and sexual dysfunction, with or without adrenal insufficiency or cognitive or behavioral deficits
- **All males** with primary adrenocortical insufficiency, with or without evidence of neurologic abnormality
- **Middle-aged or older women** with progressive paraparesis, abnormalities of sphincter control, and sensory disturbances mainly affecting the legs. It may be difficult to establish the diagnosis of X-ALD in a female with a negative family history. Diagnosis is based upon clinical features (most commonly progressive spastic paraparesis) and a panel of laboratory tests.

Neuroimaging. Brain MRI is always abnormal in neurologically symptomatic males and often provides the first diagnostic lead. In approximately 85% of affected individuals, MRI shows a characteristic pattern of symmetric enhanced T-2 signal in the parieto-occipital region with contrast enhancement at the advancing margin.

Testing

Very long chain fatty acids (VLCFA). Three parameters are analyzed:

- Concentration of C26:0
- Ratio of C24:0 to C22:0
- Ratio of C26:0 to C22:0

Table 1 summarizes mean results for normal controls, affected males, and carrier females. The VLCFA assay is performed in a limited number of laboratories worldwide. For laboratories offering biochemical testing, see Testing.

- **Males.** The plasma concentration of very long chain fatty acids (VLCFA) is abnormal in 99.9% of males with X-ALD irrespective of age. All three parameters are elevated in the majority of males, though some variation is observed. The discriminant function reported in Moser et al (1999) fully separates normal control males from affected males.
- **Females.** Increased concentration of VLCFA in plasma and/or cultured skin fibroblasts is present in approximately 85% of females; 20% of known carriers have normal plasma concentration of VLCFA. The discriminant function reported in Moser et al (1999) is not able to distinguish all carriers from the normal control range.

ALD protein. In approximately 70% of carriers, the ALD protein (ALDP) is immunonegative. When the familial mutation is not known, this test can be used in females for carrier detection if ALDP is known to be immunonegative.

Note: Extreme skewing of X-chromosome inactivation occurs on rare occasion and can result in false negative results [Moser et al 1999].

Table 1. Plasma Very Long Chain Fatty Acids (VLCFA) Values in X-ALD

	Normal	Males with X-ALD	Obligate Female Carriers
C26:0µg/mL [1]	0.24+0.14	1.30+0.45	0.68+0.29
C24:0/C22:0 [2]	0.78+0.10	1.71+0.23	1.30+0.19
C26:0/C22:0 [2]	0.01+0.003	0.07+0.03	0.04+0.02

H Moser, A Moser, S Steinberg; personal observation

1. The concentration of C26:0 is reported as µg/mL; some laboratories report this as µmol/l.

2. Lorenzo's oil, a mixture of erucic and oleic acids, is used therapeutically to normalize VLCFA levels. Thus, we routinely report erucic acid (C22:1) levels when measuring plasma VLCFA. Certain oils used in cooking, such as mustard seed oil, have naturally high levels of erucic acid and thus can lead to an elevation similar to that observed with Lorenzo oil therapy.

Adrenal function is abnormal in 90% of neurologically symptomatic boys and in 70% of men with adrenomyeloneuropathy. It is usually normal in carrier females. The most sensitive indicators of adrenal dysfunction are:

- Elevated plasma ACTH concentration;
- Impaired rise of plasma cortisol concentration in response to administered ACTH.

Note: Adrenal antibodies are not present.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *ABCD1* is the only gene associated with X-ALD.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing in individuals in which other diagnostic procedures have been inconclusive

- Carrier testing for female relatives
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Molecular genetic testing: Clinical methods

Sequence analysis. PCR and sequence analysis identified mutations in 229 of 249 (92%) hemizygous males or obligate heterozygote females [H Moser, A Moser, S Steinberg; personal observation].

Deletion/duplication analysis. Some individuals have large deletions that require Southern blot analysis for detection.

- Sixteen of the 20 individuals (in the series of 249 individuals) without a mutation identified by sequence analysis had a deletion detected by Southern blot analysis [H Moser, A Moser, S Steinberg; personal observation].
- In one of the four remaining individuals, Southern blot results suggested a duplication or rearrangement.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in X-ALD

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	*ABCD1* sequence alterations	98% [1]	Clinical Testing
Deletion/duplication analysis	Large deletions and rearrangements		

1. Mutation detection in hemizygous males and obligate heterozygotes (245/249)

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

Testing Strategy for a Male Proband

- Measurement of VLCFA is sufficient to establish the diagnosis of X-ALD in the majority of males.
- Rarely, molecular genetic testing is required to confirm the diagnosis when measurement of VLCFA is inconclusive.

Genetically Related (Allelic) Disorders

CADDS. Three males with a contiguous deletion syndrome involving the 5' end of *ABCD1*, termed CADDS (contiguous *ABCD1DXS1357E* deletion syndrome), have been described [Corzo et al 2002]. The phenotype of CADDS is earlier in onset and distinct from that resulting from mutations involving *ABCD1* alone. All three boys had neonatal cholestasis, hypotonia, and developmental delay. None had craniofacial abnormalities. All three died before age one year. The key finding that implicated *ABCD1* in this new syndrome was immunocytochemical analysis of cultured cells that demonstrated morphologically normal peroxisomes lacking the membrane protein encoded by *ABCD1*. Two of the three mothers were found to be deletion carriers.

CADDS contrasts with X-ALD, in which the earliest onset of neurologic symptoms is 2.75 years and liver disease is not observed. Plasma very long chain fatty acid (VLCFA) concentrations were elevated in CADDS; however, in contrast to the autosomal recessive

peroxisome biogenesis disorders, Zellweger syndrome spectrum (PBD, ZSS), all other peroxisomal metabolic pathways tested were normal.

Clinical Description

Natural History

The range of phenotypic expression in X-ALD is wide and cannot be predicted through levels of VLCFA or family history. Widely varying phenotypes often co-occur in a single kindred or sibship [Moser 1997, Moser et al 2001]. Many individuals with X-ALD remain asymptomatic until middle age or even later.

Symptom set 1. Childhood cerebral forms (~35% of affected individuals). Presentation occurs most commonly between age four and eight years, with a peak at age seven. It virtually never occurs before age three years and very rarely after age 15.

Affected boys present with behavioral or learning deficits, often diagnosed as attention deficit disorder or hyperactivity, which may respond to stimulant medication. These behaviors may persist for months or longer. They are followed by symptoms suggestive of a more serious underlying disorder that may include "spacing out" in school (inattention, deterioration in handwriting skills, and diminishing school performance); difficulty in understanding speech (though sound perception is normal); difficulty in reading, spatial orientation, and comprehension of written material; clumsiness; visual disturbances and occasionally diplopia; and aggressive or disinhibited behavior.

Brain MRI examination performed at this time can be strikingly abnormal even when symptoms are relatively mild.

In some boys, seizures may be the first manifestation.

While variable, the rate of progression may be rapid, with total disability in six months to two years followed by death at varying ages.

Most individuals have impaired adrenocortical function at the time that neurologic disturbances are first noted.

Symptom set 2. Adrenomyeloneuropathy (AMN) (~40-45% of affected individuals). The typical presentation is a man in his twenties or middle age who develops progressive stiffness and weakness in the legs, abnormalities of sphincter control, and sexual dysfunction. All symptoms are progressive over decades.

Approximately 40-45% of individuals with AMN show some degree of brain involvement on MRI or clinical examination. In 10-20% of individuals with AMN, brain involvement becomes severely progressive and leads to serious cognitive and behavioral disturbances that may progress to total disability and death.

Approximately 70% of men with adrenomyeloneuropathy have impaired adrenocortical function at the time that neurologic symptoms are first noted.

Symptom set 3. Addison disease only (~10% of affected individuals). Males present with signs of adrenal insufficiency between age two years and adulthood, most commonly by age 7.5 years. Presenting signs include unexplained vomiting and weakness or coma, leading to the diagnosis of Addison disease. Increased skin pigmentation resulting from excessive ACTH secretion is variably present.

Most males who present initially with adrenocortical insufficiency only develop evidence of AMN by middle age.

Presentations seen in approximately 5-10% of affected males:

- **Symptom set 4.** Headache, increased intracranial pressure, hemiparesis or visual field defect, aphasia or other signs of localized brain disease. Onset is usually between age four and ten years but may occur in adolescence or, rarely, in adults.
- **Symptom set 5.** Progressive behavioral disturbance, dementia, and paralysis in an adult
- **Symptom set 6.** Progressive incoordination and ataxia in a child or adult
- **Symptom set 7.** Neurogenic bladder and bowel abnormalities and occasionally impotence without other neurologic or endocrine disturbance in at-risk males who have a positive family history
- **Symptom set 8.** No evidence of neurologic or endocrine dysfunction

Female carriers. Approximately 20% of female carriers develop mild to moderate spastic paraparesis in middle age or later. Adrenal function is usually normal.

Genotype-Phenotype Correlations

The phenotype cannot be predicted by VLCFA plasma concentration or by the nature of the mutation. The same mutation can be associated with each of the known phenotypes. Mild phenotypes may be associated with large deletions that abolish formation of the gene product, and severe phenotypes occur with missense mutations in which abundant immunoreactive protein product is produced [Feigenbaum et al 1996, Dodd et al 1997, Moser & Moser 1999, Takano et al 1999, Pan et al 2005].

Segregation analysis suggests the action of an autosomal modifier gene, but the presence of such a gene has not been proven.

Penetrance

The biochemical phenotype of elevated plasma concentration of VLCFA has nearly 100% penetrance in males. Although the variation in clinical phenotypes is great, neurologic manifestations are present in nearly all males by adulthood.

Nomenclature

Siemerling-Creuzfeldt disease is the eponym for X-ALD.

Historically, the eponym Schilder's disease referred to several clinical entities that included X-ALD; it should now be used solely to refer to sudanophilic cerebral sclerosis.

Prevalence

The prevalence is estimated to be between 1:20,000 and 1:50,000. The minimum frequency of hemizygotes (i.e., affected males) identified in the United States is estimated to be 1:21,000 and that of hemizygotes plus heterozygotes (i.e., carrier females) 1:16,800 [Bezman et al 2001].

The prevalence appears to be approximately the same in all ethnic groups.

Differential Diagnosis

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

Conditions that may share clinical features with X-ALD include the following:

- **Symptom set 1 (childhood cerebral form).** Attention deficit disorder; epilepsy, other types of Addison disease; brain tumor. Other types of leukodystrophy including arylsulfatase deficiency (metachromatic leukodystrophy), Krabbe disease (globoid cell leukodystrophy). Subacute sclerosing encephalitis, multiple sclerosis, Lyme disease, and other dementing disorders.
- **Symptom set 2 (adrenomyeloneuropathy).** Multiple sclerosis, progressive spastic paraparesis, amyotrophic lateral sclerosis; B-12 deficiency, spinal cord tumor, cervical spondylosis
- **Symptom set 3 (Addison disease only).** Allgrove syndrome (achalasia, alacrima, autonomic disturbance, and Addison disease). Males with apparently isolated primary adrenal insufficiency (i.e., no evidence for other systemic involvement) should be evaluated with plasma VLCFA, as X-ALD is the most common genetic cause of Addison disease [Aubourg & Chaussain 2003]. The occurrence of Addison disease in female carriers for X-ALD is rare.
- **Symptom set 4.** Brain tumor, MELAS, CADASIL
- **Symptom set 5.** Alzheimer disease (see Alzheimer Disease Overview); alcoholic or toxic encephalopathy; solvent vapor exposure; psychosis
- **Symptom set 6.** Olivopontocerebellar degeneration and other progressive ataxias (see Ataxia Overview).
- **Symptom set 7.** Other causes of neurogenic bladder/bowel or impotence

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Neurologic examination
- Brain MRI
- Adrenal function tests [Dubey et al 2005]

Treatment of Manifestations

When adrenal insufficiency is identified in an affected male, corticosteroid replacement therapy is essential and can be lifesaving. (Corticosteroid replacement therapy has no effect on nervous system involvement.)

Affected boys benefit from the general supportive care of parents as well as psychological and educational support.

Physical therapy, management of urologic complications, and family and vocational counseling are of value for men with adrenomyeloneuropathy, many of whom maintain successful personal and professional lives [Silveri et al 2004].

Prevention of Primary Manifestations

Bone marrow transplantation (BMT) is an option for boys and adolescents who are in early stages of symptom set 1 who have evidence of brain involvement on MRI.

Because BMT has 20% risk of morbidity and mortality, it is only recommended for individuals with evidence of brain involvement by MRI but minimal neuropsychologic findings (performance IQ >80) and normal clinical neurologic examination.

BMT is not recommended for individuals with severe neurologic and neuropsychologic dysfunction (i.e., performance IQ <80) [Shapiro et al 2000, Baumann et al 2003, Loes et al 2003, Peters et al 2004, Mahmood et al 2005, Resnick et al 2005].

Surveillance

Adrenal function should be reevaluated periodically in males with X-ALD whose initial evaluation revealed normal adrenal cortical function [Dubey et al 2005].

Testing of Relatives at Risk

Early detection of asymptomatic or minimally symptomatic at-risk males permits timely treatment of adrenal insufficiency [Mahmood et al 2005].

Therapies Under Investigation

In a single-arm study of presymptomatic boys with a normal MRI, reduction of hexacosanoic acid (C26:0) by Lorenzo's oil was associated with a reduced risk of developing MRI abnormalities and therefore childhood cerebral disease. The authors emphasized that the benefits of therapy required the reduction of C26:0 and that the amount of reduction correlated with lowered risk. Despite this reduction, some individuals still developed childhood cerebral disease. It is emphasized that the study was an open trial without a placebo group; thus, the results should be interpreted with some caution. The use of Lorenzo's oil remains an investigational therapy [Moser et al 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Lovastatin and 4-phenylbutyrate have been proposed as possible therapeutic agents; their clinical efficacy has not yet been tested [Kemp et al 1998; Singh, Khan et al 1998; Singh, Pahan et al 1998].

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

X-ALD is inherited in an X-linked manner.

Risk to Family Members

Parents of a male or female proband

- About 93% of individuals representing index cases have inherited the *ABCD1* mutation from one parent; at most, 7% of individuals with X-ALD have *de novo* mutations.
- It is appropriate to measure plasma VLCFA concentration in the mothers of both affected males and carrier females and in the fathers of carrier females. When the disease-causing mutation has been identified in an affected family member, mutation analysis of the *ABCD1* gene can be used in the evaluation of the parents.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the parents, which can be clarified by pedigree analysis, measurement of plasma concentration of VLCFA, and molecular genetic testing.
- If the proband's mother is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers.
- If the proband's father has a disease-causing mutation in the *ABCD1* gene, all of the female sibs will be carriers and none of the male sibs will be affected.
- If neither parent is a carrier, the risk to sibs of a proband is low.

Offspring of a proband

- Affected males transmit the *ABCD1* mutation to all of their daughters and none of their sons.
- Carrier females have a 50% chance of transmitting the *ABCD1* mutation in each pregnancy. Males who inherit the mutation will be affected; females who inherit the mutation are carriers and will usually not be seriously affected.

Other family members of a proband. Depending upon their gender, family relationship, and the carrier status of the proband's parents, the proband's aunts and uncles and their offspring may be at risk of being carriers or of being affected.

Evaluation of at-risk family members is important for management and genetic counseling but is often implemented insufficiently. Several factors may contribute to insufficient evaluation:

- Establishing the diagnosis in an affected individual with severe disability may be devastating to a family. Immediate concerns may overshadow the timely testing of family members.
- Molecular genetic testing has been clinically available for a short time; its availability may not yet be generally known.
- Third party payors may not cover the cost of testing at-risk family members.
- Some at-risk family members may choose not to be tested because they fear that a positive result could impair their ability to obtain or retain medical insurance coverage.

- Individuals may have incomplete knowledge about at-risk family members and may not wish to inform them about the risk.

Carrier Detection

Testing of at-risk female relatives for carrier status is a two-step process:

1. Measurement of plasma concentration of VLCFA is performed first; if abnormal, the female is a carrier.
2. Because 20% of female carriers have normal plasma concentration of VLCFA, molecular genetic testing should be used to test those females with a normal concentration if the disease-causing *ABCD1* mutation has been identified in the family.

Related Genetic Counseling Issues

Phenotypic variability. It is important for couples at risk to be aware that widely varying phenotypes often coexist in the same kindred or sibship. Thus, families that have experienced the relatively mild phenotypes need to be advised that affected offspring may display the severe phenotype.

At-risk asymptomatic or symptomatic but undiagnosed family members. It is appropriate for at-risk males in a family to be identified and to be informed of their risk for X-ALD, while respecting principles of patient confidentiality. Identification of males with X-ALD through measurement of plasma concentration of VLCFA before symptoms occur or early in the course of the disease can allow for diagnosis and management of adrenal insufficiency before life-threatening complications occur. Such testing can also allow for correct diagnosis of early (and often nonspecific) neurologic, behavioral, and/or cognitive signs and symptoms.

However, because only about 35% of males with X-ALD develop symptoms in childhood, it is also appropriate to consider the issues raised by presymptomatic testing of individuals during childhood for typically adult-onset disorders for which no definitive treatment exists. Consensus holds that individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against testing such individuals are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications.

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

Molecular genetic testing. Prenatal testing is possible for pregnancies of women who are carriers in whom the risk of having an affected male is 25% (or 50% if the fetus is known to be male). The usual procedure is to determine sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis at about 15-18 weeks' gestation. If the karyotype is 46,XY and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Biochemical testing. If molecular genetic testing is not possible, very long chain fatty acids (VLCFA) can be measured in cultured amniocytes or cultured chorionic villus cells [Wanders et al 1998, Moser et al 1999]. False negative test results with the latter approach have been reported but may have been related to technical factors.

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 mutation has been identified in an affected family member or for those who would choose to implant only female embryos to avoid the possibility of an affected male. 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 Adrenoleukodystrophy, X-Linked

Gene Symbol	Chromosomal Locus	Protein Name
ABCD1	Xq28	ATP-binding cassette sub-family D member 1

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 Adrenoleukodystrophy, X-Linked

300100	ADRENOLEUKODYSTROPHY; ALD
300371	ATP-BINDING CASSETTE, SUBFAMILY D, MEMBER 1; ABCD1

Table C. Genomic Databases for Adrenoleukodystrophy, X-Linked

Gene Symbol	Locus Specific	Entrez Gene	HGMD
ABCD1	ABCD1	215 (MIM No. 300371)	ABCD1

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

Normal allelic variants: *ABCD1* contains ten exons and spans 20 kb of genomic DNA. The 3,664-bp transcript has 2,235 bp of coding sequence. Exon 1 is the largest, encompassing 900 bp.

Pathologic allelic variants: The X-linked adrenoleukodystrophy database (see locus-specific database link in the Genomic Databases Table above) lists 441 non-recurrent disease-causing mutations [Kemp et al 2001]. Half of the identified mutations are non-recurrent. Disease-causing mutations reported to the database include missense mutations (~61%), frameshift mutations (~23%), nonsense mutations (~10%), in-frame deletions/insertions (~4%), and large deletions (~3%).

Note: The proportion of individuals with large deletions reported is half of what the authors have found (6.4%) and is likely an underestimate because not all laboratories perform Southern blot analysis.

The most common recurring mutation is an AG deletion at nucleotide 1801-1802 in exon 5. This mutation has been reported in 7.9% of families and has been observed with approximately the same frequency in all ethnic groups.

Missense mutations have been found in all parts of the gene but are most common in the membrane domain or the ATP-binding domain, emphasizing the importance of these two domains for the function of ALDP. In the series of 249 hemizygotes and obligate heterozygotes from the authors' experience, 62% of the detected sequence variations predicted missense mutations. Two-thirds were previously reported in association with X-ALD. All of the mutations not previously reported occurred in residues conserved between human and rodent proteins and were within the transmembrane and nucleotide-binding fold domains [H Moser, A Moser, S Steinberg; personal observation].

Normal gene product: The adrenoleukodystrophy protein (ALDP) contains 745 amino acids and is located in the peroxisomal membrane. It is a member of the ATP-binding cassette (ABC) protein transporter family. It is a characteristic feature of the family of ABC transporters that they function as dimers of two related halves. ALDP represents only one of these halves and is referred to as a half-transporter. Binding of two half-transporters creates a functional transporter whereby the two membrane domains form a channel through which the substrate is transported. Each of the ABC half-transporters contains a hydrophobic membrane domain with six membrane-spanning segments. The combination of the individual components may determine the specificity of the transporter. ALDP has been shown to be able to form a homodimer. However, the peroxisomal membrane contains three additional ABC transporters: PMP70, PMP69 (P70R), and the ALD-related protein (ALDR), and it can also form heterodimers with some of these. ALDR, which has been mapped to 12q11, is of particular interest because it has 66% identity to ALDP and can substitute for the function of ALDP in restoring the capacity of X-ALD fibroblasts to metabolize very long chain fatty acids. Variations in the interactions between ALDP and its homologs may influence the phenotypic expression of the disease. The clarification of the pathogenesis of X-ALD will be aided by the study of a knockout mouse model now available.

Abnormal gene product: The gene product is absent in 70% of affected individuals and, for reasons that are not well understood, may be absent even in individuals who have missense mutations. The principal biochemical abnormality is the accumulation of saturated very long chain fatty acids, particularly hexacosanoic (C26:0) and tetracosanoic (C24:0) fatty acids, as a result of the impaired capacity to degrade these substances, a function that normally takes place in the peroxisome. It is not yet known how the defect in ALDP leads to the accumulation of very long chain fatty acids. The protein may be required for the transport of these fatty acids onto the peroxisome.

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.

The Adrenoleukodystrophy Foundation
739 Michigan Avenue
Slidell, LA 70458
Phone: 985-645-9559
Email: info@adlfoundation.org
www.aldfoundation.org

Australian Leukodystrophy Support Group
Email: leuko@vicnet.net.au
avoca.vicnet.net.au/~leuko

National Institute of Neurological Disorders and Stroke
Adrenoleukodystrophy information page

NCBI Genes and Disease
Adrenoleukodystrophy

Myelin Project
2136 Gallows Rd, Suite E
Dunn Loring, VA 22027
Phone: 800-869-3546; 703-560-5400
Fax: 703 560 0706
Email: mp@myelin.org
www.myelin.org

The Peroxisome Web Site
www.peroxisome.org

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

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Author History

- Corinne D Boehm, MS; Johns Hopkins Hospital, Baltimore (1999-2002)
- Ann B Moser, BA (1999-present)
- Hugo W Moser, MD (1999-2007*)
- Gerald Raymond, MD (2006-present
- Steven J Steinberg, PhD (2002-present)

*Hugo W Moser, MD was Professor of Neurology and Pediatrics at Johns Hopkins University School of Medicine and former Director of the Kennedy Krieger Institute in Baltimore. He was a world-renowned expert in the field of neurogenetics. He was best known for his leadership role in understanding, diagnosing, and treating adrenoleukodystrophy (ALD). Dr. Moser died of cancer on January 20, 2007 at age 82. He will be greatly missed by his family, friends, colleagues, and patients.

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