U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Raymond GV, Moser AB, Fatemi A. X-Linked Adrenoleukodystrophy. 1999 Mar 26 [Updated 2023 Apr 6]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

X-Linked Adrenoleukodystrophy

Synonym: X-ALD

Gerald V Raymond, MD,[1] Ann B Moser, BA,[2] and Ali Fatemi, MD[2]

Created: March 26, 1999; Updated: April 6, 2023.

Summary

Clinical characteristics

X-linked adrenoleukodystrophy (X-ALD) involves the central or peripheral nervous system and the adrenal cortex. The nervous system and adrenal glands are involved independently; thus, an affected male may be diagnosed with cerebral adrenoleukodystrophy (CALD), adrenomyeloneuropathy (AMN), and/or primary adrenocortical insufficiency. CALD is characterized by progressive behavioral, cognitive, and neurologic deficits; onset of symptoms ranges from childhood (typically ages 4 to 8 years) to adolescence (ages 11 to 21 years) and adulthood. AMN is characterized by leg weakness, spasticity, clumsy gait, pain, and bladder and bowel dysfunction; onset is typically in the 20s and 30s. Onset of primary adrenocortical insufficiency ranges from age two years to adulthood (most commonly by age 7.5 years). Heterozygous females are not at increased risk to develop CALD, but are at increased risk to develop AMN and primary adrenocortical insufficiency with increasing age.

Diagnosis/testing

Three scenarios for suspecting the diagnosis are: (1) positive newborn screening result, which to date is performed in more than half of the United States; (2) a male or female proband with suggestive clinical and laboratory findings; (3) a male not known to have X-ALD ascertained and diagnosed via family screening. The diagnosis is established by identification of a hemizygous *ABCD1* pathogenic variant in a male or a heterozygous *ABCD1* pathogenic variant in a female on molecular genetic testing.

Management

Targeted therapy: Newborns and asymptomatic infant boys (most commonly diagnosed following a positive newborn screening result or family screening) require immediate referral to a neurologist or biochemical geneticist who will develop a plan for scheduled neurologic examinations and brain MRIs to identify promptly

Author Affiliations: 1 Department of Genetic Medicine, Johns Hopkins Hospital, Baltimore, Maryland; Email: graymon4@jhmi.edu. 2 Department of Neurogenetics, Kennedy Krieger Institute, Baltimore, Maryland; Email: mosera@kennedykrieger.org; Email: fatemi@kennedykrieger.org.

those boys at risk to develop childhood CALD (cCALD) who will benefit from targeted therapy (either hematopoietic stem cell transplantation or, in some, an ex vivo gene therapy recently approved in the US).

Supportive care: Older males with CALD and males and females with AMN require supportive treatment by multidisciplinary specialists in relevant fields to improve quality of life, maximize function, and reduce complications. For primary adrenocortical insufficiency, newborn males and asymptomatic infant boys with confirmed X-ALD require immediate referral to a pediatric endocrinologist to screen for adrenocortical insufficiency in order to either promptly treat those with confirmed adrenal insufficiency according to published steroid replacement guidelines or institute a plan for scheduled screening throughout childhood for boys who do not yet have adrenal insufficiency. Older males require scheduled screening to detect later-onset adrenal insufficiency.

Surveillance: For boys receiving targeted therapy for neurologic disease, the treating neurologist / biochemical geneticist monitors existing manifestations, the individual's response to targeted therapy, and need for supportive care. Older males with CALD and males and females with AMN receiving supportive care require scheduled examinations by their multidisciplinary care providers to identify and address emerging issues. Boys at risk for cCALD who are possible candidates for targeted therapy require frequent assessments starting at age 12 months. For primary adrenocortical insufficiency, boys who do not yet have adrenal involvement require scheduled assessments by their treating pediatric endocrinologist throughout childhood. Males with AMN require scheduled assessment (at least yearly) by their treating endocrinologist.

Agents/circumstances to avoid: Triggers known or suspected to be associated with activation of cerebral disease, including significant head injury, coma associated with adrenal crisis, and neurosurgical procedures.

Evaluation of relatives at risk: It is appropriate to evaluate at-risk male relatives of an affected individual through measurement of plasma concentration of very long-chain fatty acids – or molecular genetic testing if the familial *ABCD1* pathogenic variant is known – in order to identify as early as possible those who would benefit from screening for primary adrenocortical insufficiency and to facilitate timely identification of young males who might benefit from targeted treatment for cCALD.

Genetic counseling

X-ALD is inherited in an X-linked manner. Approximately 95% of probands inherit an *ABCD1* pathogenic variant from one parent; at least 4% of individuals with X-ALD have a *de novo* pathogenic variant. If the mother of the proband has an *ABCD1* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%; if the father of the proband is affected (i.e., hemizygous for an *ABCD1* pathogenic variant), he will transmit the pathogenic variant to all of his daughters and none of his sons. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will typically be symptom-free in childhood but may manifest findings in adulthood. A positive newborn screening result in a female infant should prompt identification and evaluation of at-risk male relatives, as identification of males with X-ALD 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. Once the *ABCD1* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

X-Linked Adrenoleukodystrophy: Included Clinical Scenarios and Key Management Issues

Clinical Scenario		Key Management Issues
Scenario 1: Positive newborn screening (NBS) result	Male infants w/positive NBS for X-ALD & confirmed *ABCD1* pathogenic variant	Refer all male infants to: • A pediatric endocrinologist for screening for primary adrenocortical insufficiency to prevent life-threatening complications of adrenal insufficiency; • A neurologist or biochemical geneticist to develop a plan to monitor neurologic & brain MRI findings to identify promptly those at risk for cCALD &, thus, candidates for targeted therapy to prevent progression of CNS disease.
	Female infants w/positive NBS for X-ALD	Refer parents for genetic counseling to identify male relatives at risk for X-ALD & primary adrenocortical insufficiency who might warrant diagnostic evaluation & management as recommended for male infants w/ positive NBS. [1]
Scenario 2: Symptomatic individual	Childhood CALD [2, 3]	• Adrenal assessment; • Consultation w/center w/expertise in evaluating males for possible HSCT
	Adrenomyeloneuropathy	• Measure cortisol & ACTH levels to evaluate for concomitant adrenal insufficiency. • Brain MRI to evaluate for cerebral disease [1]
	Primary adrenocortical insufficiency (Addison disease)	Provide appropriate steroid replacement & consult w/ endocrinologist.
Scenario 3: Male identified by family screening	May be asymptomatic or symptomatic	Assess clinically w/appropriate endocrine studies & brain MRI.

ACTH = adrenocorticotropic hormone; CALD = cerebral adrenoleukodystrophy; CNS = central nervous system; HSCT = hematopoietic stem cell transplantation; X-ALD = X-linked adrenoleukodystrophy
For synonyms and outdated names see Nomenclature.
1. Engelen et al [2022]
2. Childhood CALD (cCALD) is also referred to as cerebral adrenoleukodystrophy (CALD), but cerebral disease is not exclusive to children.
3. Confirmed in males with elevated very long-chain fatty acids (VLCFAs) and identification of a hemizygous pathogenic variant in *ABCD1*, and in females by elevated VLCFAs or C26:0-lysophosphatidylcholine and identification of a heterozygous *ABCD1* pathogenic variant in *ABCD1*.

Diagnosis

Note: For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

Suggestive Findings

The three scenarios in which X-linked adrenoleukodystrophy (X-ALD) may be considered are a positive newborn screening result, a symptomatic individual, and a male who is asymptomatic but identified by family screening.

Scenario 1: Positive Newborn Screening Result

Newborn screening (NBS) for X-ALD has been added to the recommended uniform screening panel in the United States and, to date, more than half the states have begun screening. While the specific methodologies vary, testing is presently performed measuring the concentration of C26:0-lysophosphatidylcholine (C26:0-LPC) [Vogel et al 2015]. Some states have incorporated molecular genetic testing to assist in confirmatory testing for the proband as well as family screening (see Molecular Genetic Testing).

All male infants with a positive NBS for X-ALD and a confirmed *ABCD1* pathogenic variant (see Establishing the Diagnosis) need immediate referral to:

- A pediatric endocrinologist for screening for primary adrenocortical insufficiency and prompt treatment to prevent life-threatening complications of primary adrenal insufficiency (see Table 4);
- A biochemical geneticist or neurologist familiar with targeted treatment for childhood cerebral adrenoleukodystrophy (cCALD) to develop a plan for routine brain MRI monitoring and neurologic evaluations to identify those with early cerebral disease who may be candidates for targeted therapy to prevent progression of central nervous system disease (see Management, Targeted Therapy).

Female infants with a positive NBS do not require immediate medical follow up, as females do not have X-ALD-related medical issues in childhood. However, it is critical that their parents be referred promptly for genetic counseling to identify all male relatives at risk for X-ALD and to facilitate diagnostic workup (see Evaluation of Relatives at Risk).

Scenario 2: Symptomatic Individual

X-ALD **should be suspected** in symptomatic male and female probands with the supportive clinical and neuroimaging findings outlined in Table 1 and a family history consistent with X-linked inheritance (e.g., no male-to-male transmission). Note: Absence of a known family history does not preclude the diagnosis.

Table 1. Suggestive Findings in Males and Females with Symptomatic X-Linked Adrenoleukodystrophy

Sex	Age (years)	Presenting Phenotype (Frequency of Persons Presenting w/ Phenotype)	Clinical	Brain MRI
Male	Typically 4-8 yrs (peak 7 yrs); rarely before 3 yrs	Childhood CALD (30%-35% of males)	Progressive behavioral, cognitive, & neurologic deficits	Symmetric T_2-weighted hyperintensity, typically involving splenium of corpus callosum; active disease will have contrast enhancement.
	11-21 yrs	Adolescent CALD (~5% of males)		Similar to cCALD
	>21 yrs	Adult CALD (~20% of males)	Dementia, behavioral disturbances, & focal neurologic deficits	Similar to cCALD
	20s & 30s	AMN (40%-45% of males) Note: ~70% have impaired adrenocortical function at onset of neurologic findings.	Leg weakness, spasticity, clumsy gait, pain, bladder & bowel dysfunction	Brain & spinal cord neuroimaging are normal.
	2 yrs to adulthood (most commonly by 7.5 yrs)	Primary adrenocortical insufficiency only (~10% of males)	Primary adrenocortical insufficiency w/o apparent neurologic involvement	

Table 1. continued from previous page.

Sex	Age (years)	Presenting Phenotype (Frequency of Persons Presenting w/ Phenotype)	Clinical	Brain MRI
Female	Adulthood	AMN (~50% age >40 yrs; ~ 65% by age 65 yrs)	Primary adrenocortical insufficiency is rare & does not precede AMN (as is seen in males).	Normal except in rare exceptions

Based on Turk et al [2020], Engelen et al [2022]
AMN = adrenomyeloneuropathy; CALD = cerebral adrenoleukodystrophy; cCALD = childhood cerebral adrenoleukodystrophy

Scenario 3: Male Identified by Family Screening

Males identified by family screening may be any age, and the urgency of evaluation will depend on age at diagnosis. Boys who are at risk for cCALD should be promptly diagnosed and receive appropriate evaluations (see Table 7).

Note: Male children and adults ascertained and diagnosed with X-ALD via family screening may be asymptomatic or have features consistent with X-ALD but erroneously attributed to other causes (e.g., young males diagnosed as having worsening learning issues or autism spectrum disorder) [G Raymond, personal observation].

Establishing the Diagnosis

The diagnosis of X-ALD is established in a proband by identification of abnormally elevated very long-chain fatty acids (VLCFAs) on biochemical testing **and** identification of a hemizygous *ABCD1* pathogenic (or likely pathogenic) variant in a male or a heterozygous *ABCD1* pathogenic (or likely pathogenic) variant in a female on molecular genetic testing.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *ABCD1* variant of uncertain significance does not establish or rule out the diagnosis.

Biochemical Testing

VLCFAs may be determined in serum or plasma. The characteristic elevation is in the saturated VLCFAs (especially hexacosanoic acid, abbreviated as C26:0). The derivative species of C26:0-lysophosphatidylcholine (C26:0-LPC) is also elevated and is used in newborn screening and in some centers for all diagnostic testing [Jaspers et al 2020].

Since elevated VLCFAs are not specific to X-ALD and may be seen in other peroxisomal disorders of beta-oxidation, determination of VLCFAs should be paired with *ABCD1* molecular genetic testing.

Molecular Genetic Testing

Male proband. The diagnosis of X-ALD **is established** in a male proband with suggestive findings (see Table 1), elevated VLCFAs, and a hemizygous pathogenic variant in *ABCD1* identified by molecular genetic testing (see Table 2).

Note: Many *ABCD1* variants are private missense variants (i.e., usually found only in a single family or a small population) and, therefore, are likely novel. Thus, many such variants are interpreted by clinical diagnostic laboratories as variants of uncertain significance (VUS). For these reasons, assessment of VLCFA levels and

correlation with clinical findings are critical for interpreting *ABCD1* variants referred to as VUS. See Molecular Genetics, ***ABCD1*-specific laboratory technical considerations**.

Female proband. The diagnosis of X-ALD **is established** in a female proband with suggestive findings (see Table 1), elevated VLCFAs or C26:0-LPC, and a heterozygous pathogenic variant in *ABCD1* identified by molecular genetic testing (see Table 2).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas genomic testing does not (see Option 2).

Option 1

When the phenotypic, laboratory, and brain MRI findings strongly suggest the diagnosis of X-ALD, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel.**

- **Single-gene testing.** Sequence analysis of *ABCD1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A leukodystrophy multigene panel** that includes *ABCD1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Given the specificity of the combination of clinical and biochemical abnormalities for X-ALD, and to minimize the likelihood of identifying variants of uncertain significance on a multigene panel, single-gene testing is generally recommended when X-ALD is strongly suspected.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in X-Linked Adrenoleukodystrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ABCD1	Sequence analysis [3]	97.5% [4]
	Gene-targeted deletion/duplication analysis [5]	2.5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the *ABCD1* variant database [Mallack et al 2022a]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

X-linked adrenoleukodystrophy (X-ALD) affects the nervous system and the adrenal cortex. The involvement of nervous system and adrenal gland is independent and determines whether the affected male is diagnosed with cerebral disease, adrenomyeloneuropathy, or primary adrenocortical insufficiency.

The range of phenotypic expression in X-ALD is wide and cannot be predicted by very long-chain fatty acid (VLCFA) levels, the *ABCD1* pathogenic variant, or family history. Varying phenotypes often co-occur in a single kindred or sibship. Some individuals with X-ALD remain asymptomatic until their adult years.

Affected Males

Childhood Cerebral Adrenoleukodystrophy (cCALD)

Inflammatory cerebral demyelination may occur at almost any age in X-ALD, but it is characteristically seen as a childhood presentation. It most commonly occurs between ages four and eight years, with a peak at age seven years. It rarely occurs before age three years.

It is important to identify as early as possible males with neuroimaging findings of cCALD in order to refer them promptly to determine if they are candidates for targeted therapy that can slow the disease course (see Management, Targeted Therapy).

Affected males present with behavioral or learning deficits, often diagnosed as attention-deficit/hyperactivity disorder, which may respond to stimulant medication. These behaviors may persist for months or longer, and are followed by symptoms suggestive of a more serious underlying disorder, including "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. The presence of advanced disease on MRI even with seemingly mild neurologic findings may preclude an attempt at targeted therapy.

In some males, seizures may be the first manifestation.

While variable, the rate of disease progression may be rapid, with total disability occurring within 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.

Adrenomyeloneuropathy (AMN)

The typical presentation is a man in his adult years who develops progressive stiffness and weakness in the legs (due to spastic paraparesis), abnormalities of bladder and bowel control, abnormal sensory perception (especially of vibratory sense), and sexual dysfunction. All manifestations progress over decades.

Approximately 40%-45% of individuals with AMN show some degree of involvement on brain MRI or clinical examination. In 20%-63% of individuals with AMN, progressive brain involvement leads to serious cognitive and behavioral disturbances that may progress to total disability and death [de Beer et al 2014].

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

Primary Adrenocortical Insufficiency

Males can present with signs of adrenal insufficiency at any age, although commonly by age 7.5 years. Presenting signs include unexplained vomiting and weakness or coma, leading to the diagnosis of primary adrenocortical insufficiency. A variable finding is increased skin pigmentation resulting from excessive adrenocorticotropic hormone secretion.

Overall, adrenocortical function is abnormal in 90% of neurologically symptomatic boys and 70% of men with AMN. Most males who are initially diagnosed as having only primary adrenocortical insufficiency will develop some neurologic manifestations; however, it may be decades later.

Heterozygous Females

Heterozygous females are symptom-free in childhood. In adulthood, an AMN-like phenotype in females is reported as mild-to-moderate spastic paraparesis with bladder and bowel issues. The onset of these issues is often subtle and – if not specifically examined for – easily overlooked. The findings do correlate with age, and may not become evident until later in life. Progression is also slower than that seen in males with AMN [Huffnagel et al 2019]. For these reasons, the reported incidence of an AMN-like phenotype in heterozygous females varies between 65% and 80% [Huffnagel et al 2019, Schirinzi et al 2019].

It may be stated that adrenal insufficiency in heterozygous females is rare, and the present recommendation is not to routinely screen females for this feature. There are also rare reports of cerebral myelin involvement caused, in some females, by genetic mechanisms such as chromosomal rearrangement or skewed X-inactivation [Hershkovitz et al 2002].

Genotype-Phenotype Correlations

The X-ALD phenotype cannot be predicted by VLCFA plasma concentration or by the nature of the *ABCD1* pathogenic variant, as the same pathogenic variant can be associated with each of the known phenotypes.

Likewise, the same phenotype can be observed both with large deletions that result in absence of the gene product and with missense pathogenic variants associated with abundant immunoreactive protein product [Mallack et al 2022a].

Penetrance

Although the variation in X-ALD clinical phenotypes is great, neurologic manifestations are present in nearly all males by adulthood [Huffnagel et al 2019].

The X-ALD biochemical phenotype of elevated plasma concentration of VLCFAs has 100% penetrance in males regardless of age [Engelen et al 2022].

Nomenclature

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

Historically, the eponym Schilder's disease referred to several clinical entities including X-ALD; on occasion, families may have been given this diagnosis. Schilder's disease is still sometimes (incorrectly) used to refer to sudanophilic cerebral sclerosis and certain forms of multiple sclerosis, which may lead to diagnostic confusion.

Childhood cerebral adrenoleukodystrophy (cCALD) may also be referred to as cerebral adrenoleukodystrophy (CALD), but it should be emphasized that cerebral involvement may occur at any age.

Primary adrenocortical insufficiency may also be referred to as Addison disease.

Prevalence

The prevalence of X-ALD is estimated at between one in 14,000 and one in 17,000 male births [Gupta et al 2022].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ABCD1*.

A **contiguous deletion syndrome** involving *BCAP31* and the 5' end of *ABCD1* (termed CADDS [**c**ontiguous ***A**BCD1/**D**XS1357E* **d**eletion **s**yndrome]; OMIM 300475) has been described in males with a phenotype that is earlier in onset and distinct from the phenotypes resulting from pathogenic variants in *ABCD1* alone. Neonatal cholestasis, hypotonia, and developmental delay have been reported in males with CADDS, and all affected males died before age one year [Calhoun & Raymond 2014, van de Kamp et al 2015]. Plasma very long-chain fatty acid concentrations were elevated in males with CADDS, but the remainder of the clinical features appear to be due to the loss of *BCAP31* [Cacciagli et al 2013].

Differential Diagnosis

Peroxisomal biogenesis disorders with elevated plasma very long-chain fatty acids are summarized in Table 3.

Table 3. Peroxisomal Biogenesis Disorders with Elevated Plasma Very Long-Chain Fatty Acids

Gene	Disorder	MOI
ABCD1	X-linked adrenoleukodystrophy (topic of this *GeneReview*)	XL
ACBD5	Retinal dystrophy w/leukodystrophy (OMIM 618863)	AR
ACOX1	Acyl-coenzyme A oxidase deficiency (OMIM 264470)	AR
DNM1L	Lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM 614388)	AD AR
HSD17B4	D-bifunctional enzyme deficiency (OMIM 261515)	AR

Table 3. continued from previous page.

Gene	Disorder	MOI
PEX genes	Zellweger spectrum disorder	AR [1]
SCP2	Leukoencephalopathy w/dystonia & motor neuropathy (OMIM 613724)	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Zellweger spectrum disorder (ZSD) is typically inherited in an autosomal recessive manner; however, one *PEX6* pathogenic variant, p.Arg860Trp, has been associated with ZSD in the heterozygous state.

Females. See Hereditary Spastic Paraplegia Overview for other genetic causes of spastic paraparesis and a review of genetic and acquired conditions in the differential diagnosis of hereditary spastic paraplegia.

Management

With the institution of newborn screening and increasing numbers of individuals being diagnosed with X-linked adrenoleukodystrophy (X-ALD), clinical practice guidelines have been developed for diagnosis and treatment; see Regelmann et al [2018] (full text), Engelen et al [2022] (full text), and Mallack et al [2022b] (full text).

Evaluations Following Initial Diagnosis

Confirmed Positive Newborn Screening Result: Initial Evaluations

For male infants with a positive newborn screening (NBS) result for X-ALD, the initial evaluations summarized in Table 4 are recommended in order to prevent life-threatening complications of primary adrenal insufficiency and to develop a plan for neurologic and brain MRI monitoring to identify promptly those at risk for childhood cerebral adrenoleukodystrophy (cCALD). Boys identified with early changes on brain MRI consistent with cCALD are candidates for targeted therapy to prevent progression of central nervous system disease.

Table 4. Recommended Evaluations and Next Steps for Infants with a Confirmed Positive Newborn Screening Result for X-Linked Adrenoleukodystrophy

System/Concern	Issue	Comment
Males at risk for primary adrenocortical insufficiency [1]	Immediate referral to pediatric endocrinologist	• Screening for ACTH & cortisol levels • Follow up per Pediatric Endocrine Society published guidance recommendations [1]
	Treatment of documented primary adrenocortical insufficiency	By pediatric endocrinologist per published guidance recommendations [1]
	Institute plan for scheduled screening throughout childhood & adulthood	Recommended screening every 3-6 mos until age 10 yrs, then yearly thereafter [2]
Males at risk for cCALD	Referral to neurologist or biochemical geneticist to develop plan for neurologic & brain MRI monitoring to identify promptly those at risk for cCALD [3]	See Table 8 for age-related recommended intervals for repeat brain MRI.

Table 4. continued from previous page.

System/Concern	Issue	Comment
Genetic counseling	By genetics professionals [4]	• To inform affected persons & their families re nature, MOI, & implications of X-ALD to facilitate medical & personal decision making • To identify male relatives at risk for X-ALD (At-risk males may be identified by use of plasma or serum VLCFA levels or *ABCD1* testing. Affected males should be evaluated as recommended in this table.)

ACTH = adrenocorticotropic hormone; CALD = cerebral adrenoleukodystrophy; cCALD = childhood cerebral adrenoleukodystrophy; VLCFA = very long-chain fatty acid; X-ALD = X-linked adrenoleukodystrophy
1. Regelmann et al [2018]
2. Engelen et al [2022]
3. Mallack et al [2021b], Mallack et al [2022b]
4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Males with Symptomatic cCALD: Initial Evaluations

Recommended initial evaluations for symptomatic males with cCALD are summarized in Table 5.

Table 5. Recommended Evaluations Following Initial Diagnosis in Symptomatic Males with Childhood Cerebral Adrenoleukodystrophy (cCALD)

System/Concern	Evaluation	Comment
Neurologic impairment	By pediatric neurologist	Assess for: • Specific neurologic deficits (e.g., hemiparesis, visual field defect); • Seizures if history is suggestive. In presence of above, perform brain MRI if not performed at time of initial eval.
	Consultation w/X-ALD comprehensive center w/experience in transplantation or ex vivo gene therapy	Assess for eligibility for targeted therapy.
Behavioral issues	Behavioral assessment by developmental pediatrician, primary care physician	Assess for: • Behaviors that may respond to medication; • Aggressive or disinhibited behavior.
Developmental delay/ regression	Developmental assessment	Assess: • Educational needs; • Need for OT service; • Need for PT services incl durable medical equipment.
Speech impairment	By speech-language pathologist	Assess for aphasia & need for alternative means of communication.
Adrenocortical insufficiency	By pediatric endocrinologist	Screening tests per Pediatric Endocrine Society published guidance recommendations [1]

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [2]	• To inform affected persons & their families re nature, MOI, & implications of cCALD to facilitate medical & personal decision making • To identify male relatives at risk for X-ALD (At-risk males may be identified by use of plasma or serum VLCFA levels or *ABCD1* testing. Affected males should be evaluated as recommended in Table 4.)
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental/family support; • Home nursing referral.	

cCALD = childhood cerebral adrenoleukodystrophy; VLCFA = very long-chain fatty acid; X-ALD = X-linked adrenoleukodystrophy
1. Regelmann et al [2018]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Males and Females with Adrenomyeloneuropathy (AMN): Initial Evaluations

For recommended initial evaluations for males and females who have adrenomyeloneuropathy (AMN), see Table 6.

Table 6. Recommended Evaluations Following Initial Diagnosis in Males and Females with Adrenomyeloneuropathy (AMN)

System/Concern	Evaluation	Comment
Neurologic impairment	By neurologist	• Assess for cognitive impairment, progressive spastic gait disturbance, paralysis, ataxia, weakness, & restless legs syndrome. • Brain MRI to assess for cerebral disease (Spine MRIs are generally not helpful.) • Further services such as mental health, speech, & behavior if appropriate
Sleep disturbance	By neurologist or sleep specialist	Assess for clonus &/or pain
Neurogenic bladder	By urologist	Eval & treatment per standard practice
Bowel incontinence	By gastroenterologist	Eval & treatment of constipation or incontinence per standard practice
Sexual dysfunction	By urologist	Eval & treatment of sexual dysfunction per standard practice
Adrenocortical insufficiency	By endocrinologist	Males: yearly ACTH & cortisol levels
Genetic counseling	By genetics professionals [1]	• To inform affected persons & their families re nature, MOI, & implications of X-ALD to facilitate medical & personal decision making • To identify male relatives at risk for X-ALD (At-risk males may be identified by use of plasma or serum VLCFA levels or *ABCD1* testing. Affected males should be evaluated as recommended in Table 4.)

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for parental/family support.	

ACTH = adrenocorticotropic hormone; VLCFA = very long-chain fatty acid; X-ALD = X-linked adrenoleukodystrophy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Males Identified by Family Screening: Initial Evaluations and Next Steps

Males identified by family screening may be any age (infancy through adulthood), and the urgency of evaluation will depend on age at diagnosis. See Table 7 for recommended initial evaluations and next steps.

Table 7. Recommended Evaluations and Next Steps for Males Identified by Family Screening

System/Concern	Evaluation	Comment
Neurologic assessment	Brain MRI	• Assess for presence of cerebral disease. • Urgency will depend on age of affected person. Males age <2-10 yrs need expedited imaging (see Table 8).
Endocrine	• ACTH & cortisol levels • Referral to pediatric endocrinology	Replacement glucocorticoid therapy
Genetic counseling	By genetics professionals [1]	• To inform affected persons & their families re nature, MOI, & implications of X-ALD to facilitate medical & personal decision making • To identify male relatives at risk for X-ALD & primary adrenocortical insufficiency who might warrant diagnostic eval & treatment/screening as recommended in Table 4.
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for parental/family support.	

ACTH = adrenocorticotropic hormone; X-ALD = X-linked adrenoleukodystrophy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for X-linked adrenoleukodystrophy (X-ALD).

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Childhood Cerebral Adrenoleukodystrophy (cCALD)

Evidence clearly shows that hematopoietic stem cell transplantation (HSCT) has the best outcome when performed on an asymptomatic individual with minimal but characteristic imaging findings of cCALD [Gupta et al 2022].

Early-stage cCALD brain MRI findings are characterized by small T_2 hyperintensities centered most often within the splenium or genu of the corpus callosum; less often they may appear in the corticospinal tracts or cerebellar white matter. Since normal imaging findings may occasionally be mistaken for early disease, it is strongly recommended that all findings be confirmed by a neuroradiologist with experience in this condition [Gupta et al 2022].

See Table 8 for a recommended schedule of brain MRI monitoring of at-risk males for early identification of cCALD to detect brain abnormalities that occur well in advance of clinical disease [Loes et al 2003, Mallack et al 2021a, Mallack et al 2022b].

Table 8. Recommended Brain MRI Schedule for Early Detection of Childhood Cerebral Adrenoleukodystrophy (cCALD) Abnormalities in At-Risk Males

Age	Interval	Type of Brain MRI	Comment
12 mos - 3 yrs	Yearly	Standard T_1/T_2-weighted sequences	Use of general anesthesia is advisable until the boy can lie still.
3-12 yrs	Every 6 mos	Standard T_1/T_2-weighted sequences w/ contrast	
>12 yrs	Yearly	Standard T_1/T_2-weighted sequences	Repeat yearly; some males develop cerebral changes in adulthood.

Based on Loes et al [2003], Mallack et al [2021a], Mallack et al [2022b]
cCALD = childhood cerebral adrenoleukodystrophy

If early-stage cCALD is diagnosed, the boy should be referred to a center with expertise in monitoring and treating cCALD.

The following are NOT presently recommended for screening males at risk for cCALD:

- The routine use of advanced imaging techniques such as spectroscopy or diffusion tensor imaging outside of a research protocol with IRB approval
- The routine use of neuropsychological testing [Engelen et al 2022]

Hematopoietic stem cell transplantation (HSCT)

- **Indications and potential benefits.** HSCT is only recommended for males with evidence of early cCALD on MRI, which is associated with inflammatory demyelination.

  Note: HSCT is not recommended for individuals with severe neurologic and neuropsychological dysfunction (i.e., performance IQ <80) [Gupta et al 2022].

- **Methods used for HSCT.** Allogeneic stem cell transplant is performed. Although a matched-sib donor provides the lowest risk, other donor sources include unrelated matched donors and umbilical cord blood. Individuals undergoing an allogeneic stem cell transplant receive a preparatory regimen and appropriate post-procedure support and monitoring. Individuals continue to require monitoring following the procedure, and this may be done either at the center doing the procedure or at a site closer to home.

- **Potential risks of HSCT.** In X-ALD, HSCT has an overall survival of 82% two years following the transplant and 74% five years following the transplant. Risks involved include the preparatory regimen, transplantation itself, infections, and graft failure. These risks should be considered in the context that

untreated cCALD has only an overall 55% survival rate at age five years [Raymond et al 2019]. Factors that improve survival and absence of major functional disabilities following HSCT include matched-sib donors, early detection of disease on neuroimaging, and absence of any neurologic signs at the time of transplant [Raymond et al 2019].

Elivaldogene autotemcel (Skysona®) therapy. An ex vivo gene therapy has been recently approved in the United States. The manufactured product is elivaldogene autotemcel, marketed under the brand name Skysona® [Eichler et al 2017, Gupta et al 2022]. Using a lentiviral approach, a working copy of *ABCD1* is transfected into the patient's precursor hematopoietic cells.

- **Indications and potential benefits.** The indications are similar to those presently used in standard-risk HSCT.
  - Individuals should have early cCALD as seen on contrast-enhanced MRI.
  - They should not have neurologic signs.
  - Neuropsychological testing should indicate a performance IQ greater than 80.

  An added criterion is absence of a matched-sib donor.

  The potential benefit is that risk of graft versus host disease is less than that associated with HSCT.
- **Method of administration and dosage.** Patients must undergo hematopoietic stem cell mobilization to obtain CD34+ cells for manufacturing of cells. The minimum recommended dose is 5 x 10^6 CD34+ cells per kg. Following conditioning, manufactured cells are given intravenously.
- **Potential risks.** Hematologic malignancy including instances of myelodysplastic syndrome have occurred in individuals treated with elivaldogene. These cancers appear to be the result of the integration of the elivaldogene lentiviral vector, Lenti-D®, into proto-oncogenes. Because of the increased risk of this adverse event in some individuals, subsequent required monitoring is a complete blood count every six months in the first year and then yearly thereafter.

Supportive Care

Childhood Cerebral Adrenoleukodystrophy (cCALD)

Boys whose neurologic disease is too advanced at the time of diagnosis are not candidates for targeted therapy. Thus, supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 9).

Table 9. Supportive Treatment of Manifestations in Males with Childhood Cerebral Adrenoleukodystrophy (cCALD)

Manifestation/Concern	Treatment	Considerations/Other
Cognitive decline		Need for a 504 plan or IEP services
Seizures	With ASMs by experienced neurologist	No contraindications for type of anticonvulsant
Behavioral issues	By mental health professional	
Communication	By speech-language pathologist	Consider alternative means of communication.
Motor impairment / ADL	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Feeding issues	• Speech-language therapy or OT • Discuss gastrostomy tube placement.	
Adrenocortical insufficiency [1]	Corticosteroid replacement therapy [2]	• Children: per treating pediatric endocrinologist • Adults: per treating endocrinologist

Table 9. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement w/home nursing • Discussion of hospice

ADL = activities of daily living; ASM = anti-seizure medication; IEP = individualized education plan; OT = occupational therapy; PT = physical therapy
1. Regelmann et al [2018]
2. Corticosteroid replacement therapy has no effect on nervous system involvement.

Adrenomyeloneuropathy (AMN)

Supportive care for males and females with adrenomyeloneuropathy (AMN) to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 10).

Table 10. Supportive Treatment of Manifestations in Males and Females with Adrenomyeloneuropathy (AMN)

Manifestation/Concern	Treatment	Considerations/Other
Cognitive decline	By neuropsychologist	
Behavioral issues	By mental health providers	
Communication	By speech-language pathologist	Consider alternative means of communication.
Seizures	By neurologist	Appropriate ASMs
Motor impairment / ADL	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Neurogenic bladder	By urologist	
Bowel control	By gastroenterologist	
Sexual dysfunction	By urologist	In males only
Emotional & vocational counseling	By mental health providers	If necessary
Adrenocortical insufficiency [1]	Corticosteroid replacement therapy [2] (which can be lifesaving in males, & is rarely needed in females)	Per treating endocrinologist
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ADL = activities of daily living; ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Regelmann et al [2018]
2. Corticosteroid replacement therapy has no effect on nervous system involvement.

Surveillance

Childhood Cerebral Adrenoleukodystrophy (cCALD)

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 11 are recommended for males with cCALD.

Table 11. Recommended Surveillance for Males with Childhood Cerebral Adrenoleukodystrophy (cCALD)

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as onset of seizures, changes in tone, & movement disorders.	
Educational	Monitor developmental needs & educational progress.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Adrenocortical insufficiency	Endocrine assessment	• For those not yet known to have adrenocortical insufficiency: ACTH & cortisol levels every 6 mos • For those w/known adrenocortical insufficiency: per treating endocrinologist, but at least yearly
Family/Community	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ACTH = adrenocorticotropic hormone; OT = occupational therapy; PT = physical therapy

Adrenomyeloneuropathy (AMN)

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 12 are recommended for males and females with AMN.

Table 12. Recommended Surveillance for Males and Females with Adrenomyeloneuropathy (AMN)

System/Concern	Evaluation	Frequency
Neurologic	Assess for new manifestations such as changes in tone, symptoms of neurogenic bladder, bowel incontinence, &/or sexual dysfunction.	Yearly
Educational/ Vocational	Monitor educational & vocational training needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	

Table 12. continued from previous page.

System/Concern	Evaluation	Frequency
Adrenocortical insufficiency	Endocrine assessment	• Males not yet known to have adrenocortical insufficiency: yearly ACTH & cortisol levels • Males w/known adrenocortical insufficiency: per treating endocrinologist, but at least yearly • Females: not warranted given rarity of adrenocortical insufficiency
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ACTH = adrenocorticotropic hormone; OT = occupational therapy; PT = physical therapy

Primary Adrenocortical Insufficiency

Recommended surveillance for primary adrenocortical insufficiency in males is summarized in Table 13.

Table 13. Recommended Ages/Intervals of Surveillance for Primary Adrenocortical Insufficiency for At-Risk but Not Yet Symptomatic Males

Age	Interval	Evaluation
<2 yrs	Every 3-4 mos	Measurement of cortisol & ACTH levels
2-13 yrs	Every 4-6 mos	
>13 yrs	Every 6-12 mos	

Based on Regelmann et al [2018], Engelen et al [2022]
ACTH = adrenocorticotropic hormone

Agents/Circumstances to Avoid

Significant head injury has been associated with activation of cerebral disease [Bouquet et al 2015]. Other triggers anecdotally reported have included coma associated with adrenal crisis and neurosurgical procedures.

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk male relatives (i.e., male relatives not known to have X-ALD) of an affected individual in order to identify as early as possible those who would benefit from screening for primary adrenocortical insufficiency and to facilitate timely identification of young males who might benefit from targeted treatment for cCALD. Such testing can also allow for correct diagnosis of early (and often nonspecific) neurologic, behavioral, and/or cognitive signs and symptoms. Because these issues are not limited by age, all at-risk males should be offered diagnostic testing.

If born in the United States, males affected with X-ALD may be diagnosed by universal newborn screening soon after birth. If newborn screening data are not available for at-risk sibs, several evaluations can be considered:

- If the *ABCD1* pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the *ABCD1* pathogenic variant in the family has not been confirmed, very long-chain fatty acid analysis may be used to clarify the disease status of at-risk male relatives.

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

Therapies Under Investigation

PPAR activators have been under investigation for many years. A recent study showed the effect of leriglitazone in individuals with AMN; the primary outcome did not demonstrate efficacy. There were improvements in sway amplitude, a measure of balance [Köhler et al 2023].

AAV9-based targeted gene therapy has been explored in preclinical models of ALD, and the first human trials are being conducted. The safety and efficacy of this approach remains under investigation [Gong et al 2015, Özgür-Günes et al 2022].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, X-linked adrenoleukodystrophy (X-ALD) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *ABCD1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a female has more than one affected child and no other affected relatives and if the *ABCD1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother:
  - May be a heterozygote. Approximately 95% of probands inherit an *ABCD1* pathogenic variant from one parent.
  - May not be heterozygous, and the affected male has a *de novo ABCD1* pathogenic variant. At least 4.1% of individuals with X-ALD have a *de novo* pathogenic variant [Wang et al 2011].
  - May have somatic/germline mosaicism. Evidence of germline or somatic/germline mosaicism is present in <1% of parents.
- If an *ABCD1* pathogenic variant has been identified in an affected family member, molecular genetic testing of the mother is recommended to confirm her genetic status and allow reliable recurrence risk assessment. *ABCD1* molecular genetic testing is the preferred method for the evaluation of mothers of affected males.

Parents of a female proband

- A female proband may have inherited the *ABCD1* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.

- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant.
- Recommendations for the evaluation of the parents of a female proband:
  - If an *ABCD1* pathogenic variant has been identified in an affected family member, molecular genetic testing can be used for the evaluation of the parents.
  - Fathers of newly identified heterozygous females may be evaluated by very long-chain fatty acid (VLCFA) testing (see Related Genetic Counseling Issues).

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *ABCD1* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.

    Note: The phenotype in a male sib who inherits an *ABCD1* pathogenic variant cannot be predicted by family history, VLCFA plasma concentration, or the nature of the pathogenic variant; the same *ABCD1* pathogenic variant can be associated with each of the known X-ALD phenotypes.
  - Females who inherit the pathogenic variant will be heterozygous. Heterozygous females are symptom-free in childhood but may manifest findings in adulthood (see Clinical Characteristics, Heterozygous Females).
- If the proband represents a simplex case and if the *ABCD1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism [Wang et al 2011].

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has an *ABCD1* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50% (see **Sibs of male proband**).
- If the father of the proband is affected (i.e., hemizygous for an *ABCD1* pathogenic variant), he will transmit the pathogenic variant to all of his daughters and none of his sons.

Offspring of a proband

- Affected males transmit the *ABCD1* pathogenic variant to all of their daughters and none of their sons (see **Sibs of male proband**).
- Heterozygous females have a 50% chance of transmitting the *ABCD1* pathogenic variant in each pregnancy (see **Sibs of male proband**).
- Note: Varying phenotypes often coexist in the same family.

Other family members. Depending on their sex, family relationship, and the genetic status of the proband's parents, the proband's aunts and uncles and their offspring may be at risk of having the *ABCD1* pathogenic variant (see Related Genetic Counseling Issues).

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *ABCD1* pathogenic variant has been identified in the proband.

- Females who are heterozygous for this X-linked disorder are symptom-free in childhood but may manifest findings in adulthood (see Clinical Characteristics, Heterozygous Females).

- Identification of female heterozygotes requires either prior identification of the *ABCD1* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, then by gene-targeted deletion/duplication analysis.

Note: VLCFA analysis is not recommended as a screening method for females known to be at risk (see Establishing the Diagnosis).

Related Genetic Counseling Issues

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 – or molecular genetic testing if the familial *ABCD1* pathogenic variant is known – 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.

Considerations for female infants with positive X-ALD newborn screening (NBS) results. Females identified by NBS do not require monitoring in childhood. When older, it may be appropriate for them to meet with a genetics professional to discuss reproductive options (see **Family planning**) and broadly discuss potential issues. A positive NBS in a female infant should prompt identification and evaluation of at-risk male relatives.

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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 affected, are heterozygous, or are at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ABCD1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ALD Alliance (formerly Aidan Jack Seeger Foundation)**
  Phone: 917-750-9390
  Email: elisa@aldalliance.org
  www.aldalliance.org

- **ALD Connect**
  ALD Connect Patient Portal
- **Leukodystrophy Australia**
  Australia
  Phone: 1800 141 400
  Email: info@leuko.org.au
  leuko.org.au
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Adrenoleukodystrophy Information Page
- **NCBI Genes and Disease**
  Adrenoleukodystrophy
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Adrenoleukodystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ABCD1	Xq28	ATP-binding cassette sub-family D member 1	ABCD1 @ LOVD X-linked Adrenoleukodystrophy Database (ABCD1)	ABCD1	ABCD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Adrenoleukodystrophy (View All in OMIM)

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

Molecular Pathogenesis

ABCD1 encodes adrenoleukodystrophy protein (ALDP), a member of the ATP-binding cassette (ABC) protein transporter family. This protein serves as a transporter of certain fatty acids into the peroxisome. Failure to transport these fatty acids into the peroxisome prevents beta-oxidation and allows continued elongation of fatty acids, resulting in accumulation of very long-chain fatty acids (VLCFAs) [Turk et al 2020]. As a result, these lipids accumulate abnormally in all tissues, but predominantly affect the nervous system, adrenal cortex, and Leydig cells of the testes. The mechanisms by which accumulation of VLCFAs causes neurology or adrenal dysfunction is not very well understood [Turk et al 2020].

Mechanism of disease causation. Loss of function

***ABCD1*-specific laboratory technical considerations.** *ABCD1* contains ten exons and spans 21 kb. Sequence analysis is complicated by the presence of five known autosomal paralogs or pseudogenes. These pseudogenes, *ABCD1P1* (2p11.1), *ABCD1P2* (10p11), *ABCD1P3* (16p11), *ABCD1P4* (22q11), and *ABCD51P* (2p11.2), are 9.7 kb in length and encompass exons 7 through 10 of *ABCD1*. These duplicated fragments share 92%-96% sequence homology with *ABCD1*. Therefore, variants in these pseudogenes may be misidentified as variants in *ABCD1*, resulting in misdiagnosis of the disease. A specific set of primers have been developed for accurate variant analysis without interference of the pseudogenes [Boehm et al 1999]. Current molecular diagnostic testing approaches may utilize next-generation sequencing with specific capture probes to sequence *ABCD1*.

Chapter Notes

Author Notes

Gerald Raymond (graymon4@jhmi.edu) and Ali Fatemi (fatemi@kennedykrieger.org) are actively involved in clinical research regarding individuals with X-linked adrenoleukodystrophy (X-ALD). They would be happy to communicate with persons who have any questions regarding diagnosis of X-ALD or other considerations. A special area of focus for Dr Raymond is the confirmatory diagnostics and surveillance following identification by newborn screening.

Drs Raymond and Fatemi are also interested in hearing from clinicians treating families affected by X-ALD in whom no causative variant has been identified through molecular genetic testing.

Contact Dr Raymond to inquire about review of *ABCD1* variants of uncertain significance.

Contact Ms Ann Moser (mosera@kennedykrieger.org) to discuss technical issues with very long-chain fatty acid or C26:0-lysophosphatidylcholine determinations.

Acknowledgments

The authors' work has been supported in the past by the National Institutes of Health and the Food and Drug Administration.

Author History

Corinne D Boehm, MS; Johns Hopkins Hospital (1999-2002)
Ali Fatemi, MD (2018-present)
Ann B Moser, BA (1999-present)
Hugo W Moser, MD; Johns Hopkins University School of Medicine (1999-2007)*
Gerald V Raymond, MD (2006-present)
Steven J Steinberg, PhD; Johns Hopkins University School of Medicine (2002-2018)

* 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. Dr Moser died of cancer on January 20, 2007, at age 82. He is greatly missed by his family, friends, colleagues, and patients.

Revision History

- 6 April 2023 (bp) Comprehensive update posted live
- 15 February 2018 (ha) Comprehensive update posted live
- 9 April 2015 (me) Comprehensive update posted live
- 19 April 2012 (me) Comprehensive update posted live
- 2 June 2009 (me) Comprehensive update posted live
- 27 July 2006 (me) Comprehensive update posted live
- 15 April 2004 (me) Comprehensive update posted live
- 26 August 2002 (ss) Author revisions
- 26 February 2002 (me) Comprehensive update posted live
- 26 March 1999 (pb) Review posted live
- 2 February 1999 (hm) Original submission

References

Literature Cited

Boehm CD, Cutting GR, Lachtermacher MB, Moser HW, Chong SS. Accurate DNA-based diagnostic and carrier testing for X-linked adrenoleukodystrophy. Mol Genet Metab. 1999;66:128-36. PubMed PMID: 10068516.

Bouquet F, Dehais C, Sanson M, Lubetzki C, Louapre C. Dramatic worsening of adult-onset X-linked adrenoleukodystrophy after head trauma. Neurology. 2015;85:1991-3. PubMed PMID: 26537054.

Cacciagli P, Sutera-Sardo J, Borges-Correia A, Roux JC, Dorboz I, Desvignes JP, Badens C, Delepine M, Lathrop M, Cau P, Lévy N, Girard N, Sarda P, Boespflug-Tanguy O, Villard L. Mutations in BCAP31 cause a severe X-linked phenotype with deafness, dystonia, and central hypomyelination and disorganize the Golgi apparatus Am J Hum Genet. 2013;93:579-86. PubMed PMID: 24011989.

Calhoun AR, Raymond GV. Distal Xq28 microdeletions: clarification of the spectrum of contiguous gene deletions involving ABCD1, BCAP31, and SLC6A8 with a new case and review of the literature. Am J Med Genet A. 2014;164A:2613-7. PubMed PMID: 25044748.

Caughey AB, Krist AH, Wolff TA, Barry MJ, Henderson JT, Owens DK, Davidson KW, Simon MA, Mangione CM. USPSTF approach to addressing sex and gender when making recommendations for clinical preventive services. JAMA. 2021;326:1953-61. PubMed PMID: 34694343.

de Beer M, Engelen M, van Geel BM. Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy. Neurology. 2014;83:2227-31. PubMed PMID: 25378668.

Eichler F, Duncan C, Musolino PL, Orchard PJ, De Oliveira S, Thrasher AJ, Armant M, Dansereau C, Lund TC, Miller WP, Raymond GV, Sankar R, Shah AJ, Sevin C, Gaspar HB, Gissen P, Amartino H, Bratkovic D, Smith NJC, Paker AM, Shamir E, O'Meara T, Davidson D, Aubourg P, Williams DA. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. N Engl J Med. 2017;377:1630-8. PubMed PMID: 28976817.

Engelen M, van Ballegoij WJC, Mallack EJ, Van Haren KP, Köhler W, Salsano E, van Trotsenburg ASP, Mochel F, Sevin C, Regelmann MO, Tritos NA, Halper A, Lachmann RH, Davison J, Raymond GV, Lund TC, Orchard PJ, Kuehl JS, Lindemans CA, Caruso P, Turk BR, Moser AB, Vaz FM, Ferdinandusse S, Kemp S, Fatemi A,

Eichler FS, Huffnagel IC. International recommendations for the diagnosis and management of patients with adrenoleukodystrophy: a consensus-based approach. Neurology. 2022;99:940-51. PubMed PMID: 36175155.

Gong Y, Mu D, Prabhakar S, Moser A, Musolino P, Ren J, Breakefield XO, Maguire CA, Eichler FS. Adenoassociated virus serotype 9-mediated gene therapy for X-linked adrenoleukodystrophy. Mol Ther. 2015;23:824-34. PubMed PMID: 25592337.

Gupta AO, Raymond G, Pierpont EI, Kemp S, McIvor RS, Rayannavar A, Miller B, Lund TC, Orchard PJ. Treatment of cerebral adrenoleukodystrophy: allogeneic transplantation and lentiviral gene therapy. Expert Opin Biol Ther. 2022;22:1151-62. PubMed PMID: 36107226.

Hershkovitz E, Narkis G, Shorer Z, Moser AB, Watkins PA, Moser HW, Manor E. Cerebral X-linked adrenoleukodystrophy in a girl with Xq27-Ter deletion. Ann Neurol. 2002;52:234-7. PubMed PMID: 12210797.

Huffnagel IC, Dijkgraaf MGW, Janssens GE, van Weeghel M, van Geel BM, Poll-The BT, Kemp S, Engelen M. Disease progression in women with X-linked adrenoleukodystrophy is slow. Orphanet J Rare Dis. 2019;14:30. PubMed PMID: 30732635.

Jaspers YRJ, Ferdinandusse S, Dijkstra IME, Barendsen RW, van Lenthe H, Kulik W, Engelen M, Goorden SMI, Vaz FM, Kemp S. Comparison of the diagnostic performance of C26:0-lysophosphatidylcholine and very long-chain fatty acids analysis for peroxisomal disorders Front Cell Dev Biol. 2020;8:690 PubMed PMID: 32903870.

Köhler W, Engelen M, Eichler F, Lachmann R, Fatemi A, Sampson J, Salsano E, Gamez J, Molnar MJ, Pascual S, Rovira M, Vilà A, Pina G, Martín-Ugarte I, Mantilla A, Pizcueta P, Rodríguez-Pascau L, Traver E, Vilalta A, Pascual M, Martinell M, Meya U, Mochel F, et al. Safety and efficacy of leriglitazone for preventing disease progression in men with adrenomyeloneuropathy (ADVANCE): a randomized, double blind, multi-centre, placebo-controlled phase 2-3 trial. Lancet Neurol 2023;22:127-36. PubMed PMID: 36681445.

Loes DJ, Fatemi A, Melhem ER, Gupte N, Bezman L, Moser HW, Raymond GV (2003) Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology 61:369-74 PubMed PMID: 12913200.

Mallack EJ, Askin G, van de Stadt S, Caruso PA, Musolino PL, Engelen M, Niogi SN, Eichler FS. A longitudinal analysis of early lesion growth in presymptomatic patients with cerebral adrenoleukodystrophy. AJNR Am J Neuroradiol. 2021a;42:1904-11. PubMed PMID: 34503945.

Mallack EJ, Turk BR, Yan H, Price C, Demetres M, Moser AB, Becker C, Hollandsworth K, Adang L, Vanderver A, Van Haren K, Ruzhnikov M, Kurtzberg J, Maegawa G, Orchard PJ, Lund TC, Raymond GV, Regelmann M, Orsini JJ, Seeger E, Kemp S, Eichler F, Fatemi A. MRI surveillance of boys with X-linked adrenoleukodystrophy identified by newborn screening: meta-analysis and consensus guidelines. J Inherit Metab Dis. 2021b;44:728-39. PubMed PMID: 33373467.

Mallack EJ, Gao K, Engelen M, Kemp S. Structure and function of the ABCD1 variant database: 20 years, 940 pathogenic variants, and 3400 cases of adrenoleukodystrophy. Cells. 2022a;11:283. PubMed PMID: 35053399.

Mallack EJ, Van Haren KP, Torrey A, van de Stadt S, Engelen M, Raymond GV, Fatemi A, Eichler FS. Presymptomatic lesion in childhood cerebral adrenoleukodystrophy: timing and treatment. Neurology. 2022b;99:e512-20 PubMed PMID: 35609989.

Özgür-Günes Y, Chedik M, Stunff CL, Fovet CM, Bougneres P. Long-term disease prevention with gene therapy targeting oligodendrocytes in a mouse model of adrenomyeloneuropathy. Hum Gene Ther. 2022;33:936-49. PubMed PMID: 35166123.

Raymond GV, Aubourg P, Paker A, Escolar M, Fischer A, Blanche S, Baruchel A, Dalle JH, Michel G, Prasad V, Miller W, Paadre S, Balser J, Kurtzberg J, Nascene DR, Orchard PJ, Lund T. Survival and functional outcomes

in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2019;25:538-48. PubMed PMID: 30292747.

Regelmann MO, Kamboj MK, Miller BS, Nakamoto JM, Sarafoglou K, Shah S, Stanley TL, Marino R, et al. Adrenoleukodystrophy: guidance for adrenal surveillance in males identified by newborn screen. J Clin Endocrinol Metab. 2018;103:4324-31. PubMed PMID: 30289543.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schirinzi T, Vasco G, Aiello C, Rizzo C, Sancesario A, Romano A, Favetta M, Petrarca M, Paone L, Castelli E, Bertini ES, Cappa M. Natural history of a cohort of ABCD1 variant female carriers. Eur J Neurol. 2019;26:326-32. PubMed PMID: 30295399.

Turk BR, Theda C, Fatemi A, Moser AB. X-linked adrenoleukodystrophy: pathology, pathophysiology, diagnostic testing, newborn screening and therapies. Int J Dev Neurosci. 2020;80:52-72. PubMed PMID: 31909500.

van de Kamp JM, Errami A, Howidi M, Anselm I, Winter S, Phalin-Roque J, Osaka H, van Dooren SJ, Mancini GM, Steinberg SJ, Salomons GS. Genotype-phenotype correlation of contiguous gene deletions of SLC6A8, BCAP31 and ABCD1. Clin Genet. 2015;87:141-7. PubMed PMID: 24597975.

Vogel BH, Bradley SE, Adams DJ, D'Aco K, Erbe RW, Fong C, Iglesias A, Kronn D, Levy P, Morrissey M, Orsini J, Parton P, Pellegrino J, Saavedra-Matiz CA, Shur N, Wasserstein M, Raymond GV, Caggana M. Newborn screening for X-linked adrenoleukodystrophy in New York State: diagnostic protocol, surveillance protocol and treatment guidelines. Mol Genet Metab. 2015;114:599-603. PubMed PMID: 25724074.

Wang Y, Busin R, Reeves C, Bezman L, Raymond G, Toomer CJ, Watkins PA, Snowden A, Moser A, Naidu S, Bibat G, Hewson S, Tam K, Clarke JT, Charnas L, Stetten G, Karczeski B, Cutting G, Steinberg S (2011) X-linked adrenoleukodystrophy: ABCD1 de novo mutations and mosaicism. Mol Genet Metab. 104:160-6. PubMed PMID: 21700483.

License