Summary

Clinical characteristics. Deficiency of very long-chain acyl-CoA dehydrogenase (VLCAD), which catalyzes the initial step of mitochondrial β-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons, is associated with three phenotypes. The severe early-onset cardiac and multiorgan failure form typically presents in the first months of life with hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias, as well as hypotonia, hepatomegaly, and intermittent hypoglycemia. The hepatic or hypoketotic hypoglycemic form typically presents during early childhood with hypoketotic hypoglycemia and hepatomegaly, but without cardiomyopathy. The later-onset episodic myopathic form presents with intermittent rhabdomyolysis provoked by exercise, muscle cramps and/or pain, and/or exercise intolerance. Hypoglycemia typically is not present at the time of symptoms.

Diagnosis/testing. Diagnosis is established in an individual with abnormal acylcarnitine analysis on biochemical testing and/or identification of biallelic pathogenic variants in ACADVL on molecular genetic testing. If one ACADVL pathogenic variant is found and suspicion of VLCAD deficiency is high, specialized biochemical testing using cultured fibroblasts or lymphocytes may be needed for confirmation of the diagnosis.

Management. Treatment of manifestations: Use of intravenous (IV) glucose as an energy source, treatment of cardiac rhythm disturbance, and monitoring of rhabdomyolysis. Cardiac dysfunction may be reversible with early, intensive supportive care (occasionally including extracorporeal membrane oxygenation) and diet modification.

Prevention of primary manifestations: Individuals with the more severe forms are typically placed on a low-fat formula, with supplemental calories provided through medium-chain triglycerides. Clinical trials of triheptanoin have shown some potential benefit for exercise tolerance.

Prevention of secondary complications: Acute rhabdomyolysis is treated with ample hydration and alkalization of the urine to protect renal function and to prevent acute renal failure secondary to myoglobinuria.

Surveillance: Suggested evaluations include annual physical exam including cardiac status, echocardiography on an annual or biannual basis, and annual assessment of nutritional status to avoid obesity, which can become a significant, difficult-to-manage problem in this disorder.

Agents/circumstances to avoid: Fasting, myocardial irritation, dehydration, and high-fat diet, volatile anesthetics and those that contain high doses of long-chain fatty acids such as propofol and etomidate.

Evaluation of relatives at risk: Evaluation of older and younger sibs of a proband to identify those who would benefit from institution of treatment and preventive measures.
Pregnancy management: Labor and postpartum periods are catabolic states and place the mother at higher risk for rhabdomyolysis and subsequent myoglobinuria. A management plan for labor and delivery is necessary for the affected pregnant woman.

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

**Diagnosis**

Very long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the initial step of mitochondrial β-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons. VLCAD deficiency is associated with a range of phenotypes:

- Severe early-onset cardiac and multiorgan failure form
- Hepatic or hypoketotic hypoglycemic form
- Later-onset episodic myopathic form with intermittent rhabdomyolysis

**Suggestive Findings**

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency should be suspected in individuals with the following:

- Newborn screening test abnormality suggestive of VLCAD deficiency
- Cardiac abnormality. Severe early-onset hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias accompanied by hypotonia, hepatomegaly, and intermittent hypoglycemia
- Severe early-onset multiorgan failure
- Hepatic dysfunction associated with hepatomegaly and hypoglycemia out of proportion to the duration of fasting and/or unaccompanied by large ketones in the urine, but without cardiomyopathy. Lab testing may identify elevated transaminases or altered hepatic synthetic function.
- Myopathy associated with exercise intolerance, muscle cramps and/or pain and episodic intermittent rhabdomyolysis provoked by strenuous exercise, fasting, cold exposure, or fever; intermittent elevations in creatine phosphokinase (CK) with return to normal between episodes

**Establishing the Diagnosis**

The diagnosis of VLCAD deficiency is established in a proband with abnormal acylcarnitine analysis on biochemical testing and/or identification of biallelic pathogenic variants in ACADVL on molecular genetic testing (see Table 1). Specialized biochemical testing may be necessary if only a single pathogenic variant in ACADVL is identified.

**Biochemical Testing**

Population-based newborn screening using MS/MS technology has identified numerous affected individuals [Boneh et al 2006, Merritt et al 2014]:

- All abnormal results on newborn screening (NBS) should be followed by a confirmatory
acylcarnitine profile as well as molecular genetic testing [Boneh et al 2006]. See ACMG Algorithm, ACMG NBS ACT Sheet.

Note: A significant number of individuals with an abnormal newborn screen have one ACADVL pathogenic variant and are likely heterozygotes (i.e., carriers) detected because of the low specificity of the initial NBS acylcarnitine screening assay unless multiple marker calculations are applied [Diekman et al 2016].

**Acylcarnitine analysis.** The key metabolites that are most often abnormal in VLCAD deficiency are C14:1, C14:2, C14, and C12:1 [McHugh et al 2011]. Plasma or dried blood spot comprehensive acylcarnitine analysis using tandem mass spectrometry and measuring C4-C20 straight-chain acyl-carnitine esters, 3-hydroxy-acyl carnitine esters, and unsaturated acyl-carnitine esters is most sensitive when collected during a period of metabolic stress, such as fasting.

- Although cutoff/abnormal values vary by age, method of collection, and laboratory, a C14:1 level >1 mmol/L [Miller et al 2015] on an initial newborn screening test strongly suggests VLCAD deficiency. Individuals with this level or higher should be assumed to have VLCAD deficiency.

- Levels of C14:1 >0.8 mmol/L suggest VLCAD deficiency but may also occur in carriers and some healthy individuals having no ACADVL pathogenic variants.

- Post-analytic tools, such as those developed by the Region 4 Stork (R4S/CLIR) collaborative, may contribute to refinement of newborn screening cutoffs and inform clinicians regarding the likelihood of a true positive diagnosis of VLCAD in individual newborns [Hall et al 2014, Merritt et al 2014].

Note: (1) Diagnostic abnormalities may no longer be present if an individual has been fed or has been treated with an IV glucose infusion or if the episode prompting concern has resolved. (2) Newborn screening data have affirmed that acylcarnitine analysis during periods of physiologic wellness often fails to identify affected individuals who have the milder phenotypes. (3) Depending on the "cutoff" limits used, initial acylcarnitine screening often detects heterozygotes (unaffected carriers) [Miller et al 2015].

**Postmortem testing.** The following have been used to identify fatty acid oxidation (FAO) disorders postmortem:

- Biochemical testing of liver or bile for acylcarnitine elevations and histochemical analysis for microvesicular steatosis
- Studies on a postmortem skin biopsy
- Elevated concentrations of C8-C16 free fatty acids in plasma

If these analyses are suspicious, retrospective molecular genetic and biochemical testing of newborn blood spots can often be performed to confirm a diagnosis.

**Molecular Genetic Testing**

Molecular genetic testing approaches can include single-gene testing and use of a multigene panel. A multigene panel is used primarily when the phenotype may be attributed to VLCAD deficiency in addition to other conditions and biochemical data is unclear or unlikely to be clear – for example, during the evaluation of an adult with intermittent rhabdomyolysis.

- **Single-gene testing.** Sequence analysis of ACADVL is performed first and followed by
• A multigene panel that includes ACADVL and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this GeneReview; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

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

Note: If one ACADVL pathogenic variant is found and suspicion of VLCAD deficiency is high, functional assessment of β-oxidation through the in vitro probe study or direct VLCAD enzyme activity assay using protein extracts from cultured fibroblasts or lymphocytes is recommended. See Specialized Biochemical Testing.

Table 1.
Molecular Genetic Testing Used in VLCAD Deficiency

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test Method</th>
<th>Proportion of Probands with Pathogenic Variants Detectable by This Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACADVL</td>
<td>Sequence analysis ³</td>
<td>~99% ⁵</td>
</tr>
<tr>
<td></td>
<td>Gene-targeted deletion/duplication analysis ⁵</td>
<td>Rare; only one reported ⁶</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Miller et al [2015], Pena et al [2016]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Pervaiz et al [2011], Miller et al [2015]

Specialized Biochemical Testing

Specialized biochemical testing may be used to clarify the diagnosis, particularly when molecular testing reveals only one pathogenic variant.

Analysis of fatty acid β-oxidation in cultured fibroblasts. In vitro incubation of cultured fibroblasts with C13-palmitate or unlabeled palmitate and carnitine may provide indirect
evidence of impaired β-oxidation. Individuals with severe VLCAD deficiency typically accumulate excess tetradecanoyl (C14) carnitine, whereas individuals with less severe phenotypes may shift accumulation toward dodecanoyl (C12) carnitine. This test is often called the "in vitro probe study" and is available clinically.

**Analysis of VLCAD enzyme activity.** Measurement of VLCAD enzyme activity in leukocytes, cultured fibroblasts, liver, heart, skeletal muscle, or amniocytes by the electron transfer flavoprotein or ferricineum reduction assay can be used to confirm the diagnosis of VLCAD deficiency. Better specificity has been noted when the products are separated and quantitated by high-performance liquid chromatography or tandem mass spectrometry (MS/MS). The clinical availability of this assay has varied with time.

**Immunoreactive VLCAD protein antigen expression** (an "immunoblot"). This test uses polyclonal, specific antibodies to make a semi-quantitative assessment of expressed VLCAD antigen levels in protein extracts derived from cultured fibroblasts. Levels lower than 10% of control are consistent with VLCAD deficiency. This assay may be available only in a research setting.

**Clinical Characteristics**

**Clinical Description**

Three clinical groups of VLCAD deficiency have been reported [Andresen et al 1999].

**Severe early-onset cardiac and multiorgan failure VLCAD deficiency** typically presents in the first months of life with hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias, as well as hypotonia, hepatomegaly, and intermittent hypoglycemia. Cardiomyopathy and arrhythmias are often lethal. Ventricular tachycardia, ventricular fibrillation, and atrioventricular block have been reported [Bonnet et al 1999]. Although the morbidity resulting from cardiomyopathy may be severe, cardiac dysfunction may be reversible with early intensive supportive care and diet modification; normal cognitive outcome has been reported in these individuals. Both Pena et al [2016] and Vockley et al [2016] reported individuals who developed cardiomyopathy while being treated with a medium-chain triglyceride (MCT) oil-based diet.

**Hepatic or hypoketotic hypoglycemic VLCAD deficiency** typically presents during early childhood with hypoketotic hypoglycemia and hepatomegaly (similar to MCAD deficiency) but without cardiomyopathy. Hypoglycemia and poor feeding during the newborn period have been reported in neonates who were later diagnosed with VLCAD deficiency [Pena et al 2016].

**Later-onset episodic myopathic VLCAD deficiency**, probably the most common phenotype, presents with intermittent rhabdomyolysis provoked by exercise, muscle cramps and/or pain, and/or exercise intolerance. Hypoglycemia typically is not present at the time of symptoms in these individuals. Ascertainment in adulthood has been reported [Hoffman et al 2006].

**Pathophysiology**

The fatty acid oxidation (FAO) spiral is a series of four reactions occurring in the mitochondrial matrix. The first step is catalyzed by four highly homologous, straight-chain acyl-CoA dehydrogenases with differing, but overlapping, substrate specificities:

- Short (SCAD that uses C4-C6 fatty acyl-CoAs)
- Medium (MCAD; C6-C10 fatty acyl-CoAs)
Long (LCAD; C10-C14 fatty acyl-CoAs)
Very long (VLCAD; C14-C20 fatty acyl-CoAs)

SCAD, MCAD, and LCAD are homotetramers localized to the mitochondrial matrix; VLCAD is a homodimer associated with the inner mitochondrial membrane. These four homologs share about 40% amino acid identity or similarity within the catalytic domain; all use flavin adenine dinucleotide as the electron-accepting cofactor. Electrons are fed into the electron transport chain via ETF and ETF dehydrogenase.

With every turn of the β-oxidation spiral, the chain length is shortened by two carbon atoms. Reactions distal to the long-chain acyl-CoA dehydrogenase (LCAD) include those catalyzed by the LCHAD/trifunctional protein, including a hydratase step, dehydrogenase step, and thiolase step.

The use of fat to supply energy is important at critical points of physiologic adaptation. In utero, the fetus derives a constant supply of energy from glucose supplied continuously via the placenta. Following birth, maternal milk (of which ~60% of calories are fat) becomes the major nutrient, and therefore, fat becomes the major energy source, especially in the heart and in other highly oxidative organs including kidney and skeletal muscle [Hale et al 1985, Aoyama et al 1993].

The heart constantly uses fatty acids for energy. In contrast, the liver uses nutrients delivered directly during the absorptive phase of digestion and controls the short- and medium-term storage and distribution of energy from glycogenolysis and gluconeogenesis. However, during longer periods of fasting, the liver uses acetyl CoA to generate ketone bodies. The brain adapts to fasting by switching to a ketone economy, reducing the need for glucose as the energy source. With exercise, especially prolonged exercise, slow skeletal muscles use longer-chain FAO to generate energy. In summary, the adaptation to fasting depends on the supply of energy, the rate of consumption and preferred substrate, and physiologic backup mechanisms to provide alternative sources of energy in times of stress or transition.

As one of the first enzymes in the FAO spiral, the enzyme VLCAD controls a critical point in the supply of electrons to the respiratory chain, and also provides a pathway permissive to the production of ketones. It would be expected that significant reduction at this step of fatty acid oxidation would impair the ability to transition successfully from fetal to neonatal life, to maintain cardiac output, to adapt to long fasting, and to generate energy for exercise. All of the above difficulties have been observed in VLCAD deficiency. The most severe defects result in early-infantile cardiomyopathy, hepatomegaly, hypotonia, and intermittent hypoglycemia.

Genotype-Phenotype Correlations

As a general rule, a strong genotype-phenotype correlation exists in VLCAD deficiency [Andresen et al 1999]:

- Severe disease is associated with no residual enzyme activity, often resulting from null variants. Approximately 81% of pathogenic truncating variants in ACADVL are associated with the severe early-onset form [Andresen et al 1999]. Specific missense pathogenic variants leading to low long-chain fatty acid oxidation flux may also be associated with cardiac disease [Diekman et al 2015].
- Milder childhood and adult forms are often associated with residual enzyme activity. The common p.Val283Ala variant, in both homozygous and compound heterozygous genotypes, is typically associated with the non-cardiac phenotypes [Spierkerkoetter et al 2009, Diekman et al 2015, Miller et al 2015].
Penetrance
Severe forms are suspected to be fully penetrant.
Since the later-onset forms may have vague or intermittent symptoms, it is possible that some individuals will have no recognizable symptoms during their lifetime.

Nomenclature
When the severe phenotype of VLCAD deficiency was described initially by Hale et al [1985], it was attributed to deficiency of the enzyme LCAD. The correct identification of the deficient enzyme, VLCAD, was made by Aoyama et al [1993].

Prevalence
Complete ascertainment by newborn screening is not assured, but the incidence of VLCAD deficiency is now estimated at 1:30,000 to 1:100,000 births. More than 800 cases have been reported (clir-R4S.org consortium data, updated June 2017) [McHugh et al 2011] (full text).

Newborn screening has demonstrated that VLCAD deficiency is more prevalent than previously suspected; however, the majority of children ascertained by newborn screening are asymptomatic during the few years of observation, suggesting that these individuals may have gone undiagnosed prior to the advent of population-based screening.

Genetically Related (Allelic) Disorders
No phenotypes other than those discussed in this GeneReview are known to be associated with pathogenic variants in ACADVL.

Differential Diagnosis
Infantile cardiomyopathy with evidence of abnormal fatty acid oxidation may be seen in the following autosomal recessive disorders [Roe et al 2006]:

- Systemic primary carnitine deficiency
- Carnitine palmitoyltransferase II (CPT II) deficiency – severe infantile hepatocardiomuscular form
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) / trifunctional protein deficiency [OMIM 609016]
- Carnitine-acylcarnitine translocase deficiency [OMIM 212138]
- Severe forms of multiple acyl-CoA dehydrogenase deficiency [OMIM 231680]

The hepatic "hypoglycemic" form of VLCAD deficiency may have clinical features similar to medium-chain acyl CoA dehydrogenase (MCAD) deficiency, or to the electron transfer flavoprotein (ETF)/ETF ubiquinone (coenzyme Q) oxidoreductase defects that produce multiple acyl-CoA dehydrogenase deficiencies; however, the biochemical phenotypes are distinct.

Intermittent rhabdomyolysis is a feature of McArdle disease, CPT II deficiency, some primary myopathies, and trifunctional protein deficiency [OMIM 609015]. Rhabdomyolysis is also seen in LPIN1 deficiency, though often at younger ages than in VLCAD deficiency and typically provoked by illness rather than exercise.

Management
Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with VLCAD deficiency, the following evaluations are recommended if they have not already been completed:

- Measurement of baseline plasma (serum) creatine kinase (CK) concentration
- Measurement of baseline liver transaminases
- Cardiac echocardiography
- Electrocardiogram
- Consultation with a clinical geneticist and/or genetic counselor

Note: In the setting of acute disease, measurement of blood glucose concentration and blood ammonia concentration may be indicated.

Treatment of Manifestations

Frequently updated, succinct "emergency" care plans should detail the typical clinical issues (either those already experienced by the patient or those anticipated based on the diagnosis) and the importance of early management (e.g., use of IV glucose as an energy source, monitoring for cardiac rhythm disturbance, and monitoring of rhabdomyolysis), and avoidance of triggers (fasting, long-chain fats, and irritation of the myocardium) [Arnold et al 2009].

Cardiac dysfunction may be reversible with early, intensive supportive care (occasionally including extracorporeal membrane oxygenation) and diet modification. See Prevention of Primary Manifestations.

Prevention of Primary Manifestations

Individuals with the more severe forms of VLCAD deficiency are typically placed on a low-fat formula, with supplemental calories provided through medium-chain triglycerides (MCT). A variety of strategies for the low-fat diet are used, ranging from 13%-39% of calories as total fat, with an additional 15%-18% of calories supplied as MCT oil in those most strictly restricted for long-chain fats [Solis & Singh 2002].

Use of extra MCT has demonstrated benefit in older individuals with long-chain defects who have exercise intolerance. Gillingham et al [2006] demonstrated improved exercise tolerance in individuals given 0.5 g/kg lean body weight 20 minutes prior to exercise. [Behrend et al 2012].

Triheptanoin has been used in a few individuals with the goal of providing calories as well as anaplerotic carbons. Formal clinical trials of triheptanoin are in progress (see Therapies Under Investigation). A retrospective analysis of individuals who developed cardiomyopathy and improved after intensive supportive care and a change from MCT to triheptanoin indicates some potential benefit [Vockley et al 2016]. A Phase II open-label trial of the effect of triheptanoin on exercise tolerance showed some potential benefits. The major adverse effect was diarrhea [Vockley et al 2017].

Severe exercise (e.g., military training) has unmasked symptoms in previously asymptomatic adults [Hoffman et al 2006, Laforêt et al 2009], emphasizing that exercise should be guided by the individual's tolerance level.

The use of carnitine supplementation is controversial [Arnold et al 2009]: consensus as to whether additional carnitine is detrimental or efficacious has not been established. The major concern stems from studies in a mouse model of VLCAD deficiency. Mice given L-carnitine
supplementation accumulated higher levels of long-chain acylcarnitines, of concern because of potential myocardial toxicity. In addition, in mice with VLCAD deficiency, the drop in muscle carnitine after exercise was not prevented by supplementation [Primassin et al 2008]. The relevance of this mouse model to humans with VLCAD deficiency is controversial.

**Prevention of Secondary Complications**

Acute rhabdomyolysis is treated with ample hydration and alkalization of the urine to protect renal function and to prevent acute renal failure secondary to myoglobinuria.

**Surveillance**

There are no current published guidelines for surveillance during interval health visits.

Suggested evaluations include:

- Annual physical exam, including cardiac status
- Consideration of echocardiography on an annual or biannual basis, particularly in individuals with previous cardiac dysfunction or those with significant exercise intolerance
- Annual assessment of nutritional status. Obesity can become a significant problem, and is not easy to remedy in individuals with exercise intolerance and requirement for active management of fasting.
- Assessment of essential fatty acid deficiency, particularly in those individuals with severely restricted long-chain dietary fat

**Agents/Circumstances to Avoid**

Avoid the following:

- Fasting, including periods of preparation and recovery from planned surgery or sedation [Vellekoop et al 2011]
- Myocardial irritation (e.g., cardiac catheterization)
- Dehydration (risk for acute tubular necrosis)
- High-fat diet (long-chain fats) including ketogenic or carbohydrate-restricted diets for the purpose of weight loss. Careful weight reduction has been accomplished by restricting long-chain fats and calories, supplementing with calories provided through medium-chain triglycerides (MCT), and limiting overnight catabolism with uncooked cornstarch [Zweers et al 2012].
- Volatile anesthetics and those that contain high doses of long-chain fatty acids such as propofol and etomidate [Vellekoop et al 2011]. However, the use of propofol for short-duration procedures has been evaluated in individuals with LCHAD deficiency and not found to cause adverse events [Martin et al 2014].

**Evaluation of Relatives at Risk**

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from institution of treatment and preventive measures (see Management, Prevention of Primary Manifestations).

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
If the pathogenic variants in the family are not known, plasma or dried blood spot acylcarnitine analysis may not be sufficiently sensitive, and direct VLCAD assay of lymphocytes or FAO probe studies of cultured fibroblasts may be required.

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

**Pregnancy Management**

During pregnancy, placental and fetal β-oxidation may temporize or even improve maternal fatty acid β-oxidation [Mendez-Figueroa et al 2010]. However, labor and postpartum periods are catabolic states and place the mother at higher risk for rhabdomyolysis and subsequent myoglobinuria. A management plan for labor and delivery has been proposed by Mendez-Figueroa et al [2010].

**Therapies Under Investigation**

Several clinical trials of triheptanoin are either in progress or recently completed [Vockley et al 2017].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) for access to 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, 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. —ED.*

**Mode of Inheritance**

VLCAD deficiency is inherited in an autosomal recessive manner.

**Risk to Family Members**

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ACADVL* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with VLCAD deficiency are obligate heterozygotes (carriers) for an *ACADVL* pathogenic variant.

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

**Carrier (Heterozygote) Detection**

**Molecular genetic testing.** Carrier testing for at-risk family members is possible if the pathogenic variants in the family have been identified.

**Biochemical genetic testing.** Carrier status increases the likelihood of detection in a newborn screening program, as individuals with half of the normal VLCAD enzyme activity may have acylcarnitine levels near the upper limits of the normal range and the lower limits of the "possibly affected" range, particularly under the conditions of stress imposed by perinatal transition. However, testing of acylcarnitines, particularly in the unstressed individual, is not reliable for identifying heterozygotes.

Functional testing of fibroblasts, using the various protocols of palmitate oxidation and incorporation into small acylcarnitine species, also does not typically identify carriers.

A direct VLCAD enzyme assay may provide better evidence of a carrier state than the options described above, but in most cases molecular genetic testing is preferred. In addition, the clinical availability of the VLCAD enzyme assay has varied with time.

**Related Genetic Counseling Issues**

The genetic status of full sibs should be determined, since many individuals with VLCAD deficiency are not symptomatic during early childhood. 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, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

**Prenatal Testing and Preimplantation Genetic Diagnosis**

**Molecular genetic testing.** Once the ACADVL pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

**Biochemical genetic testing.** Prenatal diagnosis of VLCAD deficiency based on the pattern of incorporation of labeled carbons (ranging from palmitate into shorter chain acylcarnitines) by cultured amniocytes that is similar to the fibroblast in vitro acylcarnitine profile has been described. Assay of VLCAD enzyme activity can distinguish between affected and unaffected cells. Absence of immunoreactive VLCAD on western blot analysis in those with severe VLCAD deficiency should provide additional information. As experience with and clinical availability of these assays is limited in the US, molecular genetic testing is preferred for prenatal testing.
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.

- **My46 Trait Profile**
  Very long-chain acyl-CoA dehydrogenase deficiency

- **National Library of Medicine Genetics Home Reference**
  Very long-chain acyl-coenzyme A dehydrogenase deficiency

- **Save Babies Through Screening Foundation, Inc.**
  P. O. Box 42197
  Cincinnati OH 45242
  **Phone:** 888-454-3383
  **Email:** email@savebabies.org
  www.savebabies.org

- **STAR-G (Screening, Technology and Research in Genetics)**
  **Email:** info@newbornscreening.info
  Very long chain acyl-coenzyme A dehydrogenase

- **FOD Family Support Group (Fatty Oxidation Disorder)**
  PO Box 54
  Okemos MI 48805-0054
  **Phone:** 517-381-1940
  **Fax:** 866-290-5206 (toll-free)
  **Email:** deb@fodsupport.org; fodgroup@gmail.com
  www.fodsupport.org

- **United Mitochondrial Disease Foundation (UMDF)**
  8085 Saltsburg Road
  Suite 201
  Pittsburg PA 15239
  **Phone:** 888-317-8633 (toll-free); 412-793-8077
  **Fax:** 412-793-6477
  **Email:** info@umdf.org
  www.umdf.org

### 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.

Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus-Specific Databases</th>
<th>HGMD</th>
<th>ClinVar</th>
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</table>
View in own window
Table B.

OMIM Entries for Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency (View All in OMIM)

<table>
<thead>
<tr>
<th>OMIM ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>201475</td>
<td>ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY OF; ACADVLD</td>
</tr>
<tr>
<td>609575</td>
<td>ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN; ACADVL</td>
</tr>
</tbody>
</table>

Molecular Genetic Pathogenesis

Very long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the initial step of mitochondrial β-oxidation of long-chain fatty acids with a chain length of 14 to 20 carbons.

Gene structure. ACADVL comprises 20 exons spanning approximately 5.4 kb. For a detailed summary of gene and protein information, see Table A, Gene.

Pathogenic variants. See Table 2. Hundreds of pathogenic variants are known, including splice site, nonsense, missense, and frameshift variants; they occur throughout the VLCAD protein.

The most common pathogenic allele, c.848T>C (p.Val283Ala), is observed in symptomatic compound heterozygotes and in homozygotes. It accounts for approximately 10% [Miller et al 2015] to 29% [Pena et al 2016] of all pathogenic alleles among individuals detected by newborn screening.

Recurring pathogenic variants have often been reported; however, their frequency has not been well established.

Racial and ethnic variants are reported. For example, p.Thr409Met is observed more commonly among individuals of Pacific Island ancestry than in other populations.

In vitro functional assays have been used to characterize putative pathogenic missense variants and to investigate the clinical and biochemical aspects of VLCAD deficiency [Gobin-Limballe et al 2007, Goetzman et al 2007].

Table 2.

Selected ACADVL Pathogenic Variants

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change (Alias)</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.848T&gt;C</td>
<td>p.Val283Ala (Val243Ala)</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Description</td>
<td>Gene</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>c.779C&gt;T</td>
<td>p.Thr260Met (Thr220Met)</td>
<td>NM_000018.2 NP_000009.1</td>
</tr>
<tr>
<td>c.1226C&gt;T</td>
<td>p.Thr409Met (Thr369Met)</td>
<td></td>
</tr>
<tr>
<td>c.1322G&gt;A</td>
<td>p.Gly441Asp (Gly401Asp)</td>
<td></td>
</tr>
<tr>
<td>c.1405C&gt;T</td>
<td>p.Arg469Trp (Arg429Trp)</td>
<td></td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions. Note: Earlier references used protein nomenclature consistent with the mature protein and are provided in parentheses.

**Normal gene product.** The mature VLCAD protein of 615 amino acids has a large, tightly conserved functional domain common to the acyl-CoA dehydrogenases. The major isoform encodes a precursor protein of 655 amino acids with a mitochondrial targeting sequence of 40 amino acids that is removed during uptake, resulting in the mature membrane-associated protein of 615 amino acid residues as reported by Aoyama et al [1995] and Strauss et al [1995].

**Abnormal gene product.** Loss of VLCAD enzyme activity causes disease. The majority of pathogenic variants reduce enzyme activity and/or result in reduced stability leading to lower steady state levels in mitochondria.

**References**

**Literature Cited**


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Martin JM, Gillingham MB, Harding CO. Use of propofol for short duration procedures in


