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Lysosomal Acid Lipase Deficiency

Synonyms: Acid Lipase Deficiency, LAL Deficiency

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Summary

Clinical characteristics

The phenotypic spectrum of lysosomal acid lipase (LAL) deficiency ranges from the infantile-onset form (Wolman disease) to later-onset forms collectively known as cholesterol ester storage disease (CESD).

Wolman disease is characterized by infantile-onset malabsorption that results in malnutrition, storage of cholesterol esters and triglycerides in hepatic macrophages that results in hepatomegaly and liver disease, and adrenal gland calcification that results in adrenal cortical insufficiency. Unless successfully treated with hematopoietic stem cell transplantation (HSCT), infants with classic Wolman disease do not survive beyond age one year.

CESD may present in childhood in a manner similar to Wolman disease or later in life with such findings as serum lipid abnormalities, hepatosplenomegaly, and/or elevated liver enzymes long before a diagnosis is made. The morbidity of late-onset CESD results from atherosclerosis (coronary artery disease, stroke), liver disease (e.g., altered liver function ± jaundice, steatosis, fibrosis, cirrhosis and related complications of esophageal varices, and/or liver failure), complications of secondary hypersplenism (i.e., anemia and/or thrombocytopenia), and/or malabsorption. Individuals with CESD may have a normal life span depending on the severity of disease manifestations.

Diagnosis/testing

Diagnosis of LAL deficiency is suspected in individuals with characteristic clinical findings such as hepatomegaly, elevated transaminases, and a typical serum lipid profile: high total serum concentrations of cholesterol, low-density lipoprotein, and triglycerides; and low serum concentration of high-density lipoprotein. The diagnosis is confirmed by identification of either biallelic pathogenic variants in *LIPA* or deficient LAL enzyme activity in peripheral blood leukocytes, fibroblasts, or dried blood spots.

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Management

Treatment of manifestations:

- Both Wolman disease and CESD: Enzyme replacement therapy (ERT) with sebelipase alfa was recently approved by the FDA and is administered at a dose of 1 mg/kg body weight every other week; this treatment can be life saving for those with severe Wolman syndrome and life improving with prolonged survival in those who have CESD. Consider referral to a liver specialist. Liver transplantation may be indicated when liver disease progresses to cirrhosis and liver failure.
- Wolman disease: Consultation with a nutrition team to limit malnutrition if possible, including use of parenteral nutrition; corticosteroid and mineralocorticoid replacement in the presence of adrenal insufficiency.
- CESD: Reduce cholesterol through the use of statins, cholestyramine, and a diet low in cholesterol and triglycerides. Aggressive reduction of additional cardiovascular risk factors and lipophilic vitamins may also be beneficial. Consult with a nutrition team for children with failure to thrive or adults with weight loss.

Prevention of primary manifestations: Successful hematopoietic stem cell transplantation can correct the metabolic defect.

Prevention of secondary complications: Use nonspecific beta-blockers in those with esophageal varices to reduce the risk of bleeding.

Surveillance: No standard guidelines for surveillance of CESD have been developed.

- For children: Monitor growth and nutritional status; evaluate fasting lipid levels, platelet count, and liver enzymes every six months.
- For adults: reevaluate every 6-12 months depending on disease severity. Monitor nutritional status. Evaluate fasting lipid levels, platelet count, and liver enzymes routinely. Evaluate those with severe liver disease for esophageal varices by upper endoscopy every three years. Monitor and treat those with hepatosplenomegaly thrombocytopenia to prevent bleeding complications.
- For children and adults: monitor hepatosplenic volume and screen for hepatocellular carcinoma with serial liver and spleen imaging.

Agents/circumstances to avoid: In the presence of thrombocytopenia avoid use of nonsteroidal anti-inflammatory drugs.

Evaluation of relatives at risk: It is appropriate to evaluate the sibs of a proband in order to identify those who would benefit from early treatment and surveillance.

Genetic counseling

LAL deficiency is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal testing of a pregnancy at increased risk are possible if the *LIPA* pathogenic variants in the family have been identified.

GeneReview Scope

Lysosomal Acid Lipase Deficiency: Included Phenotypes [1]
• Cholesterol ester storage disease • Wolman disease

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

The phenotypic spectrum of lysosomal acid lipase (LAL) deficiency ranges from infantile-onset form (Wolman disease) to later-onset forms, collectively known as cholesterol ester storage disease (CESD). LAL deficiency cannot be diagnosed on clinical findings alone.

Suggestive Findings

Wolman disease is suspected in infants with hepatomegaly, vomiting, diarrhea, and failure to thrive. Adrenal calcification on abdominal imaging greatly increases suspicion for Wolman disease [Anderson et al 1999, Boldrini et al 2004].

Cholesterol ester storage disease (CESD) is suspected in individuals (ranging in age from early childhood to adulthood) with signs of increased lipid storage such as hepatomegaly, liver disease, lipid deposition in the intestinal walls, and/or xanthelasma.

Preliminary Testing

Serum concentrations of lipids and lipoproteins are almost always abnormal (Table 1).

- Total serum concentration of cholesterol is often high, as are serum concentrations of low-density lipoprotein (LDL) and triglycerides.
- Serum concentration of high-density lipoprotein (HDL) is typically low.

Note: Normal serum lipid levels do not exclude the diagnosis of LAL deficiency [Drebber et al 2005, Chatrath et al 2009, Decarlis et al 2009, Pisciotta et al 2009].

Table 1. Lipid Values Found in 33 Individuals with LAL Deficiency

		Cholesterol [1]			Triglycerides [2]
		Total	LDL	HDL	
Normal		<200	<130	>50	<150
In reported cases	**Range**	106-428	147-292	8-87	60-443
	Average	291	228	30	200
% of cases > or < normal range		88% > nml	100% > nml	96% < nml	71% > nml

Elleder et al [1990], Klima et al [1993], Seedorf et al [1995], Gasche et al [1997], Anderson et al [1999], vom Dahl et al [1999], Lohse et al [2000], Tadiboyina et al [2005], Dalgiç et al [2006], Bindu et al [2007], Chatrath et al [2009], Hooper et al [2008], Decarlis et al [2009], Pisciotta et al [2009], Fasano et al [2012]
1. Values in mg/dL

Establishing the Diagnosis

The diagnosis **is confirmed** by identification of either biallelic pathogenic (or likely pathogenic) variants in *LIPA* or deficient LAL enzyme activity in peripheral blood leukocytes, fibroblasts, or dried blood spots.

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 likely pathogenic variants. (2) Identification of biallelic *LIPA* variants of uncertain significance (or of one known *LIPA* pathogenic variant and one *LIPA* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

- **Single-gene testing.** Sequence analysis of *LIPA* is performed first. Consider gene-targeted deletion/duplication analysis if only one pathogenic variant is identified.
- **A multigene panel** that includes *LIPA* 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 are likely to change 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 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.
- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of lysosomal acid lipase deficiency.

  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 Lysosomal Acid Lipase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method [3]	
		One Variant Detected	Two Variants Detected
LIPA	Sequence analysis [4]	**Wolman disease**	
		1/7 probands	6/7 probands
		CESD	
		2/31 probands	29/31 probands
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]	Unknown; none reported [7]

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. Klima et al [1993], Ameis et al [1995], Muntoni et al [1995], Seedorf et al [1995], Gasche et al [1997], Anderson et al [1999], vom Dahl et al [1999], Lohse et al [2000], Drebber et al [2005], Tadiboyina et al [2005], Hooper et al [2008], Pisciotta et al [2009], Lee et al [2011], Fasano et al [2012]
4. 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.
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.
6. Large deletions appear to be rare, but have been reported [Lee et al 2011].
7. Examples of homozygosity for exon or whole-gene deletions have not been reported.

Assay of lysosomal acid lipase (LAL) enzyme activity. Residual enzyme activity levels are more significantly decreased in Wolman syndrome (≤5% of controls) compared to a generally less severe but overlapping range of loss of activity in CESD (range 2%-11% of residual activity) [Fasano et al 2012].

Note: (1) Assay of LAL enzyme activity in peripheral blood leukocytes is the confirmatory diagnostic test for LAL deficiency; however, enzyme activity can also be diagnostically measured in hepatocytes, skin fibroblasts, or dried blood spots that have been promptly transported and properly stored [Reiner et al 2014]. (2) The confirmation of significant loss of LAL enzymatic function is recommended when *LIPA* pathogenic variants identified on genome-wide sequencing (e.g., exome sequencing) first suggest the diagnosis of LAL deficiency.

Liver biopsy. Note: Use of more invasive testing, such as liver biopsy, is not necessary in the diagnostic evaluation of all persons suspected of having LAL deficiency. See Clinical Description, Liver Biopsy.

Clinical Characteristics

Clinical Description

Lysosomal acid lipase (LAL) deficiency, like other diseases caused by enzyme deficiencies, has a wide phenotypic spectrum. Infantile-onset LAL deficiency is known as Wolman disease. All later-onset LAL deficiency, which may present from early childhood to late adulthood (often with subclinical disease), is known as cholesterol ester storage disease (CESD).

Wolman Disease

Infants with Wolman disease may present as early as the first day of life with vomiting, steatorrhea, and abdominal distention [Shome et al 2002]. Other infants may come to medical attention within weeks to months due to failure to thrive [Browne et al 2003].

Hepatomegaly, the result of build-up of cholesterol esters and triglycerides in macrophages of the liver, is common and can be dramatic. Splenomegaly, the result of the same mechanism, may also be present.

Increased lipid deposition along the gastrointestinal tract leads to thickened bowel walls with resultant malnutrition and wasting [Nchimi et al 2003].

Steatosis may progress to liver failure.

Enlarged adrenal glands with calcification, a classic finding in Wolman disease, can lead to adrenal cortical insufficiency.

Infants with Wolman disease do not usually survive beyond the first year of life. Treatment with hematopoietic stem cell transplantation (HSCT) has had mixed results, and requires further study [Gramatges et al 2009]. Death results from a combination of malnutrition, liver disease, and adrenal cortical insufficiency.

Cholesterol Ester Storage Disease (CESD)

Although CESD may present in childhood in a manner similar to Wolman disease with failure to thrive and delayed milestones [Bindu et al 2007], it has also been identified in individuals with atypical phenotypes such as elevated liver enzymes or serum lipid abnormalities identified on routine screening [Drebber et al 2005] and apparent autosomal recessive hypercholesterolemia without mutation of the expected gene [Stitziel et al 2013] (see Differential Diagnosis, **Autosomal recessive hypercholesterolemia**).

Atherosclerosis due to hyperlipidemia accounts for much of the morbidity associated with late-onset CESD, such as coronary artery disease and catastrophic vascular events including stroke [Elleder et al 1990]. In one family the phenotype resembled autosomal recessive hypercholesterolemia (see Differential Diagnosis) with extremely high total and low-density lipoprotein cholesterol levels, and abnormal hepatic accumulation of cholesterol without other features of CESD [Stitziel et al 2013].

Hepatomegaly with or without splenomegaly is frequently present as a result of cholesterol ester and triglyceride build-up in macrophages. Organomegaly, often among the first findings noted, may be present for years before a diagnosis is reached [Ameis et al 1995, vom Dahl et al 1999]. Individuals with splenomegaly may develop anemia and/or thrombocytopenia due to secondary hypersplenism.

Liver disease is common. It may present as altered liver function with or without jaundice, steatosis, fibrosis, or cirrhosis. Liver disease can lead to esophageal varices, which are associated with risk for hemorrhage and can be life-threatening [Gasche et al 1997]. Some individuals may experience liver failure.

Hepatocellular carcinoma has occurred in the setting of advanced cirrhosis [Riva et al 2008].

Lipid deposition in the wall of the intestinal tract can contribute to diarrhea and weight loss [Anderson et al 1999, Drebber et al 2005].

On occasion, signs of hyperlipidemia (e.g., xanthelasma, particularly of the palpebral area) may be visible [Elleder et al 1990, vom Dahl et al 1999].

Enlarged adrenal glands with punctate calcifications can be present, more often in those with more severe disease [Boldrini et al 2004].

Individuals with CESD may have a normal life span depending on the severity of disease manifestations.

Liver Biopsy

Liver biopsy demonstrates microvesicular steatosis or "fatty liver." To help distinguish LAL deficiency (both Wolman and CESD) from common diagnoses with overlapping findings (see Differential Diagnosis), the following findings on liver biopsy are used:

- Presence of additional supportive findings including "sea-blue" histiocytes, large Kupffer cells with increased vacuoles, lipid droplets, and/or cholesterol crystals [Boldrini et al 2004, Drebber et al 2005, Pisciotta et al 2009]
- Immunohistochemistry including use of the lysosomal markers cathepsin D, lysosomal-associated membrane protein 1 (LAMP1), LAMP2, and lysosomal integral membrane protein 2 [Hůlková & Elleder 2012]
- Identification of Maltese cross-type birefringence in frozen sections [Hůlková & Elleder 2012]

Genotype-Phenotype Correlations

In general, null allelic variants with no residual enzyme function result in Wolman disease and pathogenic variants that allow for residual LAL enzyme activity result in CESD.

The c.894G>A pathogenic variant, associated with residual enzyme activity, has been identified in European and Hispanic populations and, to a lesser extent, in Asian populations. Although this variant has not been identified in African Americans, it cannot be concluded that this population is not at risk for this condition [Scott et al 2013]. Variant c.894G>A is the most common observed in CESD, accounting for more than 50% of reported pathogenic variants [Bernstein et al 2013]. Nearly all individuals with CESD reported in the published literature are compound heterozygous or homozygous for c.894G>A. Of note, three members of one family homozygous for the c.894G>A variant had an atypical phenotype that resembled autosomal recessive hypercholesterolemia (see Differential Diagnosis) [Stitziel et al 2013].

Among individuals with the same genotype, varying levels of residual enzyme activity have been reported; therefore, the predictive value of genotype is only in distinguishing Wolman disease from CESD.

The level of residual LAL enzyme activity identified on enzyme assay is not useful for predicting disease course, as manifestations of disease vary greatly among individuals with similar levels of enzyme activity.

Nomenclature

Other names used for lysosomal acid lipase (LAL) deficiency in the past that are no longer in use include:

- Acid cholesterol ester hydrolase deficiency
- Cholesterol ester hydrolase deficiency storage disease

Cholesterol ester storage disease is also known as cholesteryl ester storage disease.

Prevalence

Due to the rarity and under-recognition of LAL deficiency, precise prevalence rates are not known at this time. Estimates in a German cohort suggested 1:50,000 for CESD and 1:350,000 for Wolman disease; however, LAL deficiency may be found to be more common as milder phenotypes continue to be recognized [Muntoni et al 2007].

LAL deficiency may be more common in individuals of Iranian-Jewish ancestry: one study suggested rates as high as 1:4200 in the Iranian-Jewish population of the Los Angeles area due to a c.260G>T founder variant [Valles-Ayoub et al 2011]. This pathogenic variant has been reported both in individuals with Wolman disease and in those with CESD [Valles-Ayoub et al 2011, Pagani et al 1996].

Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* are known to be associated with mutation of *LIPA*.

Differential Diagnosis

Acid sphingomyelinase deficiency (Niemann-Pick disease, types A and B). Overlapping clinical features of lysosomal acid lipase (LAL) deficiency and Niemann-Pick disease types A and B are hepatosplenomegaly, which is common in both, and lipid profiles in Niemann-Pick disease A and B which may be similar to those in LAL deficiency (i.e., low HDL with hyperlipidemia).

In contrast, the interstitial lung disease and ophthalmologic findings common to Niemann-Pick disease are not observed in LAL deficiency.

Biochemical analysis distinguishes between the two disorders [vom Dahl et al 1999]. Mutation of *SMPD1* is causative. Inheritance is autosomal recessive.

Gaucher disease (GD). Overlapping clinical features of lysosomal acid lipase (LAL) deficiency and GD are hepatosplenomegaly and thrombocytopenia.

In contrast, the adrenal calcifications typical of Wolman disease (and occasionally CESD) and the abnormal lipid profile typical of LAL deficiency are not seen in GD. The bone manifestations common to GD type 1 are not observed in CESD.

Biochemical analysis can distinguish between the two diseases [vom Dahl et al 1999]. Mutation of *GBA1* (formerly *GBA*) is causative. Inheritance is autosomal recessive.

Familial hypercholesterolemia. CESD may initially be confused with familial hypercholesterolemia because of increased serum concentration of total cholesterol and LDL; however, serum concentrations of HDL and triglycerides are usually still in the normal range. Liver disease and organomegaly are not observed in familial hypercholesterolemia. Mutation of *LDLR*, *APOB*, or *PCSK9* accounts for 60%-80% of familial hypercholesterolemia. Inheritance is autosomal dominant.

Autosomal recessive hypercholesterolemia (ARH) (OMIM 603813). CESD manifesting as extremely high total and low-density lipoprotein cholesterol levels may resemble ARH [Stitziel et al 2013]. Mutation of *LDLRAP1* is causative. Inheritance is autosomal recessive.

Hepatosplenomegaly is common to many storage disorders, including other lysosomal storage disorders. Other storage disorders can often be distinguished from LAL deficiency based on associated features:

- Contractures, skeletal dysplasia, and coarse features which can be found in mucolipidosis II and the mucopolysaccharidoses (MPS I, MPS II, MPS IVA, MPS IVB) are absent in LAL deficiency.
- Hypoglycemia, kidney disease, and cardiomyopathy, which can be seen in the glycogen storage diseases (GSD I, GSD II, GSD III, GSD IV, GSD V, GSD VI), are absent in LAL deficiency.

Biochemical analysis can distinguish between storage disorders.

Liver disease in CESD is commonly misattributed to hepatitis, non-alcoholic fatty liver disease, or cryptogenic cirrhosis. Nonalcoholic fatty liver disease, which is associated with obesity, is a common finding on liver biopsy; therefore, body mass index should be considered along with other signs and symptoms when considering the cause of "fatty liver" disease.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with lysosomal acid lipase (LAL) deficiency, the following evaluations are recommended:

- Complete blood count
- Complete fasting lipid profile, if not done at the time of diagnosis
- Liver function tests
- Upper endoscopy to evaluate individuals with severe liver disease for the presence of esophageal varices
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Enzyme replacement therapy (ERT) with sebelipase alfa was approved by the FDA in late 2015.

- Results from a Phase III clinical trial of 66 affected individuals demonstrated that ERT can be life saving for those with severe Wolman syndrome and life improving with prolonged survival in those who have cholesterol ester storage disease [Burton et al 2015].
- ERT is administered intravenously at a dose of 1 mg/kg body weight every other week.

Wolman Disease

Symptoms should generally be treated in a routine manner, while keeping in mind the limited life expectancy of infants with untreated Wolman disease.

Malabsorption and malnutrition. Consultation with a nutrition team should be provided in an attempt to limit malnutrition to the extent possible. Parenteral nutrition is offered in many instances of intractable malabsorption.

Hepatomegaly and liver disease. Liver transplantation can be considered for individuals who progress to cirrhosis and liver failure.

Adrenal cortical insufficiency. Corticosteroid and mineralocorticoid replacement is indicated in the presence of insufficiency.

Hematopoietic stem cell transplantation (HSCT) has overall had mixed results, and requires further study [Gramatges et al 2009]. While successful engraftment can correct the metabolic defect [Stein et al 2007, Tolar et al 2009], HSCT can be associated with morbidity and mortality [Yanir et al 2013].

Consider discussion of comfort care options.

CESD

Hyperlipidemia. Attempts should be made to reduce cholesterol through the use of statins, cholestyramine, ezetimibe, and a diet low in cholesterol and triglycerides [Gasche et al 1997, Dalgiç et al 2006, Chatrath et al 2009, Abello et al 2010].

Lipophilic vitamin supplementation may also be beneficial.

Aggressive reduction of additional cardiovascular disease risk factors should be encouraged.

Nutrition. Consultation with a nutrition team should be provided to children experiencing failure to thrive and to adults experiencing weight loss. Additionally, a nutrition team can assist individuals in the implementation of a diet low in cholesterol and triglycerides.

Liver transplantation can be considered for individuals who progress to cirrhosis and liver failure. At least four case reports of successful liver transplantation for CESD have been reported, with post-operative improvement of lipid profiles and successful transplant out to five years in one individual [Ambler et al 2013].

Prevention of Secondary Complications

Individuals found to have esophageal varices should be placed on nonspecific beta-blockers to reduce the risk of bleeding; beta-blockers have not been shown to prevent the formation of esophageal varices.

Surveillance

No standard guidelines for the surveillance of individuals with LAL deficiency have been developed. The following screening practices can be considered to monitor for the most common symptoms associated with CESD.

Children

- Special attention should be paid to growth and nutritional status. Chronic diarrhea or failure to thrive could indicate malabsorption.
- Consider monitoring fasting lipid levels, platelet count, and liver enzymes every six months.

Adults with CESD should be evaluated every six to 12 months depending on disease severity.

- Special attention should be paid to nutritional status. Chronic diarrhea or weight loss could indicate malabsorption.
- Monitor routinely fasting lipid levels, platelet count, and liver enzymes.
- Individuals with severe liver disease should be evaluated for esophageal varices by upper endoscopy every three years.
- Individuals with hepatosplenomegaly should be monitored and treated for thrombocytopenia to prevent bleeding complications.

Both children and adults. Obtain serial liver and spleen imaging to monitor for hepatosplenic volume and to screen for hepatocellular carcinoma which has arisen in the setting of advanced cirrhosis [Riva et al 2008]. Consensus on optimal screening protocols has not been published.

Agents/Circumstances to Avoid

Those with thrombocytopenia should avoid use of nonsteroidal anti-inflammatory drugs.

Evaluation of Relatives at Risk

It is appropriate to evaluate the sibs of a proband in order to identify those who would benefit from early institution of treatment.

- If the *LIPA* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the *LIPA* pathogenic variants in the family are not known, assay of lysosomal acid lipase (LAL) enzyme activity can be used to assist in the identification of affected sibs.

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

Therapies Under Investigation

Clinical trials are under way for enzyme replacement therapy [Valayannopoulos et al 2014].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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, 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

Lysosomal acid lipase (LAL) 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 *LIPA* pathogenic variant).
- Heterozygotes(carriers) are asymptomatic.

Sibs of a proband

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

Offspring of a proband

- The offspring of an individual with lysosomal acid lipase deficiency are obligate heterozygotes (carriers of a *LIPA* pathogenic variant).
- The risk that offspring will inherit a second *LIPA* pathogenic variant depends on the reproductive partner's carrier status. *LIPA* molecular genetic testing should be offered to the reproductive partner of an affected individual to determine carrier status.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LIPA* pathogenic variants in the family.

Note: Because of the overlap of lysosomal acid lipase (LAL) enzymatic activity between carriers and non-carriers, assay of LAL enzyme activity is not an appropriate method to determine carrier status.

Related Genetic Counseling Issues

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/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 carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *LIPA* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

- **LAL-D Aware**
  laldaware.org
- **MedlinePlus**
  Lysosomal acid lipase deficiency
- **National Institute of Neurological Disorders and Stroke**
  Acid Lipase Disease
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  childliverdisease.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs

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. Lysosomal Acid Lipase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LIPA	10q23.31	Lysosomal acid lipase/ cholesteryl ester hydrolase	LIPA database	LIPA	LIPA

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 Lysosomal Acid Lipase Deficiency (View All in OMIM)

278000	CHOLESTERYL ESTER STORAGE DISEASE; CESD
613497	LIPASE A, LYSOSOMAL ACID; LIPA
620151	WOLMAN DISEASE; WOLD

Molecular Pathogenesis

In the normal state, the enzyme lysosomal acid lipase (LAL) degrades LDL cholesterol esters and triglycerides in lysosomes. The intracellular free cholesterol that results from the degradation of these molecules is transferred to the endoplasmic reticulum, where it interacts with transcription factors that suppress:

- HMG-CoA reductase activity, which reduces the cellular synthesis of cholesterol;
- LDL receptor gene transcription, which results in reduced intracellular uptake of LDL.

In the disease state, deficient LAL enzyme activity leads to accumulation of cholesterol esters and triglycerides within lysosomes. Less free intracellular cholesterol results in heightened synthesis of endogenous cholesterol and endocytosis via LDL receptors. The relationship between the disease state and LDL receptor gene expression and activity is not entirely understood [Reiner et al 2014]. However, the overall result of decreased LAL enzyme activity is lysosomal accumulation of cholesterol esters and triglycerides and increased levels of plasma cholesterol.

Gene structure. *LIPA* comprises ten exons spread across 36 kb. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. A variety of pathogenic variants have been reported to cause LAL deficiency, including missense variants, nonsense variants, single- and double-nucleotide insertions and deletions, complex insertion/deletions, and splice site variants [Ameis et al 1995, Seedorf et al 1995, Anderson et al 1999, Hooper et al 2008, Pisciotta et al 2009].

The most common pathogenic variant resulting in CESD, c.894G>A, involves a G-to-A transition at the last base of exon 8 disrupting the normal donor splice consensus sequence (Table 3). Typically, this results in alternative splicing and subsequent skipping of exon 8. In the presence of this pathogenic variant approximately 3%-5% of transcripts are correctly spliced, allowing for residual enzyme activity.

Table 3. Selected *LIPA* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.260G>T [2]	p.Gly87Val (Gly66Val)	NM_001127605.1 NP_001121077.1
c.894G>A (934G>A) (E8SJ)	See footnote 3.	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Founder variant; see Prevalence.
3. At splice donor site of exon 8, resulting in alternative splicing and subsequent skipping of exon 8

Normal gene product. The enzyme lysosomal acid lipase A is expressed in lysosomes and is responsible for the hydrolysis of cholesterol esters and triacylglycerols. It is a member of a family of highly conserved acid lipases, which also includes human gastric lipase, rat lingual lipase, and bovine pregastric lipase [Zschenker et al 2001].

The catalytic active site of LAL is composed of amino acid residues Ser153, Asp324, and His353. The active-site serine is part of a lipase consensus sequence connecting a β-strand to an α-helix, known as the nucleophilic elbow, which facilitates interaction between the nucleophile and the histidine and ester carbon in the appropriately oriented complex [Lohse et al 1997].

Abnormal gene product. Disease results from loss of function of LAL caused by *LIPA* pathogenic variants that generate truncated proteins or proteins with altered conformations or reduced activity.

Chapter Notes

Revision History

- 1 September 2016 (ma) Revision: enzyme replacement therapy (Management)
- 30 July 2015 (me) Review posted live
- 4 October 2012 (mfm) Original submission

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