



## Familial Lipoprotein Lipase Deficiency

Synonym: Familial LPL Deficiency

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Created: October 12, 1999; Updated: June 22, 2017.

### Summary

#### Clinical characteristics

Familial lipoprotein lipase (LPL) deficiency usually presents in childhood and is characterized by very severe hypertriglyceridemia with episodes of abdominal pain, recurrent acute pancreatitis, eruptive cutaneous xanthomata, and hepatosplenomegaly. Clearance of chylomicrons from the plasma is impaired, causing triglycerides to accumulate in plasma and the plasma to have a milky (lactescent or lipemic) appearance. Symptoms usually resolve with restriction of total dietary fat to  $\leq 20$  g/day.

#### Diagnosis/testing

The diagnosis of LPL deficiency is established in a proband by the identification of biallelic pathogenic variants in *LPL* on molecular genetic testing.

#### Management

*Treatment of manifestations:* Treatment is based on medical nutrition therapy to maintain plasma triglyceride concentration below 1000 mg/dL. Maintenance of triglyceride levels below 2000 mg/dL prevents recurrent abdominal pain. Restriction of dietary fat to  $\leq 20$  g/day or 15% of a total energy intake is usually sufficient to reduce plasma triglyceride concentration and to keep the individual with familial LPL deficiency free of symptoms. An acute pancreatitis episode is treated with standard care.

*Prevention of secondary complications:* Prevention of recurrent acute pancreatitis decreases the risk of developing diabetes mellitus.

*Surveillance:* Monitoring of plasma triglycerides.

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*Agents/circumstances to avoid:* Agents known to increase endogenous triglyceride concentration such as alcohol, oral estrogens, diuretics, isotretinoin, glucocorticoids, selective serotonin reuptake inhibitors, and beta-adrenergic blocking agents; fish oil supplements are contraindicated because they contribute to chylomicron levels.

*Pregnancy management:* For pregnant women with LPL deficiency, extreme dietary fat restriction to <2 g/day during the second and third trimesters of pregnancy with close monitoring of plasma triglyceride concentration is recommended.

*Other:* The lipid-lowering drugs that are used to treat other disorders of lipid metabolism are not effective in individuals with familial LPL deficiency.

## Genetic counseling

Familial LPL 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 relatives and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family are known.

## Diagnosis

### Suggestive Findings

Familial lipoprotein lipase (LPL) deficiency **should be suspected** in individuals (particularly those age <40 years) with the following clinical and supportive laboratory findings.

#### Clinical findings

- Recurrent acute pancreatitis
- Eruptive cutaneous xanthomata
- Hepatosplenomegaly

#### Supportive laboratory findings

- Impaired clearance of chylomicrons from plasma causing the plasma to have a milky (lactescent or lipemic) appearance
- Plasma triglyceride concentrations greater than 2000 mg/dL in the untreated state, regardless of fasting status

### Establishing the Diagnosis

The diagnosis of LPL deficiency **is established** in a proband by the identification of biallelic pathogenic variants in *LPL* on molecular genetic testing (see Table 1).

A consensus diagnostic algorithm has been published [Stroes et al 2017] (see [Figure 3](#)).

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *LPL* is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *LPL* and other genes of interest for the chylomicronemia syndrome (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](#).

**Table 1.** Molecular Genetic Testing Used in Familial Lipoprotein Lipase Deficiency

Gene <sup>1</sup>	Method	Proportion of Probands with Pathogenic Variants <sup>2</sup> Detectable by Method
LPL	Sequence analysis <sup>3</sup>	~97% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	~3% <sup>6</sup>

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. 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. Brunzell & Deeb [2001], Gilbert et al [2001]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may 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. Brunzell & Deeb [2001]

**Measurement of lipoprotein lipase enzyme activity.** Affected individuals have low or absent LPL enzyme activity in an assay system that contains either normal plasma or apolipoprotein C-II (apoC-II; a cofactor of LPL) and excludes hepatic lipase (HL). This assay is not routinely available and is generally only performed at specialist centers.

- LPL enzyme activity can be assayed in plasma taken ten minutes following intravenous administration of heparin (60 U/kg body weight). The absence of LPL enzyme activity in postheparin plasma is diagnostic of familial LPL deficiency.
- LPL enzyme activity may be assayed directly in biopsies of adipose tissue.

## Clinical Characteristics

### Clinical Description

Familial lipoprotein lipase (LPL) deficiency usually presents in childhood with episodes of abdominal pain, recurrent acute pancreatitis, eruptive cutaneous xanthomata, and hepatosplenomegaly. Males and females are affected equally.

Approximately 25% of affected children develop symptoms before age one year and the majority develop symptoms before age ten years; however, some individuals present for the first time during pregnancy. The severity of symptoms correlates with the degree of chylomicronemia. Chylomicrons are large triglyceride-rich lipoprotein particles that appear in the circulation shortly after the ingestion of dietary fat; normally, they are cleared from plasma after an overnight fast. The degree of chylomicronemia in LPL deficiency varies by dietary fat intake.

The abdominal pain, which can vary from mildly bothersome to incapacitating, is usually mid-epigastric with radiation to the back. It may be diffuse and mimic an acute abdomen, often leading to unnecessary abdominal exploratory surgery. The pain probably results from chylomicronemia leading to pancreatitis.

Kawashiri et al [2005] reported that individuals with LPL deficiency can lead a fairly normal life on a diet very low in total fat content. The secondary complications of pancreatitis – diabetes mellitus, steatorrhea, and pancreatic calcification – are unusual in individuals with familial LPL deficiency and rarely occur before middle age. Pancreatitis in LPL deficiency may rarely be associated with total pancreatic necrosis and death.

About 50% of individuals with familial LPL deficiency have eruptive xanthomas, small yellow papules localized over the trunk, buttocks, knees, and extensor surfaces of the arms. Xanthomas are deposits of lipid in the skin that result from the extravascular phagocytosis of chylomicrons by macrophages. They can appear rapidly when plasma triglyceride concentration exceeds 2000 mg/dL and can sometimes regress if plasma triglyceride is normalized.

Xanthomas may become generalized. As a single lesion, they may be several millimeters in diameter; rarely, they may coalesce into plaques. They are usually not tender unless they occur at a site susceptible to repeated abrasion.

Hepatomegaly and splenomegaly often occur when plasma triglyceride concentrations are markedly increased. The organomegaly results from triglyceride uptake by macrophages, which become foam cells.

When triglyceride concentrations exceed 4000 mg/dL, the retinal arterioles and venules, and often the fundus itself, develop a pale pink color ("lipemia retinalis"), caused by light scattering by large chylomicrons. This coloration is reversible and vision is not affected.

Reversible neuropsychiatric findings, including mild dementia, depression, and memory loss, have also been reported with chylomicronemia [Heilman & Fisher 1974, Chait et al 1981].

## Genotype-Phenotype Correlations

As most pathogenic *LPL* variants have been reported in individual case reports or small case series, reliable systematic correlation of genotype-phenotype relationships is challenging. There are no known genotype-phenotype correlations.

## Nomenclature

Familial LPL deficiency is the most common form of the familial chylomicronemia syndrome, which was formerly known as "type 1 hyperlipoproteinemia."

## Prevalence

The prevalence of familial LPL deficiency is approximately one in 1,000,000 in the general US population.

The disease has been described in all races. The prevalence is much higher in some areas of Quebec, Canada as a result of a founder effect.

Consanguinity is observed in some families with familial LPL deficiency caused by homozygous pathogenic *LPL* variants.

## Genetically Related (Allelic) Disorders

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

**Mild lipid abnormalities not associated with familial LPL deficiency** have been reported with common variants of *LPL*, such as the p.Asn291Ser allele. The p.Asn291Ser allele does not appear to have a **major** effect on plasma lipid concentration or on risk for coronary disease in the general population; however, it may be associated with hypertriglyceridemia in the presence of the *APOE* E2 allele, diabetes mellitus, familial combined hyperlipidemia, hepatic lipase (HL) deficiency, and [glycogen storage disease type Ib](#). It is possible that the association of the p.Asn291Ser allele with these disorders is only a reflection of the relatively high frequency of this allele in the general population. Nonetheless, the allele likely predisposes to mild hypertriglyceridemia, but is insufficient in the absence of a secondary factor to cause more severe hypertriglyceridemia.

## Differential Diagnosis

Familial lipoprotein lipase (LPL) deficiency should be considered in young persons with the chylomicronemia syndrome, defined as abdominal pain, eruptive xanthomata, plasma triglyceride concentrations greater than 2000 mg/dL, and fasting lipemic plasma. However, the majority of individuals with chylomicronemia and plasma triglyceride concentration greater than 2000 mg/dL do not have familial LPL deficiency; rather, they have one of the more common genetic disorders of triglyceride metabolism (i.e., familial combined hyperlipidemia and monogenic familial hypertriglyceridemia). Hypertriglyceridemia can also be polygenic, due to both heterozygous rare large-effect variants and accumulations of common rare small-effect variants in several genes and loci [Hegele et al 2014]. With such genetic predisposition, clinical expression of chylomicronemia typically requires the presence of secondary, non-genetic factors [Brunzell & Deeb 2001].

Secondary causes of hypertriglyceridemia include: diabetes mellitus; paraproteinemia and lymphoproliferative disorders; use of alcohol; and therapy with estrogen, glucocorticoids, selective serotonin reuptake inhibitors, atypical antipsychotic agents, isotretinoin, or certain antihypertensive agents. In one series of 123 individuals evaluated for marked hypertriglyceridemia, 110 had an acquired cause of hypertriglyceridemia combined with a common genetic form of hypertriglyceridemia, five had familial LPL deficiency, five had other rare genetic forms of hypertriglyceridemia, and three had an unknown cause [Chait & Brunzell 1983].

Other than LPL deficiency, the chylomicronemia syndrome may be caused by biallelic pathogenic variants in apolipoprotein C-II (*APOC2*), apolipoprotein A-V (*APOA5*), lipase maturation factor 1 (*LMF1*) or *GPIHBP1* (see Table 2).

**Table 2.** Genetic Causes of Primary Monogenic Chylomicronemia

Gene (Gene Product)	Homozygote Prevalence	Gene Product Function	Clinical Features	Molecular Features	% of Monogenic Variants	References
<i>LPL</i> (LPL)	~1 per million individuals <sup>1</sup>	Hydrolysis of triglycerides & peripheral uptake of FFA	Severe chylomicronemia in infancy or childhood	Severely reduced or absent LPL enzyme activity	95.0	Murthy et al [1996], Jap et al [2003], Gotoda et al [2012], Martín-Campos et al [2014]
<i>APOC2</i> (apoC-II)	10 families reported	Required cofactor of LPL	Severe chylomicronemia in childhood or adolescence	Absent or nonfunctional apoC-II	2.0	Gotoda et al [2012], Okubo et al [2015]
<i>GPIHBP1</i> (GPI-HBP1)	10 families reported	Stabilizes binding of chylomicrons near LPL; supports lipolysis	Chylomicronemia in late adulthood	Absent or defective GPI-HBP1	2.0	Beigneux et al 2009, Gin et al [2012]

Table 2. continued from previous page.

Gene (Gene Product)	Homozygote Prevalence	Gene Product Function	Clinical Features	Molecular Features	% of Monogenic Variants	References
<i>APOA5</i> (apoA-V)	Three families reported	Enhancer of LPL activity	Chylomicronemia in late adulthood	Absent or defective apoA-V	0.6	Calandra et al [2006], Nilsson et al [2011]
<i>LMF1</i> (LMF1)	Two families reported	Chaperone molecule required for proper LPL folding and/or expression	Chylomicronemia in late adulthood	Absent or defective LMF1	0.4	Péterfy [2012]

From Brahm & Hegele [2015]; reprinted by permission of Macmillan Publishers, Ltd.

apoA-V = apolipoprotein A-V; apoC-II = apolipoprotein C-II; FFA = free fatty acid; GPI-HBP1 = glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; LMF1 = lipase maturation factor 1; LPL = lipoprotein lipase

1. Gotoda et al [2012]

- **Familial apolipoprotein C-II (apoC-II) deficiency** (OMIM 207750). ApoC-II is a cofactor for LPL. Familial apoC-II deficiency is an extremely rare autosomal recessive disorder that differs from familial LPL deficiency in that (1) symptoms generally develop at a later age (13-60 years) and (2) individuals may develop chronic pancreatic insufficiency with steatorrhea and insulin-dependent diabetes mellitus. The diagnosis is based on the identification of biallelic pathogenic variants in *APOC2*, on assay of plasma apoC-II concentration or activation of a purified LPL standard, and on gel electrophoresis of VLDL apolipoproteins. Infusion of normal plasma into an individual with familial apoC-II deficiency results in dramatic reduction of the plasma triglyceride concentration. Treatment is a low-fat diet throughout life.
- **Familial apolipoprotein A-V deficiency** (OMIM 144650). It has been suggested that apoA-V facilitates the interaction of endothelial heparan sulfate with apoC-II on triglyceride-rich lipoproteins and the interaction of apoC-II with LPL on the vascular endothelium. Several families with apoA-V deficiency have been reported to have severe hypertriglyceridemia. Biallelic large-effect loss-of-function pathogenic variants in *APOA5* can lead to familial chylomicronemia syndrome, while heterozygous carriers are predisposed to hypertriglyceridemia, but often demonstrate a normal clinical and biochemical phenotype in the absence of secondary non-genetic factors.
- **Familial lipase maturation factor 1 (LMF1) deficiency** (OMIM 246650). LMF1 is a transmembrane protein localized to the endoplasmic reticulum involved in the maturation of both LPL and hepatic lipase (HL). One affected individual, homozygous for a biallelic *LMF1* pathogenic variant, had very low LPL activity, modestly low HL activity, and chylomicronemia [Péterfy et al 2007].
- **Familial glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) deficiency** (OMIM 615947). GPIHBP1 appears to be a binding site for LPL on the capillary endothelial surface, perhaps through binding with apoA-V [Beigneux et al 2007]. Several individuals with GPIHBP1 deficiency have been described. Biallelic large-effect loss-of-function variants of *GPIHBP1* can lead to familial chylomicronemia syndrome, while heterozygous carriers are predisposed to hypertriglyceridemia, but often demonstrate a normal clinical and biochemical phenotype in the absence of secondary non-genetic factors. Recently, autoantibodies against GPIHBP1 were shown to cause chylomicronemia syndrome [Beigneux et al 2017].

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial lipoprotein lipase (LPL) deficiency, measurement of plasma triglyceride concentration is recommended.

Consultation with a clinical geneticist and/or genetic counselor may also be considered.

### Treatment of Manifestations

**Medical nutrition therapy.** Morbidity and mortality can be prevented by maintaining plasma triglyceride concentration at less than 2000 mg/dL; a good clinical goal is less than 1000 mg/dL [Viljoen & Wierzbicki 2012]. Restriction of dietary fat to no more than 20 g/day or 15% of total energy intake is usually sufficient to reduce plasma triglyceride concentration and to keep the individual with familial LPL deficiency free of symptoms.

Medium-chain triglycerides may be used for cooking, as they are absorbed directly into the portal vein without becoming incorporated into chylomicron triglyceride.

The success of therapy depends on the individual's acceptance of the fat restriction, including both unsaturated and saturated fat. Note: Fish oil supplements, which are effective in disorders of excess hepatic triglyceride production, are not effective in LPL deficiency and are contraindicated (see Agents/Circumstances to Avoid).

The enlarged liver and spleen can return to normal size within one week of lowering of triglyceride concentrations.

The xanthomas can clear over the course of weeks to months. Recurrent or persistent eruptive xanthomas indicate inadequate therapy.

Pancreatitis associated with the chylomicronemia syndrome is treated in the manner typical for other forms of pancreatitis.

- Discontinuation of oral fat intake stops chylomicron triglyceride formation, and replacement with hypocaloric parenteral nutrition decreases VLDL triglyceride production.
- Administration of excess calories, as in hyperalimentation, is contraindicated in the acute state. The intravenous administration of lipid emulsions may lead to persistent or recurrent pancreatitis.

If recurrent pancreatitis with severe hypertriglyceridemia occurs, total dietary fat intake needs to be reduced.

### Prevention of Primary Manifestations

See Treatment of Manifestations.

### Prevention of Secondary Complications

Prevention of recurrent acute pancreatitis decreases the risk of developing diabetes mellitus. Fat malabsorption is very rare.

### Surveillance

Plasma triglyceride levels need to be followed over time to evaluate the affected individual's success in following the very low-fat dietary recommendations. When the triglyceride level is above 1000 mg/dL, a fasting sample is not required for this evaluation. Other components of the lipid profile do not need to be routinely measured.

Affected individuals who develop abdominal pain need to contact their physician.

## Agents/Circumstances to Avoid

Avoidance of agents known to increase endogenous triglyceride concentration such as alcohol, oral estrogens, diuretics, isotretinoin, glucocorticoids, selective serotonin reuptake inhibitors, and beta-adrenergic blocking agents is recommended.

Fish oil supplements are contraindicated as they contribute to chylomicron levels.

## Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk sibs during infancy. Early diagnosis and implementation of dietary fat intake restriction can prevent symptoms and related medical complications.

Evaluations can include:

- Measurement of plasma triglyceride concentration;
- Molecular genetic testing if the pathogenic variants in the family are known.

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

## Pregnancy Management

During pregnancy in a woman with LPL deficiency, extreme dietary fat restriction to less than two grams per day during the second and third trimester with close monitoring of plasma triglyceride concentration can result in delivery of a normal infant with normal plasma concentrations of essential fatty acids [Al-Shali et al 2002].

One woman with LPL deficiency delivered a normal child following a one-gram per day fat diet and treatment with gemfibrozil (600 mg/day) [Tsai et al 2004]. Despite concerns about the possibility of essential fatty acid deficiency in the newborn, normal essential fatty acids were found in cord blood, as were normal levels of fibrate metabolites.

See [MotherToBaby](#) for further information on medication use during pregnancy.

## Therapies Under Investigation

*LPL* gene therapy is available in Europe and the US for the treatment of familial LPL deficiency. It consists of the *LPL* Ser447Ter variant in an adeno-associated virus serotype 1 (alipogene tiparvovec). Twenty percent of the general population has the Ser447Ter allelic variant, which results in a prematurely truncated LPL that is associated with increased lipolytic function and an anti-atherogenic lipid profile and can therefore be regarded as a naturally occurring gain-of-function variant (reviewed by Gaudet et al [2013]). Note that the standard nomenclature for this variant is NP\_000228.1:p.Ser474Ter (NM\_000237.2:c.1421C>G). Several other targeted therapies are in development or under investigation, including inhibitors of microsomal triglyceride transfer protein (MTP) [Sacks et al 2014], diacylglycerol acyl transferase 1 (DGAT1) [Meyers et al 2015], apoC-III [Gaudet et al 2014], and angiopoietin-like protein 3 (ANGPTL3) [Gryn & Hegele 2015].

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.

## Other

The lipid-lowering drugs that are used to treat other disorders of lipid metabolism are not effective in individuals with familial LPL deficiency.

Although plasmapheresis and antioxidant therapy have been suggested as treatment for pancreatitis, they do not appear to be needed for either acute therapy or long-term care.



## 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

Familial LPL deficiency is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *LPL* pathogenic variant).
- Heterozygotes are asymptomatic but may have moderately elevated plasma triglyceride concentrations and may be at mild risk for premature atherosclerosis.

### 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 are asymptomatic but may have moderately elevated plasma triglyceride concentrations and may be at mild risk for premature atherosclerosis.

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

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

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *LPL* pathogenic variants in the family. The lipid phenotype of heterozygotes varies widely from completely normal to moderate-to-severe hypertriglyceridemia and cannot be used to predict carrier status.

## Related Genetic Counseling Issues

See 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.

## Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and in 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. In practice, prenatal testing is rarely requested because of the availability of effective treatment.

## 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](#).

- **Medline Plus**  
Familial lipoprotein lipase deficiency
- **National Library of Medicine Genetics Home Reference**  
Familial lipoprotein lipase deficiency

## 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.** Familial Lipoprotein Lipase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>LPL</i>	8p21.3	Lipoprotein lipase	LPL @ LOVD	LPL	LPL

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 Familial Lipoprotein Lipase Deficiency ([View All in OMIM](#))

238600	HYPERLIPOPROTEINEMIA, TYPE I
609708	LIPOPROTEIN LIPASE; LPL

**Gene structure.** *LPL* comprises ten exons; the last one encodes the long untranslated 3'-end of the mRNA (NM\_000237.2). The sequence of *LPL* is highly conserved among mammalian species.

**Pathogenic variants.** More than 220 pathogenic variants have been identified [Brunzell & Deeb 2001, Gilbert et al 2001]; see Table A, **HGMD**. Approximately 70% of these variants are missense, 10% nonsense, and 18% nucleotide insertions and deletions; a few splice site variants are also known. About 3% of pathogenic variants have an exon or multiexon deletion, duplication, insertion, or complex rearrangement.

**Normal gene product.** Lipoprotein lipase (LPL) is a glycoprotein that is synthesized in adipose tissue and cardiac and skeletal muscle, but not in the postpartum liver. It is transported to the luminal surface of the capillary endothelium of extrahepatic tissues. It is essential for the hydrolysis of chylomicron and VLDL triglycerides to provide free fatty acids to tissue for energy production. LPL has two major domains: a larger NH<sub>2</sub>-terminal domain linked by a short region to a COOH-terminal domain of approximately half its size. The globular NH<sub>2</sub>-terminal domain specifies the catalytic properties of the lipase, whereas the COOH-terminal

domain specifies substrate specificity and heparin-binding properties. *LPL* encodes a protein of 475 amino acids that becomes a mature protein of 448 residues after cleavage of a signal peptide ([NP\\_000228.1](#)).

**Abnormal gene product.** Pathogenic deletions and nonsense and splice site variants presumably lead to absent or truncated LPL with defective catalytic activity. Most of the variants are in the highly conserved central homology region [Brunzell & Deeb 2001, Gilbert et al 2001]. Many missense variants result in LPL deficiency secondary to LPL homodimer instability.

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## Chapter Notes

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### Revision History

- 22 June 2017 (ma) Comprehensive update posted live
- 15 December 2011 (me) Comprehensive update posted live
- 28 July 2009 (me) Comprehensive update posted live
- 1 October 2007 (cd) Revision: deletion/duplication analysis available; prenatal testing available; mutation analysis for p.Gly188Glu done by sequence analysis
- 24 April 2006 (me) Comprehensive update posted live
- 9 April 2004 (me) Comprehensive update posted live
- 18 February 2002 (me) Comprehensive update posted live
- 12 October 1999 (me) Review posted live
- April 1999 (jb) Original submission

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