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APOE p.Leu167del-Related Lipid Disorders – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

APOE p.Leu167del is a rare genetic variant described in 38 cases in the literature with a range of clinical phenotypes. Three phenotypes can be associated with the *APOE* p.Leu167del variant:

- Inherited lipemic splenomegaly (also known as sea-blue histiocytosis) characterized by hypertriglyceridemia and splenomegaly. Variable manifestations include thrombocytopenia, liver function abnormalities, and cardiovascular disease
- Autosomal dominant hypercholesterolemia (ADH) characterized by markedly elevated LDL cholesterol levels that leads to premature morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD)
- Familial combined hyperlipidemia (FCHL) characterized by variable elevations of total cholesterol, triglycerides, or LDL cholesterol and a high risk of premature ASCVD

It has been suggested that the phenotype associated with the *APOE* p.Leu167del variant may depend on multiple factors, including sex, *APOE* genotype, control of hyperlipidemia, gene-gene interactions, gene-environment interactions, or perhaps epigenetic and other non-mendelian effects.

Diagnosis/testing

Diagnosis relies on detection of a heterozygous *APOE* p.Leu167del pathogenic variant. Determining whether the second *APOE* allele is the benign variant e2 or the benign variant e3 may be of some clinical predictive value.

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Management

Treatment of manifestations: No formal management guidelines exist. Individuals with hyperlipidemia should be treated according to their overall cardiovascular risk profile. Treatment for individuals with documented ASCVD or at high risk of developing ASCVD begins with lifestyle changes (adherence to a heart-healthy diet, exercise, tobacco avoidance, maintenance of a healthy weight) and may also include statin, fibrate, high-dose fish oil, and/or niacin therapy. Although no interventions are known to prevent disease progression, it has been suggested that treatment of dyslipidemia may prevent development of splenomegaly. Splenectomy should be avoided as it may worsen hyperlipidemia. Liver function abnormalities and thrombocytopenia are managed in a routine manner. Diabetes mellitus (if present) should be well controlled.

Surveillance: No formal surveillance guidelines exist. The authors suggest the following:

- Lipoprotein profile one year after diagnosis and every 2-5 years thereafter (if normal). If abnormal, follow at regular intervals for treatment of hyperlipidemia.
- Liver function panel, albumin, INR (prothrombin time) one year after diagnosis and every 2-5 years thereafter (if normal)
- Platelet count one year after diagnosis and every 2-5 years thereafter (if normal)

Agents/circumstances to avoid: Splenectomy, which may worsen the hypertriglyceridemia. For those with splenomegaly: contact sports given the increased risk for splenic rupture.

Evaluation of relatives at risk: Clarifying the genetic status of relatives at risk of inheriting the *APOE* p.Leu167del variant allows early adoption of preventive measures and surveillance.

Pregnancy management: In a woman with the *APOE* p.Leu167del variant, triglyceride levels should be measured when pregnancy is identified and at least one to two times later in pregnancy as severe hypertriglyceridemia (>500 mg/dL) in pregnancy increases the risk for pancreatitis and fetal and maternal death. Before taking a medication during pregnancy, a pregnant woman should discuss with her physician the risks and benefits of that medication.

Genetic counseling

The *APOE* p.Leu167del variant is inherited in an autosomal dominant manner. The proportion of *APOE* p.Leu167del-related lipid disorders caused by *de novo* mutation is unknown. The phenotype associated with the *APOE* p.Leu167del variant appears to depend on multiple factors. Each child of an affected individual has a 50% chance of inheriting the variant. Prenatal testing for at-risk pregnancies is possible; however, requests for prenatal testing for conditions such as *APOE* p.Leu167del-related lipid disorders are not common.

GeneReview Scope

APOE p.Leu167del-Related Lipid Disorders: Included Phenotypes [1]
• Inherited lipemic splenomegaly • Autosomal dominant hypercholesterolemia • Familial combined hyperlipidemia

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

Diagnosis

Establishing the diagnosis of an *APOE* p.Leu167del-related lipid disorder is considered from two perspectives:

- Use of molecular genetic testing to confirm the molecular diagnosis in an individual with clinical findings that suggest one of the three associated phenotypes
- Use of clinical evaluation to establish the clinical findings in an individual with the *APOE* p.Leu167del pathogenic variant

The diagnosis of an *APOE* p.Leu167del-related lipid disorder relies on detection of a heterozygous *APOE* p.Leu167del pathogenic variant.

- The *APOE* p.Leu167del pathogenic variant, which is a three base-pair deletion that results in deletion of the amino acid leucine at position 167 of the protein apolipoprotein E (see Molecular Genetics and Table 4), has to date occurred in *cis* configuration (i.e., on the same allele) with the *APOE* benign variant e3.
- Determining whether the second *APOE* allele is the benign variant e2 or e3 (see Molecular Genetics, **Benign variants**) may be of some clinical predictive value as the presence of e2 as the second allele may predispose to development of splenomegaly or may increase the plasma concentration of atherogenic remnant lipoproteins and intermediate density lipoproteins [Nguyen et al 2000] (Table 1). While the association of the *APOE* e2 benign variant with *APOE* p.Leu167del-related lipid disorders is significant, it is neither fully specific nor sensitive.

  Note: While genetic testing to determine whether the second *APOE* allele is the benign variant e2 or e3 is recommended, distinguishing the *APOE* e4 allele from the wild type *APOE* e3 allele is minimally useful – and possibly harmful, given the increased risk for Alzheimer disease associated with the e4 allele.

Three phenotypes can be associated with *APOE* p.Leu167del-related lipid disorders:

- Inherited lipemic splenomegaly (also known as sea-blue histiocytosis)
- Autosomal dominant hypercholesterolemia (ADH)
- Familial combined hyperlipidemia (FCHL)

Clinical Findings

Inherited Lipemic Splenomegaly Phenotype

Hypertriglyceridemia. The mean lipoprotein values in the seven individuals reported to date with *APOE* p.Leu167del-related inherited lipemic splenomegaly are summarized in Table 1 [Okorodudu et al 2013]. Note: Elevated triglycerides cause serum to have a lipemic (turbid to milky white) appearance.

Table 1. Mean Lipoprotein Values by *APOE* Benign Variant Genotype in 7 Individuals Heterozygous for *APOE* p.Leu167del with Splenomegaly

APOE Benign Variant Genotype [1]	N (Male)	TC [2] (mg/dL + SD)	HDL-C [3] (mg/dL + SD)	TG [4] (mg/dL + SD)
e3*/e2 [5, 6]	4 (3)	194 ± 81	43 ± 9	590 ± 454

Table 1. continued from previous page.

APOE Benign Variant Genotype [1]	N (Male)	TC [2] (mg/dL + SD)	HDL-C [3] (mg/dL + SD)	TG [4] (mg/dL + SD)
e3*/e3 [7]	3 (3)	151 ± 65	24 ± 3	218 ± 74

Adapted from Okorodudu et al [2013]
N = number reported
TC = total cholesterol
HDL-C = high-density lipoprotein cholesterol
TG = triglyceride
SD = standard deviation
1. To date, the *APOE* p.Leu167del variant has occurred in *cis* configuration (i.e., on the same allele) with the e3 benign variant. These two alleles in *cis* configuration are designated here as e*. See Molecular Genetics, **Benign variants**.
2. (<200 mg/dL)
3. (≥40 mg/dL or ≥50 mg/dL in a woman)
4. (<150 mg/dL)
5. All individuals with this genotype had splenomegaly. Three of four lipid panels were measured pre-splenectomy.
6. One individual also had a pathogenic variant in *LPL* (see Familial Lipoprotein Lipase Deficiency), attributed to have a causal relationship with hypertriglyceridemia [Nguyen et al 2000]. Thus, this individual had a digenic relation to inherited lipemic splenomegaly.
7. One individual (the son of the person described in footnote 3) also had a pathogenic variant in *LPL*.

Splenomegaly results from the accumulation of lipid-laden macrophages that have a characteristic sea-blue histiocytic appearance on routine stains:

- Splenomegaly is seen in some individuals with *APOE* p.Leu167del-related lipid disorders, but not all (Table 2). When encountered, splenomegaly has been clinically detected between the second and fifth decade of life. The majority of reported individuals had some degree of hypertriglyceridemia preceding the diagnosis of splenomegaly.
- The four individuals who underwent splenectomy had markedly enlarged spleens that weighed between 727 g and 1200 g (normal 70 - 250 g) [Nguyen et al 2000, Faivre et al 2005, Rahalkar et al 2008, Okorodudu et al 2013]. All four had markedly worsened hypertriglyceridemia after splenectomy (see Management).

Thrombocytopenia is attributed to splenic sequestration.

Autosomal Dominant Hypercholesterolemia (ADH) Phenotype

Clinical findings include the following:

- Very high LDL cholesterol levels from birth (>95th percentile for age and sex)
- Premature atherosclerosis
- Tendon xanthomas. Development of tendon xanthomas requires prolonged exposure to high LDL and may not occur in mildly affected or treated individuals. Tendon xanthomas have been described in one of the two sibs reported by Awan et al [2013], but not other individuals with the *APOE* p.Leu167del variant and the ADH phenotype.

Note: Triglycerides are typically normal; however, hypertriglyceridemia can sometimes be observed in ADH due to common genetic and environmental factors contributing to triglyceride elevation.

Familial Combined Hyperlipidemia (FCHL) Phenotype

Clinical findings include the following:

- Familial aggregation of total plasma cholesterol and/or triglyceride concentrations >90th percentile adjusted for age and sex in association with a strong family history of premature coronary heart disease

- Three different lipid phenotypes:
  - Increased total cholesterol (Frederickson type IIa hyperlipidemia)
  - Increased total cholesterol and increased triglycerides (Frederickson type IIb hyperlipidemia)
  - Isolated hypertriglyceridemia (Frederickson type IV hyperlipidemia).

  Note: The lipid phenotype can also vary in a given individual over time, making the diagnosis of FCHL challenging [Veerkamp et al 2004].

Clinical Characteristics

Clinical Description

To date, only 38 individuals with the *APOE* p.Leu167del pathogenic variant have been reported [Nguyen et al 2000, Faivre et al 2005, Rahalkar et al 2008, Solanas-Barca et al 2012, Awan et al 2013, Okorodudu et al 2013]. The three phenotypes observed in individuals with this variant are inherited lipemic splenomegaly (also known as sea-blue histiocytosis), autosomal dominant hypercholesterolemia (ADH), and familial combined hyperlipidemia (FCHL).

Of these 38 individuals, only seven have had splenomegaly and are thus characterized as having the inherited lipemic splenomegaly phenotype [Okorodudu et al 2013]. The other 29 have had a phenotype consistent with either ADH or FCHL. It is important to note that ADH and FCHL are well-described medical disorders that can have overlapping manifestations and that *APOE* p.Leu167del is a rare cause of ADH and FCHL (see Differential Diagnosis).

Given the limited number of reports in the literature to date, little is known about the natural history of the phenotypes associated with the *APOE* p.Leu167del variant.

Inherited Lipemic Splenomegaly

Inherited lipemic splenomegaly is characterized by hypertriglyceridemia and splenomegaly in individuals with the *APOE* pathogenic variant p.Leu167del in whom other metabolic causes of hypertriglyceridemia, splenomegaly, and/or sea-blue histiocytosis have been excluded. Individuals must have splenomegaly in order to be diagnosed with inherited lipemic splenomegaly.

The association of the pathogenic variant *APOE* p.Leu167del and sea-blue histiocyte disease was first described by Nguyen et al [2000]. Since then, three additional reports have been published [Faivre et al 2005, Rahalkar et al 2008, Okorodudu et al 2013] (see Table 2). All affected individuals on whom data were available have had hypertriglyceridemia (except the mother in Nguyen et al [2000] and splenomegaly. Other variable manifestations include thrombocytopenia, liver function abnormalities, and cardiovascular disease.

The age of onset is unknown. All individuals with splenomegaly have been in their late 20s to 50s. It is thought that hyperlipidemia directly causes splenomegaly as it has been shown in vitro that *APOE* p.Leu167del stimulates cholesterol ester accumulation by splenic macrophages which can result in splenomegaly [Faivre et al 2005, Okorodudu et al 2013]. Splenomegaly can then cause sequestration-related thrombocytopenia. Abnormal uptake of cholesterol esters by hepatic macrophages could promote liver dysfunction, or liver dysfunction could occur independently in association with fatty liver, insulin resistance, and hypertriglyceridemia. Cardiovascular disease is likely multifactorial and related to allelic variants in multiple genes as well as environmental factors, such as visceral adiposity, insulin resistance, and diabetes mellitus.

The proband in Okorodudu et al [2013] provides the only long-term data for an affected individual. He has been followed at the same institution from age 29 years to the present (age 76 years). He was reported to have had intermittent splenomegaly and mild thrombocytopenia (as low as 115,000/L) since age 13 years. At age 29 years he had hypertriglyceridemia with triglyceride level of 629 mg/dL while on no medication. With aggressive

medical and dietary treatment of his hypertriglyceridemia, splenomegaly resolved. Since age 50 years he has displayed mild thrombocytopenia with a platelet count above 150,000/L. He has not had liver function abnormalities. He underwent coronary artery bypass surgery for CHD at age 70 years.

Given the resolution of splenomegaly in the proband reported by Okorodudu et al [2013], it is hypothesized that aggressive medical management of hyperlipidemia can prevent splenomegaly and associated splenic sequestration. Splenectomy should be avoided given the severely worsened hypertriglyceridemia in persons undergoing splenectomy (see Management).

Table 2. Findings in Families in Which ≥1 Individuals with the *APOE* p.Leu167del Pathogenic Variant Exhibit Lipemic Splenomegaly

Reference	Subject	Age [1]	Sex	Finding				
				Splenomegaly / Splenectomy	↑TG [2]	↓PLT	↑LFT [3]	CAD
Nguyen et al [2000]	Proband #1	29	M	+ / +	+	+	+	+
	Mother	NA	F	+ / –	–	NA	NA	+
	Proband #2	49	M	+ / +	+	+	+	+
Faivre et al [2005]	Proband	47	M	+ / +	+	+	+	–
	Mother	NA	F	– / –	+	–	NA	–
	Brother	NA	M	+ / –	+	+	+	+
Rahalkar et al [2008]	Single case	49	M	+ / +	NA	–	–	–
Okorodudu et al [2013]	Proband	76	M	+ / –	+	+	-	+
	Son	43	M	– / –	+	–	–	–
	Granddaughter	13	F	– / –	NA	–	–	–

CAD = coronary artery disease; LFT = liver function test; NA = not available; PLT = platelets; TG = triglycerides

1. Age (in years) at which the *APOE* p.Leu167del variant was identified in the subject

2. Triglyceride level >150 mg/dL prior to splenectomy. The majority of patients were on lipid-modifying agents. All who underwent splenectomy subsequently developed hypertriglyceridemia or worsening of triglyceride levels.

3. The relationship of liver enzyme elevations to the *APOE* p.Leu167del pathogenic variant is questionable, since fatty liver disease is common in people with hypertriglyceridemia [Nguyen et al 2000, Faivre et al 2005].

Autosomal Dominant Hypercholesterolemia (ADH)

In individuals with ADH, elevated LDL cholesterol levels lead to tendon xanthomas and premature morbidity and mortality from atherosclerotic cardiovascular disease (ASCVD). Early treatment of hypercholesterolemia in other causes of ADH (e.g., mutation of one of three genes – *LDLR*, *APOB,* and *PCSK9* – which accounts for 60%-80% of ADH) has been shown to prevent the formation of xanthomas as well as prevent or delay onset of early atherosclerosis and cardiovascular complications (see Management).

Early treatment of hypercholesterolemia in individuals with the *APOE* p.Leu167del variant is hypothesized to confer the same benefits as for other etiologies of ADH.

Familial Combined Hyperlipidemia (FCHL)

The phenotype of FCHL is highly variable. Depending on genetic and environmental factors, affected individuals may have variable degrees of elevated total cholesterol, triglycerides, or LDL cholesterol. Affected individuals are at high risk for premature atherosclerotic cardiovascular disease (ASCVD). In general, early recognition and treatment of hyperlipidemia can prevent the morbidity and mortality of ASCVD. Whether the clinical course of *APOE* p.Leu167del-related FCHL phenotype differs from that of other causes of FCHL is not known.

Genotype-Phenotype Correlations

At this time genotype-phenotype correlations are incompletely understood.

It has been suggested that the phenotypic expression of the *APOE* p.Leu167del variant may be related to multiple factors, including sex, *APOE* genotype, and control of hyperlipidemia [Solanas-Barca et al 2012, Okorodudu et al 2013].

- Six of the seven individuals with splenomegaly have been male (Table 2).
- A more severe phenotype is generally seen in individuals with the *APOE* p.Leu167del pathogenic variant and the *APOE* allele e2 as the second allele.
- It has been hypothesized that medical control of hypertriglyceridemia can prevent or induce resolution of splenomegaly [Okorodudu et al 2013].

Penetrance

To date the *APOE* p.Leu167del variant has been found only in families with hyperlipidemia. Among the 38 people described with this allele, only one (a girl age 14 years) had a normal lipoprotein profile with LDL cholesterol at the 75th percentile for age and sex.

Nomenclature

The designation sea-blue histiocytosis was coined by Silverstein [Silverstein et al 1970]. In inherited lipemic splenomegaly, splenomegaly results from the accumulation of lipid-laden macrophages that have a characteristic sea-blue histiocytic appearance with the usual hematologic stains. However, as sea-blue histiocytes are not specific for inherited lipemic splenomegaly (see Differential Diagnosis), the authors prefer "inherited lipemic splenomegaly" which includes the two major features of the disorder: lipemic serum due to hypertriglyceridemia and splenomegaly.

In the literature the pathogenic variant has been referred to as both *APOE* p.Leu149del and *APOE* p.Leu167del. Consistent with the Human Genome Variation Society (www.hgvs.org), the authors have elected to call it *APOE* p.Leu167del based on expressed peptide sequence.

Autosomal dominant hypercholesterolemia (ADH) is a preferred designation that should be distinguished from familial hypercholesterolemia. The latter term can be either more specific than ADH, referring to LDL receptor deficiency, or more general, referring to both autosomal dominant and autosomal recessive hypercholesterolemia.

Familial combined hyperlipidemia (FCHL) is a common and diverse phenotype, generally not mendelian, which may simply represent the intersection of familial genetic and environmental influences on blood cholesterol and triglycerides.

Prevalence

Inherited lipemic splenomegaly. The pathogenic variant *APOE* p.Leu167del is rare. It was not present in more than 7800 unselected individuals, but was present in one of three individuals presenting in a lipid clinic with splenomegaly and hypertriglyceridemia [Okorodudu et al 2013]. A total of seven individuals with inherited lipemic splenomegaly related to *APOE* p.Leu167del have been described (see Table 2).

Autosomal dominant hypercholesterolemia (ADH). ADH is a common disorder of lipid metabolism that occurs in one out of every 500 individuals in the general population. The *APOE* p.Leu167del variant is a rare cause of ADH.

- In a French database of nine families with ADH of unknown cause, one family (including 14 affected individuals) and one unrelated individual (whose father died of myocardial infarction at age 51 years) were found to have the *APOE* p.Leu167del variant.
- In the family with 14 cases, hypercholesterolemia clearly segregated with the *APOE* p.Leu167del variant [Marduel et al 2013].

Familial combined hyperlipidemia (FCHL) is a common disorder of lipid metabolism that occurs in up to 6% of the general population [Solanas-Barca et al 2012]. The *APOE* p.Leu167del variant was reported in 1.4% of a group of patients with FCHL [Solanas-Barca et al 2012].

Differential Diagnosis

Inherited Lipemic Splenomegaly

It is important to note that the pathogenic variant *APOE* p.Leu167del is likely not the only variant predisposing to splenomegaly in persons with hypertriglyceridemia; only one of three persons with splenomegaly and hypertriglyceridemia in the Duke Lipid Clinic had the *APOE* p.Leu167del pathogenic variant [Okorodudu et al 2013].

Table 3 lists other possible etiologies for the hyperlipidemia, splenomegaly with lipid accumulation, and thrombocytopenia observed in inherited lipemic splenomegaly.

Table 3. Diseases with Splenomegaly and Dyslipidemia

Disease Name	Gene (MOI)	Major Finding	Other Clinical Findings
APOE p.Leu167del-related disorders	*APOE* (AD)	Leucine residue deletion in *APOE*	• Splenomegaly • Hyperlipidemia • Thrombocytopenia
Acid lysosomal lipase deficiency (cholesterol ester storage disease; Wolman disease)	*LIPA* (AR)	Accumulation of TG & cholesterol ester	• Adrenal gland calcification & insufficiency • Hepatic fibrosis • Cirrhosis
Fabry disease (A-galactosidase A deficiency)	*GLA* (XL)	Accumulation of ceramide trihexoside	• Skin angiokeratomas & telangiectasias • Acroparesthesias • Left ventricular hypertrophy • Stroke • Renal failure
Gaucher disease (glucocerebrosidase deficiency)	*GBA* (AR)	Accumulation of glucocerebrosides	• Type 1: bone erosion & anemia • Type 2: severe neurologic involvement & death age <1 yr • Type 3a/b/c: infantile onset w/ neurologic deficits
Hemophagocytic lymphohistiocytosis	*PRF1, UNC13D, STX11, STXBP2* (AR)	Immune dysregulation & increased lymphocytes	• Prolonged fever • Lymphadenopathy • Icterus • Rash • Edema • Seizures
Lecithin:cholesterol acyltransferase (LCAT) deficiency. (partial deficiency = fish eye disease)	*LCAT* (AR)		• Very low HDL • Anemia • Renal insufficiency • Striking corneal opacities • Fish eye disease = corneal opacities only

Table 3. continued from previous page.

Disease Name	Gene (MOI)	Major Finding	Other Clinical Findings
Acid sphingomyelinase deficiency (Niemann-Pick type A or type B) disease)	*SMPD1* (AR)	Accumulation of sphingomyelin & cholesterol	• Xanthomatous rash • Anemia • Fever • Cherry-red macular spot • Pulmonary infiltrates • Neurologic deterioration
Tangier disease	*ABCA1* (AR)	Accumulation of cholesteryl ester	• Very low HDL & ApoA-1 • Low LDL & high TG • Enlarged orange tonsils, very mild corneal opacifications, peripheral neuropathy, variable premature CHD

ApoA-I = apolipoprotein A-I; CHD = coronary heart disease; HDL = high density lipoprotein; LDL = low density lipoprotein; MOI = mode of inheritance; TG = triglyceride

Autosomal Dominant Hypercholesterolemia (ADH)

ADH is genetically heterogeneous. Mutation of *LDLR* (encoding the LDL receptor), *APOB* (encoding apolipoprotein B-100), and *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) is said to account for 81% of ADH. The *APOE* p.Leu167del variant has recently been identified as an additional genetic cause of ADH [Marduel et al 2013].

Familial Combined Hyperlipidemia (FCHL)

FCHL, a common and diverse disorder of lipid metabolism that occurs in up to 6% of the general population [Solanas-Barca et al 2012], may account for one third to one half of familial causes of early coronary heart disease [Williams et al 1990].

FCHL is a genetically complex disorder with reduced penetrance. Most cases of FCHL are considered polygenic with the interaction of multiple susceptibility genes and the environment. Many of the genes contributing to FCHL are unknown; however, the *APOE* p.Leu167del variant was recently reported in 1.4% of a study population of patients with FCHL [Solanas-Barca et al 2012].

The lipid phenotype can vary among family members. Environmental factors thought to affect disease expression are visceral adiposity, insulin resistance, and diabetes mellitus.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *APOE* p.Leu167del-related lipid disorder, the following evaluations are recommended:

- Baseline lipoprotein profile, including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
- Liver function panel, albumin, INR (prothrombin time)
- Platelet count
- Physical examination to screen for splenomegaly. If splenomegaly is suspected, an abdominal ultrasound examination could be performed to further characterize the extent of splenomegaly.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

There are no formal management guidelines for *APOE* p.Leu167del-related lipid disorders.

Given the limited number of reports of individuals with an *APOE* p.Leu167del-related lipid disorder and the clinical variability among affected individuals, it is unknown which individuals with the *APOE* p.Leu167del variant will develop hyperlipidemia, splenomegaly, and/or severe thrombocytopenia. However, the authors postulate that untreated hyperlipidemia may worsen the phenotype.

Hyperlipidemia. Discussion of the management of hyperlipidemia is beyond the scope of this article. For more in-depth discussion on management, see the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [Stone et al 2014] (full text). It should be noted that using risk prediction models in genetic dyslipidemia may markedly underestimate an individual's risk of developing ASCVD.

Treatment for individuals with documented ASCVD or at high risk of developing ASCVD begins with lifestyle changes (adherence to a heart-healthy diet, exercise, tobacco avoidance, maintenance of a healthy weight). Medical therapy may include a statin (generally the mainstay of therapy to reduce ASCVD risk), a fibrate, high-dose fish oil, and/or niacin. If present, diabetes mellitus should be well controlled, as uncontrolled diabetes can worsen hypertriglyceridemia.

In patients with fasting triglyceride levels:

- >500 mg/dL, the first goal of treatment should be to lower triglyceride levels to prevent pancreatitis.
- >1000 mg/dL, elimination of fat from the diet is essential.
- <500-1000 mg/dL, the focus may shift to the avoidance of high glycemic carbohydrates. Additionally, if identified, excessive intake of sucrose- or fructose-containing food and beverages should be limited.

Although caloric restriction with the goal of weight loss can also be helpful in lowering triglyceride levels, it should not be the primary focus in patients with severe hypertriglyceridemia.

Splenomegaly. Although no interventions are known to prevent disease progression, it has been suggested that treatment of dyslipidemia may prevent development of splenomegaly [Okorodudu et al 2013].

Splenectomy should be avoided as it may worsen hyperlipidemia. Patients who underwent splenectomy were reported to have markedly worsened hypertriglyceridemia after splenectomy [Nguyen et al 2000, Faivre et al 2005, Rahalkar et al 2008, Okorodudu et al 2013].

Liver function abnormalities and **thrombocytopenia** should be managed by specialists in gastroenterology and hematology, respectively.

- **Liver function abnormalities.** Counsel patients to notify their health care provider regarding any of the following signs:
  - Persistent nausea
  - Vomiting
  - Abdominal pain
  - Yellow discoloration of the skin
- **Thrombocytopenia.** Counsel patients to notify their health care provider regarding any of the following signs:
  - Bruising
  - Bleeding
  - Any new petechial rash

Prevention of Secondary Complications

Patients with splenomegaly should avoid contact sports given the increased risk for splenic rupture.

Surveillance

There are no formal guidelines regarding surveillance. The authors suggest obtaining the following:

- Lipoprotein profile one year after diagnosis and every two to five years thereafter (if normal). If abnormal, follow at regular intervals for treatment of hyperlipidemia.
- Liver function panel, albumin, INR (prothrombin time) one year after diagnosis and every two to five years thereafter (if normal). Counsel patients regarding the signs of liver dysfunction.
- Platelet count one year after diagnosis and every two to five years thereafter (if normal). Counsel patients to notify their provider immediately in the event of bleeding or petechial rash.

Agents/Circumstances to Avoid

Avoid the following:

- Splenectomy as it worsens the hypertriglyceridemia
- For those with splenomegaly: contact sports given the increased risk for splenic rupture

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk of inheriting the *APOE* p.Leu167del variant in order to identify as early as possible those who would benefit from preventive measures and surveillance.

- Molecular genetic testing can be used to determine if a family member has inherited the *APOE* p.Leu167del variant.
- If the *APOE* p.Leu167del variant is found, testing for the presence of an *APOE* e2 allele (see Diagnosis) is recommended.

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

Pregnancy Management

A woman with the *APOE* p.Leu167del variant should have triglyceride levels measured when pregnancy is identified and at least one to two times later in pregnancy as severe hypertriglyceridemia (>500 mg/dL) in pregnancy increases the risk for pancreatitis and fetal and maternal death. Of note, hypercholesterolemia alone does not present a risk in pregnancy.

Treatment of hypertriglyceridemia in pregnant women is similar to that for nonpregnant individuals. The goal of therapy is to achieve fasting triglyceride levels below 500 mg/dL (see Treatment of Manifestations regarding dietary advice to lower triglycerides).

If acceptable triglyceride levels are not achieved in a pregnant woman with dietary changes alone, medical therapy may be required.

- Medical management in pregnancy usually consists of fibrates (pregnancy category C). Prior to taking a medication during pregnancy, a pregnant woman should discuss with her physician the risks and benefits of the specific medication being prescribed.
- Due to theoretic concerns regarding the role of cholesterol in embryonic development and the fact that hypercholesterolemia alone does not present a risk in pregnancy, statin therapy is contraindicated during

pregnancy. Women who are taking a statin should discontinue the use of this medication prior to conception, if possible, or as soon as the pregnancy is recognized. However, inadvertent exposure early in gestation is unlikely to lead to a significantly increased risk for adverse fetal outcomes [Pollack et al 2005].
- Fish oil could be considered, but could alter prostaglandin metabolism in the fetus.
- Severe hypertriglyceridemia-induced pancreatitis can require apheresis and use of intravenous insulin and glucose. In these circumstances, consultation with a lipid specialist is recommended.

Therapies Under Investigation

Search Clinical Trials.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

APOE p.Leu167del-related lipid disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with an *APOE* p.Leu167del-related lipid disorder have a parent with clinical manifestations of *APOE* p.Leu167del-related lipid disorders (i.e., inherited lipemic splenomegaly, autosomal dominant hypercholesterolemia [ADH], familial combined hyperlipidemia [FCHL]).
- The proportion of *APOE* p.Leu167del-related lipid disorders caused by *de novo* pathogenic variants is unknown.
- If the *APOE* variant p.Leu167del found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- Recommendations for the evaluation of parents of a proband in whom the *APOE* p.Leu167del variant appears to be *de novo* include testing for the *APOE* p.Leu167del variant and, if positive, for the presence of an *APOE* e2 allele.
- The family history of some individuals with an *APOE* p.Leu167del variant may appear to be negative because of failure to recognize a lipid disorder in family members, early death of the parent before the onset of symptoms, or late onset of a related lipid disorder in a parent with the *APOE* p.Leu167del variant. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs of inheriting the *APOE* p.Leu167del variant is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband of inheriting the *APOE* p.Leu167del variant appears to be low.

- The sibs of a proband with clinically unaffected parents are still at increased risk of inheriting the *APOE* p.Leu167del variant because of the possibility of reduced penetrance in a parent.
- If the *APOE* p.Leu167del variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Each child of an individual with an *APOE* p.Leu167del variant has a 50% chance of inheriting the variant.

Other family members. The risk to other family members depends on the status of the proband's parents. If a parent has the *APOE* p.Leu167del variant, his or her family members may be at risk.

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 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 or at risk.

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 Testing

Once the *APOE* p.Leu167del variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While decisions regarding prenatal testing are the choice of the parents, discussion of these issues is appropriate.

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.

- **HEART UK**
  United Kingdom
  Phone: 0845 450 5988
  Email: ask@heartuk.org.uk
  www.heartuk.org.uk

- **Learn Your Lipids**
  www.learnyourlipids.com

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. APOE p.Leu167del-Related Lipid Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
APOE	19q13.32	Apolipoprotein E	alsod/APOE genetic mutations ALS mutation database (APOE) APOE database	APOE	APOE

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 APOE p.Leu167del-Related Lipid Disorders (View All in OMIM)

107741	APOLIPOPROTEIN E; APOE
269600	SEA-BLUE HISTIOCYTE DISEASE

Molecular Pathogenesis

Apolipoprotein E (APOE), a 34,000 molecular mass protein, is a major apolipoprotein that controls lipoprotein metabolism. APOE is a component of chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (LDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). As a ligand for the LDL receptor, APOE is required for receptor-mediated clearance of chylomicron and VLDL remnants from circulation. APOE is a ligand for the LDL receptor. The *APOE* p.Leu167del variant destabilizes a leucine zipper motif in a critical region of APOE that may weaken the ability of intermediate density lipoproteins and chylomicron remnants to bind to the LDL receptor [Awan et al 2013, Marduel et al 2013].

APOE is synthesized primarily in the liver. However, other organs and tissues synthesize APOE, including the spleen, macrophages, brain, kidneys, gonads, and adrenals. The widespread production of APOE indicates its importance in lipid transport and possibly in additional unrelated roles.

Gene structure. *APOE* comprises four exons and three introns spanning 3,597 nucleotides. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Three common benign variants (e2, e3, e4 [or ε2, ε3, ε4]) encode three isoforms (variants) of the APOE protein (APOE2, APOE3, APOE4, respectively) that differ in amino acid sequence at positions 130 and 176.*

- APOE2 has cysteine at both positions.
- APOE3 has cysteine at 130 and arginine at 176.
- APOE4 has arginine at both sites.

*Note: The polymorphic amino acid residues are referred to as:

- 130 and 176 when numbering begins at the initiating AUG codon and includes the signal peptide;
- 112 and 158 when numbering begins at the mature peptide after cleavage of the signal peptide NP_000032.1.

The allelic variants e2, e3, and e4 are designated by their common names in the literature and not by conventions of the Human Genome Variation Society.

Many studies have sought an association between the *APOE* e2, e3, and e4 alleles and various phenotypes, including for example:

- The homozygous *APOE* e2 genotype (e2/e2) is associated with type III hyperlipoproteinemia, a relatively rare disorder characterized by elevated total cholesterol and triglycerides with early cardiovascular disease and tendinous/tuberous xanthomas [Eichner et al 2002].
- The *APOE* e4 allele is a risk factor for Alzheimer disease. [Farrer et al 1997].

Pathogenic variants. See Table 4.

Table 4. *APOE* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.500_502delTCC (499_501delCTC)	p.Leu167del [2] (Leu149del) [3]	NM_000041.2 NP_000032.1

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. Nomenclature in the preprocessed peptide (including the signal peptide)
3. Nomenclature in the processed peptide (after cleavage of the signal peptide)

Normal gene product. The NM_000041.2 transcript encodes a 317-amino acid apolipoprotein E precursor. After cleavage of the 18-amino acid signal peptide, mature APOE is secreted as a 299-amino acid protein with a relative molecular mass of 34,200.

APOE accounts for a significant fraction of the normal variation in plasma cholesterol levels. Studies have estimated the total variance for LDL cholesterol accounted for by APOE at between 1% and 8.3%. APOE contributes more to normal cholesterol variability than any other protein identified in cholesterol metabolism thus far [Eichner et al 2002].

Although other rare protein variants exist, the variant (isoform) proteins APOE2, APOE3, and APOE4 (encoded by the three common benign variants e2, e3, and e4, respectively) have been studied the most. APOE3, the most common protein isoform, is seen in more than 60% of all populations studied [Eichner et al 2002].

The different isoforms have different affinity for binding to the LDL receptor. APOE3 and APOE4 bind with nearly equal affinity whereas APOE2 binds with less than 2% of this affinity [Eichner et al 2002].

- APOE2 is associated with lower LDL cholesterol except for 2% of *APOE* e2 homozygotes who develop type III hyperlipoproteinemia.
- APOE4 is associated with higher total and LDL cholesterol levels. This may relate to a higher affinity of APOE4 for VLDL and LDL, whereas APOE2 and APOE3 binding preference is for HDL. The relative enrichment of APOE4 in VLDL is thought to cause accelerated hepatic uptake and consequent downregulation of LDL receptor expression, thus leading to increased levels of LDL in persons heterozygous for *APOE* e4 [Marduel et al 2013].

On average, APOE2 lowers total cholesterol levels by approximately 14 mg/dL and APOE4 raises them by approximately 8 mg/dL [Eichner et al 2002].

Abnormal gene product. The effect of the *APOE* p.Leu167del pathogenic variant on the APOE protein has been less well studied than the common variants APOE2 and APOE4 (see **Normal gene product**). As Leu167 is the fourth residue in a six-amino acid motif that is highly conserved among species, it is likely that deletion of this amino acid would alter the general structure of this highly conserved part of APOE and would influence

interaction with lipids and the affinity of APOE to multiple receptors [Marduel et al 2013]. Exact changes are unknown, as only a few individuals with this pathogenic variant have been described.

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Chapter Notes

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