TABLE 421-3 PRIMARY HYPERLIPOPROTEINEMIAS CAUSED BY KNOWN SINGLE-GENE MUTATIONS

Genetic Disorder	Protein (Gene) Defect	Lipoproteins Elevated	Clinical Findings	Genetic Transmission	Estimated Incidence
Hypertriglyceridemia					
Lipoprotein lipase deficiency	LPL (*LPL*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	~1/1,000,000
Familial apoC-II deficiency	ApoC-II (*APOC2*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
ApoA-V deficiency	ApoA-V (*APOA5*)	Chylomicrons, VLDL	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	<1/1,000,000
GPIHBP1 deficiency	*GPIHBP1*	Chylomicrons	Eruptive xanthomas, pancreatitis	AR	<1/1,000,000
Combined Hyperlipidemia					
Familial hepatic lipase deficiency	Hepatic lipase (*LIPC*)	VLDL remnants, HDL	Pancreatitis, CHD	AR	<1/1,000,000
Familial dysbetalipoproteinemia	ApoE (*APOE*)	Chylomicron remnants, VLDL remnants	Palmar and tuberoeruptive xanthomas, CHD, PVD	AR	~1/10,000
Hypercholesterolemia					
Familial hypercholesterolemia	LDL receptor (*LDLR*)	LDL	Tendon xanthomas, CHD	AD	~1/250 to 1/500
Familial defective apoB-100	ApoB-100 (*APOB*)	LDL	Tendon xanthomas, CHD	AD	<~1/1500
Autosomal dominant hypercholesterolemia, type 3	PCSK9 (*PCSK9*)	LDL	Tendon xanthomas, CHD	AD	<1/1,000,000
Autosomal recessive hypercholesterolemia	ARH (*LDLRAP*)	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000
Sitosterolemia	*ABCG5* or *ABCG8*	LDL	Tendon xanthomas, CHD	AR	<1/1,000,000

Abbreviations: AD, autosomal dominant; apo, apolipoprotein; AR, autosomal recessive; ARH, autosomal recessive hypercholesterolemia; CHD, coronary heart disease; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PVD, peripheral vascular disease; VLDL, very-low density lipoprotein.

and pronounced chylomicronemia never develop pancreatitis, eruptive xanthomas, or hepatosplenomegaly. Premature CHD is not generally a feature of familial chylomicronemia syndromes.

The diagnoses of LPL and apoC-II deficiency are established enzymatically in specialized laboratories by assaying TG lipolytic activity in postheparin plasma. Blood is sampled after an IV heparin injection to release the endothelial-bound LPL. LPL activity is profoundly reduced in both LPL and apoC-II deficiency; in patients with apoC-II deficiency, it normalizes after the addition of normal plasma (providing a source of apoC-II). Molecular sequencing of the genes can be used to confirm the diagnosis.

The major therapeutic intervention in familial chylomicronemia syndrome is dietary fat restriction (to as little as 15 g/d) with fat-soluble vitamin supplementation. Consultation with a registered dietician familiar with this disorder is essential. Caloric supplementation with medium-chain TGs, which are absorbed directly into the portal circulation, can be useful, but there is uncertainty about their hepatic safety with prolonged use. If dietary fat restriction alone is not successful in resolving the chylomicronemia, fish oils have been effective in some patients. In patients with apoC-II deficiency, apoC-II can be provided by infusing fresh-frozen plasma to resolve the chylomicronemia in the acute setting. Management of patients with familial chylomicronemia syndrome is particularly challenging during pregnancy when VLDL production is increased. A gene therapy approach, called alipogene tiparvovec, is approved for LPL deficiency in Europe; it involves multiple intramuscular injections of an adeno-associated viral vector encoding a gain-of-function LPL variant, leading to skeletal myocyte expression of LPL.

APOA-V DEFICIENCY Another apolipoprotein, ApoA-V, facilitates the association of VLDL and chylomicrons with LPL and promotes their hydrolysis. Individuals harboring loss-of-function mutations in both *APOA5* alleles develop hyperchylomicronemia. Heterozygosity for variants in *APOA5* that reduce its function contributes to the polygenic basis of hypertriglyceridemia.

GPIHBP1 DEFICIENCY Homozygosity for mutations that interfere with GPIHBP1 synthesis or folding cause severe hypertriglyceridemia by compromising the transport of LPL to the vascular endothelium. The frequency of chylomicronemia due to mutations in GHIHBP1 has not been established but appears to be very rare.

FAMILIAL HYPERTRIGLYCERIDEMIA (FHTG) FHTG is characterized by elevated fasting TGs without a clear secondary cause, average to below average LDL-C levels, low HDL-C levels, and a family history of hypertriglyceridemia. Plasma LDL-C levels are often reduced due to defective conversion of TG-rich particles to LDL. In contrast to FCHL, apoB levels are not elevated. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. Unlike in FCHL, this condition is not generally associated with a significantly increased risk of CHD. However, if the hypertriglyceridemia is exacerbated by environmental factors, medical conditions, or drugs, the TGs can rise to a level at which acute pancreatitis is a risk. Indeed, management of patients with this condition is mostly geared toward reduction of TGs to prevent pancreatitis.

Individuals with this phenotype generally have reduced lipolysis of TRLs, although overproduction of VLDL by the liver can also contribute. No single gene has been identified in which mutations cause this disorder, whereas combinations of gene variants have been shown to cause this phenotype. A more appropriate term for this condition might be *polygenic hypertriglyceridemia.*

It is important to consider and rule out secondary causes of the hypertriglyceridemia as discussed above. Increased intake of simple carbohydrates, obesity, insulin resistance, alcohol use, estrogen treatment, and certain medications can exacerbate this phenotype. Patients who are at high risk for CHD due to other risk factors should be treated with statin therapy. In patients who are otherwise not at high risk for CHD, lipid-lowering drug therapy can frequently be avoided with appropriate dietary and lifestyle changes. Patients with plasma TG levels >500 mg/dL after a trial of diet and exercise should be considered for drug therapy with a fibrate or fish oil to reduce TGs in order to prevent pancreatitis.

DYSLIPIDEMIA CAUSED BY IMPAIRED HEPATIC UPTAKE OF APOB-CONTAINING LIPOPROTEINS

Impaired uptake of LDL and remnant lipoproteins by the liver is another common cause of dyslipidemia. As discussed above, the LDL receptor is the major receptor responsible for uptake of LDL and remnant particles by the liver. Downregulation of LDL receptor activity or genetic variation that reduces the activity of the LDL receptor pathway leads to elevations in LDL-C. One major factor that reduces LDL receptor activity is a diet high in saturated and *trans* fats. Other medical conditions that reduce LDL receptor activity include hypothyroidism and estrogen