mechanism of VLDL overproduction remains poorly understood but has been attributed to the effects of hypoalbuminemia leading to increased hepatic protein synthesis. Effective treatment of the underlying renal disease often normalizes the lipid profile, but most patients with chronic nephrotic syndrome require lipid-lowering drug therapy.

CUSHING'S SYNDROME (See also Chap. 406) Endogenous or exogenous glucocorticoid excess is associated with increased VLDL synthesis and secretion and hypertriglyceridemia. Patients with Cushing's syndrome frequently have dyslipidemia especially characterized by hypertriglyceridemia and low HDL-C, although elevations in plasma levels of LDL-C can also be seen.

Primary (Genetic) Causes of VLDL Overproduction Genetic variation influences hepatic VLDL production. A number of genes have been identified in which common and low-frequency variants likely contribute to increased VLDL production, likely involving interactions with diet and other environmental factors. The best recognized inherited condition associated with VLDL overproduction is familial combined hyperlipidemia.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL) FCHL is generally characterized by elevations in plasma levels of TGs (VLDL) and LDL-C (including small dense LDL) and reduced plasma levels of HDL-C. It is estimated to occur in approximately 1 in 100–200 individuals and is an important cause of premature coronary heart disease (CHD); approximately 20% of patients who develop CHD under age 60 have FCHL. FCHL can manifest in childhood but is usually not fully expressed until adulthood. The disease clusters in families, with affected family members typically have one of three possible phenotypes: (1) elevated plasma levels of LDL-C, (2) elevated plasma levels of TGs due to elevation in VLDL, or (3) elevated plasma levels of both LDL-C and TG. The lipoprotein profile can switch among these three phenotypes in the same individual over time and may depend on factors such as diet, exercise, weight, and insulin sensitivity. Patients with FCHL almost always have significantly elevated plasma levels of apoB. The levels of apoB are disproportionately high relative to the plasma LDL-C concentration, indicating the presence of small, dense LDL particles, which are characteristic of this syndrome.

Individuals with this phenotype generally share the same metabolic defect, namely overproduction of VLDL by the liver. The molecular etiology of this condition remains poorly understood, and no single gene has been identified in which mutations cause this disorder. It is likely that defects in a combination of genes can cause the condition, suggesting that a more appropriate term for the disorder might be *polygenic combined hyperlipidemia*.

The presence of a mixed dyslipidemia (plasma TG levels between 200 and 600 mg/dL and total cholesterol levels between 200 and 400 mg/dL, usually with HDL-C levels <40 mg/dL in men and <50 mg/dL in women) and a family history of mixed dyslipidemia and/or premature CHD strongly suggests the diagnosis. Individuals with this phenotype should be treated aggressively due to significantly increased risk of premature CHD. Decreased dietary intake of simple carbohydrates, aerobic exercise, and weight loss can all have beneficial effects on the lipid profile. Patients with diabetes should be aggressively treated to maintain good glucose control. Most patients with FCHL require lipid-lowering drug therapy, starting with statins, to reduce lipoprotein levels and lower the risk of cardiovascular disease.

LIPODYSTROPHY Lipodystrophy is a condition in which the generation of adipose tissue generally or in certain fat depots is impaired. Lipodystrophies are often associated with insulin resistance and elevated plasma levels of VLDL and chylomicrons due to increased fatty acid synthesis and VLDL production, as well as reduced clearance of TG-rich particles. This disorder can be especially difficult to control. Patients with congenital generalized lipodystrophy are very rare and have nearly complete absence of subcutaneous fat, accompanied by profound insulin resistance and leptin deficiency, and accumulation of TGs in multiple tissues including the liver. Some patients with generalized lipodystrophy have been treated successfully with leptin administration. Partial lipodystrophy is somewhat more common and can be caused by mutations in several different genes, most notably lamin A. Partial lipodystrophy is usually characterized by increased truncal fat accompanied by markedly reduced or absent subcutaneous fat in the extremities and buttocks. These patients generally have insulin resistance, often quite severe, accompanied by type 2 diabetes, hepatosteatosis, and dyslipidemia. The dyslipidemia is usually characterized by elevated TGs and cholesterol and can be difficult to manage clinically. Patients with partial lipodystrophy are at substantially increased risk of atherosclerotic vascular disease and should therefore be treated aggressively for their dyslipidemia with statins and, if necessary, additional lipid-lowering therapies.

DYSLIPIDEMIA CAUSED BY IMPAIRED LIPOLYSIS OF TRIGLYCERIDE-RICH LIPOPROTEINS

Impaired lipolysis of the TGs in TG-rich lipoproteins (TRLs) also commonly contributes to dyslipidemia. As noted above, LPL is the key enzyme responsible for hydrolyzing the TGs in chylomicrons and VLDL. LPL is synthesized and secreted into the extracellular space from adipocytes, myocytes, and cardiomyocytes. It is then transported from the subendothelial to the vascular endothelial surfaces by GPIHPB1. LPL is also synthesized in macrophages. Individuals with impaired LPL activity, whether secondary or due to a primary genetic disorder, have elevated fasting TGs and low levels of HDL-C, usually without elevation in LDL-C or apoB. Insulin resistance, in addition to causing excessive VLDL production, can also cause impaired LPL activity and lipolysis. A number of common and low-frequency genetic variants have been described that influence LPL activity, and single-gene Mendelian disorders that reduce LPL activity have also been described (Table 421-3).

Secondary Causes of Impaired Lipolysis of TRLs • ***OBESITY AND INSULIN RESISTANCE*** (See also Chaps. 415e, 416, and 417) In addition to hepatic overproduction of VLDL, as discussed above, obesity, insulin resistance, and type 2 diabetes have been reported to be associated with variably reduced LPL activity. This may be due in part to the effects of tissue insulin resistance leading to reduced transcription of LPL in skeletal muscle and adipose, as well as to increased production of the LPL inhibitor apoC-III by the liver. This reduction in LPL activity often contributes to the dyslipidemia seen in these patients.

Primary (Genetic) Causes and Genetic Predisposition to Impaired Lipolysis of TRLs • ***FAMILIAL CHYLOMICRONEMIA SYNDROME*** As noted above, LPL is required for the hydrolysis of TGs in chylomicrons and VLDLs, and apoC-II is a cofactor for LPL. Genetic deficiency or inactivity of either protein results in impaired lipolysis and profound elevations in plasma chylomicrons. These patients can also have elevated plasma levels of VLDL, but chylomicronemia predominates. The fasting plasma is turbid, and if left at 4°C (39.2°F) for a few hours, the chylomicrons float to the top and form a creamy supernatant. In these disorders, collectively called the *familial chylomicronemia syndrome*, fasting TG levels are almost invariably >1000 mg/dL. Fasting cholesterol levels are also elevated but to a lesser degree.

LPL deficiency has autosomal recessive inheritance and has a frequency of approximately 1 in 1 million in the population. *ApoC-II deficiency* is also recessive in inheritance pattern and is even less common than LPL deficiency. Multiple different mutations in the LPL and *APOC2* genes cause these diseases. Obligate LPL heterozygotes often have mild-to-moderate elevations in plasma TG levels, whereas individuals heterozygous for mutation in apoC-II do not have hypertriglyceridemia.

Both LPL and apoC-II deficiency usually present in childhood with recurrent episodes of severe abdominal pain due to acute pancreatitis. On funduscopic examination, the retinal blood vessels are opalescent (lipemia retinalis). Eruptive xanthomas, which are small, yellowish-white papules, often appear in clusters on the back, buttocks, and extensor surfaces of the arms and legs. These typically painless skin lesions may become pruritic. Hepatosplenomegaly results from the uptake of circulating chylomicrons by reticuloendothelial cells in the liver and spleen. For unknown reasons, some patients with persistent