therapy. Usually, patients with familial hypercholesterolemia require multiple agents to lower cholesterol levels to the target range. In patients who do not tolerate the medications or who have limited receptor function, liver transplantation to provide functional receptors, ileal bypass surgery to decrease gastrointestinal absorption of bile acids, or LDL apheresis to remove excess LDL may be considered. Both lomitapide and mipomersen may also be considered as adjuvant therapy.

Familial Defective Apolipoprotein B100

In this autosomal dominant disorder, a defect in the apo B100 protein results in impaired binding of LDL particles to the LDL receptor. The disorder affects as many as 1 in 750 Caucasians with hypercholesterolemia. The clinical presentation is similar to familial hypercholesterolemia, with elevated total cholesterol and LDL-cholesterol levels associated with premature CHD and tendon xanthomas. However, the homozygous and heterozygous clinical forms of familial defective apo B100 are milder than familial hypercholesterolemia, because apo E–mediated clearance of remnant particles is still functional. Total cholesterol concentration ranges from 350 to 550 mg/dL in the homozygous and 200 to 350 mg/dL in the heterozygous disorder. DNA analysis can identify the apo B100 gene mutation and confirm the diagnosis, but genetic diagnosis is not necessary to initiate therapy. A low-cholesterol, low-fat diet in combination with a statin, bile acid resin, and/or niacin is recommended to lower cholesterol levels to target ranges.

Elevated Plasma Lipoprotein(a)

Lp(a) is a specialized form of LDL that is assembled extracellularly from apolipoprotein(a) and LDL. Lp(a), when present at elevated levels, interferes with fibrinolysis by competing with plasminogen. This leads to decreased thrombolysis and increased clot formation. Lp(a) also binds macrophages, promoting foam cell formation and atherosclerotic plaques. Screening should be considered in individuals who have a family or personal history of premature CHD without dyslipidemia and in those for whom cholesterol-lowering therapy has failed. The diagnosis can be made by documenting Lp(a) levels higher than 30 mg/dL in a patient with premature CHD. The primary goal of therapy is to lower LDL levels with agents such as statins. If LDL goals cannot be achieved, then Lp(a)-lowering therapy with niacin and neomycin may be considered.

Polygenic Hypercholesterolemia

Hypercholesterolemia in a population is mostly due to small influences of many different genes. The exact nature of these genetic defects is poorly defined, but apo E may play a role in the pathogenesis. Apo E4 on chylomicrons and VLDL remnants has a high affinity for the LDL receptor. Elevated binding of apo E4–containing lipoproteins to LDL receptors may downregulate LDL receptor synthesis and increase circulating LDL levels. Environmental factors such as diet can influence production of chylomicrons and VLDL, resulting in downregulation of the LDL receptor in conditions with high apo E4. This leads to an increased propensity for CHD, and treatment with LDL-lowering agents is recommended based on risk factors (see Table 69-7).

Familial Combined Hyperlipoproteinemia

Familial combined hyperlipoproteinemia (FCHL) is an autosomal dominant polygenic disorder that affects 1% to 2% of the population. Factors such as diet, glucose intolerance, and medications can influence the phenotypic presentation. In FCHL, the liver synthesizes excess VLDL. VLDL is hydrolyzed by LPL to produce LDL. Mutations in the *LPL* gene affecting its expression or function can decrease the efficiency of VLDL catabolism. Dysfunction of LPL is observed in one third of patients with FCHL. Diminished LPL activity increases circulating VLDL-triglyceride; furthermore, fewer VLDL remnant particles are available for HDL synthesis. Therefore, FCHL needs to be considered in all patients whose total cholesterol level is greater than 250 mg/dL, triglycerides greater than 175 mg/dL, or HDL-cholesterol less than 35 mg/dL.

There are no definitive diagnostic tests, but family screening can help confirm the diagnosis. The phenotype of FCHL is variable, with individuals displaying high LDL-cholesterol, high VLDL-triglyceride, or both based on the genetic defect and environmental factors. Patients also typically have high apo B (>120 mg/dL) and a low ratio of LDL-cholesterol to apo B100 (<1.2). They accumulate small dense LDL particles, which are thought to be atherogenic and contribute to premature CHD. Xanthomas or xanthelasmas are not a feature of this disorder. Affected individuals require a low-fat, low-cholesterol diet plus multiple lipid-lowering drugs to achieve target goals. Fibric acid derivatives, which hydrolyze the triglyceride core of VLDL particles and increase LDL production, are recommended for treatment of the hypertriglyceridemia. Patients with FCHL often additionally require a statin or niacin to lower their LDL-cholesterol level.

Familial Dysbetalipoproteinemia

Apo E on the surface of lipoprotein particles binds LDL receptors and facilitates clearance of remnant particles from the circulation. The apo E2 allele has a lower affinity for LDL receptors than apo E3 or apo E4. In individuals who are homozygous for apo E2, LPL hydrolyzes the triglyceride core and the resulting cholesterol-rich chylomicrons. VLDL and IDL remnant particles accumulate in the circulation. Expression of this phenotype usually requires a precipitating condition that increases lipoprotein production (e.g., diabetes, alcohol consumption) or decreases clearance (e.g., hypothyroidism). In addition to the more common autosomal recessive mutation of apo E described earlier, several apo E mutations have been described that result in an autosomal dominant phenotype manifesting in childhood. Premature CHD, peripheral vascular disease, and xanthomas involving the palmer crease are characteristic clinical features. Individuals with familial dysbetalipoproteinemia have elevated levels of total cholesterol (300 to 400 mg/dL) and triglycerides (300 to 400 mg/dL). Definitive diagnosis requires genetic testing to identify apo E2 homozygosity or mutation. Treatment of coexisting conditions such as diabetes and hypothyroidism can normalize lipid levels in apo E2 homozygotes. If target levels are not achieved, dietary therapy and lipid-lowering drugs such as fibric acid derivatives and HMG-CoA reductase inhibitors should also be considered.