buttocks. The devastating consequence of homozygous FH is accelerated ASCVD, which often presents in childhood or early adulthood. Atherosclerosis often develops first in the aortic root, where it can cause aortic valvular or supravalvular stenosis, and typically extends into the coronary ostia, which become stenotic. Symptoms can be atypical, and sudden death is not uncommon. Untreated, receptor-negative patients with homozygous FH rarely survive beyond the second decade; patients with receptor-defective LDL receptor defects have a better prognosis but almost invariably develop clinically apparent atherosclerotic vascular disease by age 30, and often much sooner. Carotid and femoral disease develops later in life and is usually not clinically significant.

Homozygous FH should be suspected in a child or young adult with LDL >400 mg/dL without secondary cause. Cutaneous xanthomas, evidence of CVD, and hypercholesterolemia in both parents all are supportive of the diagnosis. Although the specific mutations in the LDL receptor can usually be identified by DNA sequencing, this is not generally performed, and the diagnosis is usually made on clinical grounds.

Patients with homozygous FH must be treated aggressively to delay the onset and progression of CVD. Receptor defective patients sometimes respond to statins and other LDL-lowering drug classes such as a cholesterol absorption inhibitor or a bile acid sequestrant, which upregulate the LDL receptor activity. Two drugs that reduce the hepatic production of VLDL and thus LDL, a small-molecule inhibitor of the microsomal TG transfer protein (MTP) and an antisense oligonucleotide to apoB, are approved in the United States for the treatment of adults with homozygous FH and can be considered. PCSK9 inhibitors, which work through increasing LDL receptor availability, appear to have some benefit in receptor-defective patients and are under clinical development. LDL apheresis is used to lower plasma LDL levels in these patients and can promote regression of xanthomas as well as slow the progression of atherosclerosis. Because the liver is quantitatively the most important tissue for removing circulating LDLs via the LDL receptor, liver transplantation is effective in decreasing plasma LDL-C levels in this disorder but is infrequently used because of the associated problems with immunosuppression.

FAMILIAL DEFECTIVE APOB-100 (FDB) FDB, also known as autosomal dominant hypercholesterolemia (ADH) type 2, is a dominantly inherited disorder that clinically resembles heterozygous FH with elevated LDL-C levels and normal TGs. FDB is caused by mutations in the gene encoding apoB-100, specifically in LDL receptor–binding domain of apoB-100. Several different mutations have been identified, but a single mutation predominates: substitution of glutamine for arginine at position 3500. The mutation results in a reduction in the affinity of LDL binding to the LDL receptor, so LDL is removed from the circulation at a reduced rate. FDB is less common than FH but is more prevalent in individuals of central European descent; the Lancaster County (United States) Amish are a founder population in which the prevalence of FDB is as high as 1 in 10 individuals. FDB is characterized by elevated plasma LDL-C levels with normal TGs; tendon xanthomas can be seen, although not as frequently as in FH, and there is an associated increase in risk of CHD. Patients with FDB cannot be clinically distinguished from patients with heterozygous FH, although patients with FDB tend to have somewhat lower plasma levels of LDL-C than FH heterozygotes, presumably due to the fact that IDL clearance is not impaired in this disorder. Homozygotes for FDB mutations have higher LDL-C levels than FDB heterozygotes but are not as severely affected as homozygous FH patients. The apoB-100 gene mutations can be detected directly through sequencing of the receptor-binding region of the apoB gene or genotyping for the most common mutation, but genetic diagnosis is not generally performed because there is no direct implication for clinical management. As with FH, patients are treated with statins first and, if necessary, with additional classes of LDL-lowering drugs.

AUTOSOMAL DOMINANT HYPERCHOLESTEROLEMIA DUE TO MUTATIONS IN PCSK9 (ADH-PCSK9 OR ADH3) ADH-PCSK9, also known as autosomal dominant hypercholesterolemia (ADH) type 3, is a very rare autosomal dominant disorder caused by gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a secreted protein that binds to the LDL receptor, targeting it for degradation. Normally, after LDL binds to the LDL receptor, it is internalized along with the receptor, and in the low pH of the endosome, the LDL receptor dissociates from the LDL and recycles to the cell surface. When PCSK9 binds the receptor, the complex is internalized and the receptor is directed to the lysosome, rather than to the cell surface. The missense mutations in PCSK9 that cause hypercholesterolemia enhance the activity of PCSK9. As a consequence, the number of hepatic LDL receptors is reduced. Patients with ADH-PCSK9 are similar clinically to patients with FH. They may be particularly responsive to PCSK9 inhibitors in clinical development. Loss-of-function mutations in PCSK9 cause low LDL-C levels (see below).

AUTOSOMAL RECESSIVE HYPERCHOLESTEROLEMIA (ARH) ARH is a very rare disorder that is mostly seen in individuals of Sardinian descent. The disease is caused by mutations in a protein, ARH (also called LDLR adaptor protein, LDLRAP), which is required for LDL receptor–mediated endocytosis in the liver. ARH binds to the cytoplasmic domain of the LDL receptor and links the receptor to the endocytic machinery. In the absence of LDLRAP, LDL binds to the extracellular domain of the LDL receptor, but the lipoprotein-receptor complex fails to be internalized. ARH, like homozygous FH, is characterized by hypercholesterolemia, tendon xanthomas, and premature coronary artery disease (CAD). The levels of plasma LDL-C tend to be intermediate between the levels present in FH homozygotes and FH heterozygotes, and CAD is not usually symptomatic until the third decade. LDL receptor function in cultured fibroblasts is normal or only modestly reduced in ARH, whereas LDL receptor function in lymphocytes and the liver is negligible. Unlike FH homozygotes, the hyperlipidemia responds to treatment with statins, but these patients usually require additional therapy to lower plasma LDL-C to acceptable levels.

SITOSTEROLEMIA Sitosterolemia is a rare autosomal recessive disease that can result in severe hypercholesterolemia, tendon xanthomas, and premature ASCVD. Sitosterolemia is caused by loss-of-function mutations in either of two members of the ATP-binding cassette (ABC) half transporter family, *ABCG5* and *ABCG8*. These genes are expressed in enterocytes and hepatocytes. The proteins heterodimerize to form a functional complex that transports plant sterols such as sitosterol and campesterol, and animal sterols, predominantly cholesterol, across the biliary membrane of hepatocytes into the bile and across the intestinal luminal surface of enterocytes into the gut lumen. In normal individuals, <5% of dietary plant sterols are absorbed by the proximal small intestine. The small amounts of plant sterols that enter the circulation are preferentially excreted into the bile. Thus, levels of plant sterols are kept very low in tissues. In sitosterolemia, the intestinal absorption of sterols is increased and biliary and fecal excretion of the sterols is reduced, resulting in increased plasma and tissue levels of both plant sterols and cholesterol. The increase in hepatic sterol levels results in transcriptional suppression of the expression of the LDL receptor, resulting in reduced uptake of LDL and substantially increased LDL-C levels. In addition to the usual clinical picture of hypercholesterolemia (i.e., tendon xanthomas and premature ASCVD), these patients also have anisocytosis and poikilocytosis of erythrocytes and megathrombocytes due to the incorporation of plant sterols into cell membranes. Episodes of hemolysis and splenomegaly are a distinctive clinical feature of this disease compared to other genetic forms of hypercholesterolemia and can be a clue to the diagnosis.

Sitosterolemia should be suspected in a patient with severe hypercholesterolemia without a family history of such or who responds dramatically to dietary therapy and/or ezetimibe but not statins. Sitosterolemia can be diagnosed by a laboratory finding of a substantial increase in the plasma level of sitosterol and/or other plant sterols. It is important to make the diagnosis, because bile acid sequestrants and cholesterol-absorption inhibitors are the most effective agents to reduce LDL-C and plasma plant sterol levels in these patients.