alcohol intake or hepatic steatosis. *HFE*-associated hemochromatosis is inherited as an autosomal recessive trait, and heterozygotes have no, or minimal, increase in iron stores. However, this slight increase in hepatic iron can act as a cofactor that may modify the expression of other diseases such as porphyria cutanea tarda (PCT) or nonalcoholic steatohepatitis (NASH).

Mutations in other genes involved in iron metabolism are responsible for non-*HFE*-associated hemochromatosis, including juvenile hemochromatosis, which affects persons in the second and third decades of life (Table 414-1). Mutations in the genes encoding hepcidin, TFR2, and hemojuvelin (Fig. 414-1) result in clinicopathologic features that are indistinguishable from *HFE*-associated hemochromatosis. However, loss-of-function mutations in ferroportin, which is responsible for the efflux of iron from most cell types, result in iron loading of reticuloendothelial macrophages as well as parenchymal cells.

■ PATHOPHYSIOLOGY AND THE ROLE OF HEPCIDIN

Normally, the body-iron content of 3–4 g is maintained such that intestinal mucosal absorption of iron is equal to iron loss. This amount is ~1 mg/d in men and 1.5 mg/d in menstruating women. In hemochromatosis, mucosal absorption is greater than body requirements and amounts to ≥4 mg/d. The progressive accumulation of iron increases plasma iron and saturation of transferrin and results in a progressive increase of plasma ferritin **(Fig. 414-2)**. The discovery of a key regulatory hormone that allows the bone marrow and other tissues to communicate their iron requirements has transformed our understanding of the coordination of absorption, mobilization, and storage of iron to meet body iron requirements. It was called hepcidin based upon its antibacterial activity ("**HEPatic** bacterio**CID**al prote**IN**"). This liver-derived peptide represses basolateral iron export from intestinal enterocytes and iron release from macrophages and other cells by binding to ferroportin. Hepcidin, in turn, responds to signals in the liver mediated by HFE, TFR2, and hemojuvelin (Fig. 414-1). The development of hepcidin agonists represents a promising new therapeutic approach for iron overload disorders caused by low hepcidin levels.