the anterior surface of the lens (lenticonus); (2) an X-linked form associated with diffuse leiomyomatosis; (3) an autosomal recessive form; and (4) an autosomal dominant form. Both autosomal recessive and dominant forms can cause renal disease without deafness or lenticonus.

Incidence The incidence of AS is about 1 in 10,000 births in the general population and as high as 1 in 5000 in some ethnic groups. About 80% of AS patients have the classical X-linked variant.

Molecular Defects Most patients have mutations in four of the six genes for the chains of type IV collagen (*COL4A3*, *COL4A4*, *COL4A5*, and *COL4A6*). The genes for the proteins are arranged in tandem pairs on different chromosomes in an unusual head-to-head orientation and with overlapping promoters; i.e., the *COL4A1* and *COL4A2* genes are head-to-head on chromosome 13q34, the *COL4A3* and *COL4A4* genes are on chromosome 2q35–37, and the *COL4A5* and *COL4A6* genes are on chromosome Xq22. The X-linked variants are caused by either mutations in the *COL4A5* gene or by partial deletions of both of the adjacent *COL4A4* and *COL4A5* genes. The autosomal recessive variants are caused by mutations in either the *COL4A3* or *COL4A4* gene. The mutations responsible for the autosomal dominant variants are still unknown, but they have been mapped to the same locus as the *COL4A3* and *COL4A4* genes.

Diagnosis The diagnosis of classic AS is based on X-linked inheritance of hematuria, sensorineural deafness, and lenticonus. The lenticonus together with hematuria is pathognomonic of classic AS. The sensorineural deafness is primarily in the high-tone range. It can frequently be detected only by an audiogram and is usually not progressive. Because of the X-linked transmission, women are generally underdiagnosed and are usually less severely affected than men. The hematuria usually progresses to nephritis and may cause renal failure in late adolescence in affected males and at older ages in some women. Renal transplantation is usually successful.

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428 Hemochromatosis

Lawrie W. Powell

DEFINITION

Hemochromatosis is a common inherited disorder of iron metabolism in which dysregulation of intestinal iron absorption results in deposition of excessive amounts of iron in parenchymal cells with eventual tissue damage and impaired function in a wide range of organs. The iron-storage pigment in tissues is called *hemosiderin* because it was believed to be derived from the blood. The term *hemosiderosis* is used to describe the presence of stainable iron in tissues, but tissue iron must be quantified to assess body-iron status accurately (see below and Chap. 126). *Hemochromatosis* refers to a group of genetic diseases that predispose to iron overload, potentially leading to fibrosis and organ failure. Cirrhosis of the liver, diabetes mellitus, arthritis, cardiomyopathy, and hypogonadotropic hypogonadism are the major clinical manifestations.

Although there is debate about definitions, the following terminology is widely accepted.

1. *Hereditary hemochromatosis* is most often caused by a mutant gene, termed *HFE*, which is tightly linked to the HLA-A locus on chromosome 6p (see "Genetic Basis," below). Persons who are homozygous for the mutation are at increased risk of iron overload and account for 80–90% of clinical hereditary hemochromatosis in persons of northern European descent. In such subjects, the presence of hepatic fibrosis, cirrhosis, arthropathy, or hepatocellular carcinoma constitutes iron overload–related disease. Rarer forms of non-*HFE* hemochromatosis are caused by mutations in other genes involved in iron metabolism (Table 428-1). The disease can be recognized during its early stages when iron overload and organ damage are minimal. At this stage, the disease is best referred to as *early hemochromatosis* or *precirrhotic hemochromatosis*.
2. *Secondary iron overload* occurs as a result of an iron-loading anemia, such as thalassemia or sideroblastic anemia, in which erythropoiesis is increased but ineffective. In the acquired iron-loading disorders, massive iron deposits in parenchymal tissues can lead to the same clinical and pathologic features as in hemochromatosis.

TABLE 428-1 CLASSIFICATION OF IRON OVERLOAD STATES

Hereditary Hemochromatosis	
Hemochromatosis, *HFE*-related (type 1)	
C282Y homozygosity	
C282Y/H63D compound heterozygosity	
Hemochromatosis, non-*HFE*-related	
Juvenile hemochromatosis (type 2A) (hemojuvelin mutations)	
Juvenile hemochromatosis (type 2B) (hepcidin mutation)	
Mutated transferrin receptor 2, *TFR2* (type 3)	
Mutated ferroportin 1 gene, *SLC11A3* (type 4)	
Acquired Iron Overload	
Iron-loading anemias	Chronic liver disease
Thalassemia major	Hepatitis C
Sideroblastic anemia	Alcoholic cirrhosis, especially when advanced
Chronic hemolytic anemias	Nonalcoholic steatohepatitis
Transfusional and parenteral iron overload	Porphyria cutanea tarda
Dietary iron overload	Dysmetabolic iron overload syndrome
	Post-portacaval shunting
Miscellaneous	
Iron overload in sub-Saharan Africa	
Neonatal iron overload	
Aceruloplasminemia	
Congenital atransferrinemia	

PREVALENCE

HFE-associated hemochromatosis mutations are among the most common inherited disease alleles, although the prevalence varies in different ethnic groups. It is most common in populations of northern European extraction in whom approximately 1 in 10 persons are heterozygous carriers and 0.3–0.5% are homozygotes. However, expression of the disease is variable and modified by several factors, especially alcohol consumption and dietary iron intake, blood loss associated with menstruation and pregnancy, and blood donation. Recent population studies indicate that approximately 30% of homozygous men develop iron overload–related disease and about 6% develop hepatic cirrhosis; for women, the figure is closer to 1%. Presumably there are as yet unidentified modifying genes responsible for expression and there is some early evidence to support this. Nearly 70% of untreated patients develop the first symptoms between ages 40 and 60. The disease is rarely evident before age 20, although with family screening (see "Screening for Hemochromatosis," below) and periodic health examinations, asymptomatic subjects with iron overload can be identified, including young menstruating women.

In contrast to *HFE*-associated hemochromatosis, the non-*HFE*-associated forms of hemochromatosis (Table 428-1) are rare, but they affect all races and young people (juvenile hemochromatosis).