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HEREDITARY HEMOCHROMATOSIS

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■ **Abstract** In recent years, the number of proteins implicated in iron homeostasis has increased dramatically, and genetic causes have apparently been identified for the major disorders associated with tissue iron overload. These dramatic steps forward have transformed the way we look at iron-related disorders, particularly hemochromatosis. This review presents a concept of this disease that is based on this new knowledge and stems from the idea that, beyond their genetic diversities, all known hemochromatoses originate from the same metabolic error, the genetic disruption of human tendency for circulatory iron constancy. Hepcidin, the iron hormone, seems to hold a central pathogenic place in hemochromatosis, similar to insulin in diabetes: Genetically determined lack of hepcidin synthesis or activity may cause the disease.

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INTRODUCTION

There is a tendency for living organisms to maintain a constant chemical and osmotic composition. Iron offers an interesting example of how the tendency for constancy in humans is realized through a highly integrated homeostatic

regulation executed by specialized importers, exporters, and under the strict control of regulatory hormones. Until recently, relatively few proteins of iron metabolism had been identified and even fewer steps of iron traffic characterized. Today, our appreciation of the complexities of human iron metabolism is much more profound and complete. In the past decade, the number of proteins implicated in iron homeostasis has increased dramatically; many of these have been characterized, their functions and regulatory pathways dissected; and genetic causes have apparently been identified for the major disorders associated with tissue iron overload. These dramatic steps forward have transformed the way we look at iron-related disorders, their pathogenesis, diagnosis, and treatment. One of the best examples is the disorder known as hemochromatosis or hereditary hemochromatosis.

The term "hemochromatosis" was coined in 1889 by von Recklinghausen (90) to describe the necroscopic finding of massive organ damage associated with dark tissue staining caused by what he believed to be a blood-borne pigment. It was Sheldon, however, in his monumental 1935 review of all cases published in the world's medical literature (87), who suggested that the disorder was probably hereditary. For much of the twentieth century, hemochromatosis was believed to be a monogenic disease (8, 18, 24, 26, 79). In 1996, Feder et al. (25) discovered a pathogenic mutation (C282Y) involving a novel major histocompatibility complex (MHC) class-I-like protein, which was present in the majority of hemochromatosis patients throughout the world. However, as genetic testing for HFE mutations became more widespread, it rapidly became clear that the situation was more complicated than previously thought. First of all, despite its remarkably high prevalence (approximately 5/1000 individuals of northern European descent) (55), C282Y homozygosity was characterized by low penetrance. Carriers are genetically predisposed to a chain of events that may (or may not) culminate in the severe and multiple organ damage seen by von Recklinghausen and Sheldon, but it is currently impossible to predict whether and to what extent this risk will be expressed (74). To further complicate matters, we have seen the discovery of other genes of iron metabolism whose mutations were associated with hereditary iron-overload syndromes with some, or many, or apparently even all of the phenotypic features of classic hemochromatosis: transferrin receptor 2 (*TfR2*) (11), hepcidin (*HAMP*) (82), hemojuvelin (*HJV*) (71), and ferroportin (*FPN*) (58, 69). Is the hemochromatosis label valid for these syndromes as well? Over the past century, the definition of HC and classification of this iron-overload disorder have been changing, evolving, stretching, and twisting to accommodate an increasingly rapid and rich succession of the new discoveries, in particular, those of the genetics era. The time has come to take stock and to reconsider the time-honored concepts in light of the recent dramatic achievements in the field. This review presents a concept of HC that is based on this new knowledge and stems from the idea that, beyond their genetic diversities, all known hemochromatoses originate from the same pathophysiologic event, the genetic disruption of hepcidin action.

TABLE 1 Distinguishing features of hemochromatosis

Hereditary (usually autosomal recessive) trait
Early and progressive increase of circulatory iron (i.e., increasing transferrin saturation)
Early and preferential iron deposition in parenchymal cells with potential for damage and diseases such as liver cirrhosis, cardiomyopathy, endocrinopathy, arthropathy
Unimpaired erythropoiesis and optimal response to phlebotomy

DEFINITION

Hemochromatosis is an iron-loading disorder caused by a genetically determined failure to prevent unneeded dietary iron from entering the circulatory pool and is characterized by progressive parenchymal iron overload with the potential for multiorgan damage and disease. As discussed below, this definition embraces the classic disorder related to HFE C282Y homozygosity (the prototype for this syndrome and by far the most common form) and the rare disorders more recently attributed to loss of TfR2, HAMP, or HJV. Four basic features define this disease (Table 1): hereditary nature (usually autosomal recessive); early and progressive expansion of the plasma iron compartment (increasing transferrin saturation); progressive parenchymal iron deposits with potential for severe damage and disease that may involve liver, endocrine glands, heart, and joints; and nonimpaired erythropoiesis and optimal response to therapeutic phlebotomy. If hemochromatosis is defined by the presence of all four of the features discussed above, other iron-overload syndromes can be excluded from this subset if they lack at least one of its defining characteristics (Table 2).

PATHOGENESIS

The Hemochromatosis Proteins

HFE HFE is a major histocompatibility class-I-like protein whose ancestral peptide-binding groove is too narrow to allow classic antigen presentation (48) while a possible nonclassic activity has been recently proposed (84). It is incapable of binding iron (25). Interaction between HFE and the transferrin receptor, TfR1, which mediates transferrin-bound iron uptake by most cells (34), has been fully documented although its biological effects are still uncertain, and it is unclear whether the interaction of HFE with TfR1 is key for the pathogenesis of HC (97) (12, 20).

The C282Y mutation (substitution of tyrosine for cysteine at position 282 due to a single-base change, 845G → A), the most common pathogenic mutation

TABLE 2 Human iron overload disorders

Hereditary	Acquired	Miscellaneous
Hereditary hemochromatosis (HFE-, TfR2-, HJV, HAMP-related)	Dietary Parental Long-term hemodialysis	African siderosis[d] Neonatal hemochromatosis[e]
Ferroportin disease	Chronic liver disease	
Aceruloplasminemia[a]	Hepatitis C and B	
Atransferrinemia[b]	Alcoholic cirrhosis	
H-ferritin-related iron overload[c]	NASH	
Hereditary iron-loading anemias	Porphyria cutanea tarda	
	Postportacaval shunting	
	Dysmetabolic iron overload syndrome	

[a]Ceruloplasmin is important in the release of iron from cells. Affected individuals present with progressive extrapyramidal signs, cerebellar ataxia, dementia, diabetes mellitus and hypochromic microcytic anemia (36, 96).

[b]Iron transport and delivery to the bone marrow is impaired. The main clinical feature is severe anemia, while tissue iron overload results from a compensatory increase in intestinal iron absorption (38).

[c]Mutation in the regulatory region of H ferritin leads to iron overload (41), but this single observation awaits validation by additional reports.

[d]Particularly frequent among Africans who drink a traditional beer brewed in nongalvanized steel drums, the disorder was once exclusively attributed to dietary excess; segregation analysis has led to the conclusion that an unidentified iron-loading gene may confer susceptibility to the disease (32, 59). One modifier gene could be ferroportin (33).

[e]Massive hepatic iron loading and generally fatal perinatal liver failure whose hereditary nature is uncertain, although familial cases have been described (16, 94).

of HFE, is associated with disruption of a disulfide bond in HFE that is critical for its binding to β2-microglobulin (91). The latter interaction is necessary for the stabilization, (intracytoplasmic) transport, and expression of HFE on the cell surface and endosomal membranes where HFE interacts with TfR1. The H63D mutation, a common HFE variant whose pathogenic significance is still uncertain, does not impair HFE-TfR1 interaction. Although the biological function of HFE is still unknown, circumstantial evidence indicates that it might be required for the synthesis of hepcidin, the iron hormone secreted by the hepatocytes (see below) [Figure 1 and Table 3].

TRANSFERRIN RECEPTOR 2 In 1999, the gene for a second human transferrin receptor (*TfR2*) was cloned (44). Unlike TfR1, the new receptor was found to be highly expressed in the liver and it was not regulated by intracellular iron status (43). TfR2 mediates the uptake of transferrin-bound iron by hepatocytes (44), possibly through the mechanism of receptor-mediated endocytosis similar to that described for TfR1, but its in vitro affinity for transferrin is 25- to 30-fold lower than that of TfR1 (93). Yet, TfR2-mediated transferrin-iron uptake may be of importance in hepatocytes, which express a low number of TfR1. The biologic role and function of TFR2 remain unknown, but recent studies suggest a role for TfR2 in hepcidin synthesis in the liver. In fact, its putative role in hepatocyte uptake of

TABLE 3 Hereditary iron overload disorders in humans

Disorder	Affected gene (symbol/location)	Known or postulated gene product function	Epidemiology	Genetics	Mechanism for cellular iron accumulation	Clinical onset (decade)	Main clinical manifestation	Clinical course
I. Hemochromatosis	Hemochromatosis gene (HFE/6p21.3)	Interaction with transferrin receptor 1 Hepcidin regulator	Affects Caucasians of northern European descent Highly prevalent	Autosomal recessive	Increased iron influx	3°–5°	Liver disease	Mild–severe
	Transferrin-receptor 2 (TfR2/7q22)	Uptake of iron-bound transferrin Hepcidin regulator	Rare					
	Hepcidin antimicrobial peptide (HAMP/19q13.1)	Down-regulation of iron efflux from macrophages, enterocytes, placenta	Rare			2°–3°	Hypogonadism and cardiac disease	Severe
	Hemojuvelin (HJV/1p21)	Hepcidin regulator	Rare					
II. Ferroportin disease	Solute carrier family 40 (iron-regulated transporter), member 1 (SLC40A1/2q32)	Iron export from cells including macrophages, intestine, placenta	Present in different ethnic groups worldwide	Autosomal dominant	Decreased iron efflux	4°–5°	Liver abnormalities Marginal anemia	Mild
III. Aceruloplasminemia	Ceruloplasmin (CP/3q23-q25)	Iron efflux from cells	Rare	Autosomal recessive	Decreased iron efflux	2°–3°	Neurologic manifestations Anemia	Severe
IV. A(hypo)transferrinemia	Transferrin (Tf/3q21)	Iron transport in the bloodstream	Rare	Autosomal recessive	Increased iron influx	1°–2°	Anemia	Severe

iron (44) is difficult to reconcile with the hemochromatosis phenotype observed in humans with pathogenic TfR2 mutations (11) and in TfR2 knockout mice (27). TfR2 does not seem to interact with HFE (93), but its persistent hepatic expression during iron overload might conceivably reflect a contribution to the modulation of hepcidin synthesis in this setting (see below) (Figure 1 and Table 3).

HEMOJUVELIN HJV is transcribed from a gene of 4265 bp into a full-length transcript with five spliced isoforms (71). Analyses of HJV in human tissues detect substantial expression in adult and fetal liver, heart, and skeletal muscle (71). The putative full-length protein is 426 amino acids; it contains a C-terminal GPI-anchor, suggesting that it can be present in either a soluble or a cell-associated form. The function of hemojuvelin is presently unknown. However, hepcidin levels are depressed in individuals with *HJV* mutations (71), and in HJV knockout mice (39), and a recent study in vitro suggests that HJV is a transcriptional regulator of hepcidin (49) (Table 3). In this study, cellular hemojuvelin positively regulated hepcidin mRNA expression, and recombinant soluble hemojuvelin suppressed hepcidin mRNA expression in primary human hepatocytes in a log-linear dose-dependent manner, suggesting binding competition between soluble and cell-associated hemojuvelin (Figure 1 and Table 3).

HEPCIDIN Hepcidin, the long-awaited iron hormone, is an antimicrobial defensin-like peptide produced by hepatocytes in response to inflammatory stimuli and iron (45, 72, 77). It is the product of the *HAMP* gene, constituted of three exons and two introns located on chromosome 7 and 19 in mouse and humans, respectively. Humans and rats have a single HAMP gene (77), whereas two functional genes, *Hamp 1* and *2,* are present in the mouse genome (65). Expression of hepcidin mRNA is nearly confined to the liver. The transcript encodes a precursor protein of 84 amino acids, including a putative 24-aa leader peptide; the circulating forms consist of only the C-terminal portion (20- and 25-amino-acid peptides) (40).

Evidence from transgenic mouse models indicates that hepcidin is the principal down-regulator of the transport of iron across the small intestine and the placenta and of its release from macrophages. Transgenic animals overexpressing hepcidin die perinatally due to severe iron-deficiency anemia occurring in the context of reticuloendothelial cell iron overload (65). In vivo injection of hepcidin into mice significantly reduced mucosal iron uptake and transfer to the carcass, independent of iron status or presence of HFE (46), or induces hypoferremia in humans (80). The present view is that hepcidin down-regulates iron efflux from intestine and macrophages by interacting with the main iron export protein in mammals, ferroportin (FPN). In fact, it has been recently shown that hepcidin binds to FPN in cultured cells stably expressing FPN and, following complex internalization, leads to FPN degradation (62). Moreover, hepcidin is highly concentrated in organs expressing FPN (80). This implies decreased FPN expression, and reduced iron egress from cells such as enterocytes and macrophages, whenever circulating

hepcidin levels are high, namely, during inflammation (66, 77) and iron overload (9, 28, 63, 77).

As to the regulatory role of iron on hepcidin synthesis, it might be that serum iron or transferrin saturation is the signal for hepcidin up-regulation, but the details of this stimulation are still obscure. In fact, exposure of cultured murine and human hepatocytes to iron salts (77) or iron-saturated transferrin (63) does not increase hepcidin mRNA and may even reduce it. At variance with their role in inflammation, Kupffer cells do not seem to be required for hepcidin stimulation during iron overload (50, 57).

The fact that mice with genetic disruption of the transcription factors upstream stimulatory factor 2 (*USF2*), *C-EBPa* or *SMAD-4*, all required for hepcidin transcriptional control, have a hemochromatotic phenotype (15, 64, 92), and humans lacking hepcidin have a severe form of HC (82), now places hepcidin at the center of the pathogenesis of HC (see below) (Figure 1 and Table 3).

The Common Metabolic Abnormality in All Forms of Hemochromatosis and the Central Pathogenic Role of Hepcidin

Iron is relatively difficult to absorb from the diet, and only about 10% of dietary iron (approximately 1 mg) is absorbed. In the blood of humans and related mammals, concentration of iron remains quite constant in the normal state, as the priority is to satisfy erythropoietic needs by delivering 20 mg of iron on a daily basis for incorporation into hemoglobin. Iron stores have a wider variation: Hepatic iron can range from 300 mg in a menstruated female to 1 g in an adult male, but can reach 25–30 g in a patient with hemochromatosis. This is because the excretion of iron is very limited, making it difficult for the organism to rid itself of an excess, except by bleeding. The only regulated step of iron metabolism is in fact at the level of intestinal iron absorption, and excess iron entering the body is efficiently stored in the liver (19).

The first biochemical manifestation of hemochromatosis is an increase in the transferrin saturation, which reflects an uncontrolled influx of iron into the bloodstream from enterocytes and macrophages. Duodenal transfer of iron to the plasma is inappropriately high for body iron stores (51). As a result, intestinal iron absorption generally exceeds iron loss by approximately 3 mg/day (88). In normal subjects, phlebotomy triggers sharp transient increases in absorption (from 1–2 mg/day to 5 mg/day), mainly to ensure bone marrow supplies. In hemochromatosis patients, this response is exaggerated (8–10 mg/day) and prolonged, sometimes lasting for years (17). The enhanced absorption of dietary iron by duodenal enterocytes plays an essential role in elevating total body iron, but macrophages are normally the source of most of the iron found in the plasma compartment (7). In hemochromatosis, these cells seem to release more iron than do their normal counterparts, and consequently they are invariably iron-poor (74). The release of iron from both duodenal cells and macrophages, which is mediated by the

iron exporter *FPN*, is normally downregulated by the hepatic iron-regulating hormone, hepcidin (62). Indeed, the iron-overload syndromes associated with *HFE*, *TfR2*, *HAMP*, and *HJV* mutations are all characterized by inadequate hepcidin synthesis (28, 61, 71, 75). Its expression in the liver is also significantly impaired in HFE, TfR2, and HJV knockout mice (39, 42, 60), and hepatic deposition of iron in HFE-KO animals can be prevented by hepcidin overexpression (67).

These findings suggest a unifying pathogenic model for all forms of HC in which HFE, TfR2, and HJV are all independent but complimentary regulators of hepcidin synthesis in the liver (Figure 1). When all three proteins function correctly (and the HAMP gene that encodes hepcidin is normal), the amount of iron transferred into the blood will be appropriate to body needs, and excessive iron deposition in tissues will be avoided (Figure 1*A*). The relative contributions of the three genes to this modulatory process may be different, with a more substantial role assigned to HJV based on the more severe iron overload phenotype associated with HJV mutations. Loss of one of the minor regulatory proteins (HFE- or TfR2-related HC) will result in an appreciable increase in iron influx into the bloodstream, but residual hepcidin activity will be sustained by the second minor regulator and the major regulator, the HJV gene (Figure 1*B*). The result is a mild "adult" hemochromatosis phenotype, with gradual plasma iron loading and gradual accumulation of iron in tissues (Figure 2). Loss of the major hepcidin regulator, HJV, will produce a more dramatic effect on influx of iron into the bloodstream (not unlike the one produced by loss of hepcidin itself) (Figure 1*C*) and result in a more severe "juvenile" HC (Figure 2). Combined loss of HFE and TfR2 (*HFE* + *TfR2*-related HC) would theoretically result in much more rapid and substantial increases in plasma iron and, consequently, greater iron overload in tissues as compared with the isolated loss of either HFE or TfR2: in short, a severe juvenile phenotype (Figure 2). In fact, a recent study has described patients with juvenile HC associated with combined mutations of HFE and TfR2 (75). Finally, the complete loss of hepcidin (*HAMP*-related HC), in spite of normal HFE, TfR2, and HJV, will inevitably lead to massive uncontrolled release of iron into the circulation. In all cases, this will be followed eventually by iron accumulation in parenchymatous organs.

THE EPIDEMIOLOGIC IMPACT

HFE-related hemochromatosis is the most common form of HC and the most frequently inherited metabolic disorder found in whites, with a prevalence of the pathogenic mutation ten times higher than that of cystic fibrosis. HFE-HC is an excellent illustration of the "founder effect," according to which a genetic disease can arise from a chance mutation occurring in a single individual, in this case a Celtic or Viking ancestor inhabiting northwestern Europe. The genetic defect, which caused no serious obstacle to reproduction and may even have conferred some advantages, was passed on and spread through population migration. The

distribution of the C282Y mutation coincides with its northern European origin and with the presence of the disease (81).

Organ disease is highly unlikely in simple C282Y heterozygotes. The clinical impact of the H63D mutation on the second HFE allele appears to be limited (31), and yet 1%–2% of compound C282Y/H63D heterozygotes seem to be predisposed to expression of the disease (81). The clinical significance of other rarer forms of compound heterozygosity, e.g., monoallelic C282Y or H63D mutation with substitution of cysteine for serine at amino-acid position 65 (S65C) or other rare changes on the second allele, is still being debated (74).

The frequency of TfR2 mutations is low, and so far, they have been detected in a few pedigrees throughout the world. TfR2 mutations do not appear to be restricted to northern Europeans. The *TFR2* gene is relatively large, spanning 21 kilobases and including 18 exons; thus, detection of new TFR2 mutations in single patients remains cumbersome. Analysis of TfR2 mutations should be especially considered in individuals with adult non-HFE hemochromatosis, particularly from families with high consanguinity.

The juvenile form of hemochromatosis is rare (Table 3). Most cases are due to mutations of *HJV* located on chromosome 2 (71). In this study, 12 families were found to be homozygous or compound heterozygous for six mutations in *HJV*. To date, 23 mutations have been identified in 43 juvenile HC families. One common mutation, G320V, has been reported in all studies. It is present in half of juvenile HC families. A small proportion of patients with the juvenile form of HC carry mutations in the gene encoding the iron regulatory peptide hepcidin on chromosome 19q13 (82).

CLINICAL EXPRESSION

Apart from menstruation, the body has no effective means of significantly reducing the plasma iron overload or preventing its progressive accumulation in the parenchymal cells of key organs. Therefore, without therapeutic intervention, there is a distinct risk in HC that, sooner or later, tissue iron overload will occur. The deposits are particularly evident in hepatocytes but may also be found in parenchymal cells of the endocrine glands and heart. This stage is reflected in increasing serum ferritin levels. The time of onset and pattern of organ involvement vary depending on the time course and magnitude of the plasma iron overload, which in turn are related to the underlying mutation. This is the basis for the distinction that is commonly made between the milder adult-onset syndromes (*HFE*- and *TfR2*-related) and the more severe juvenile-onset forms (*HJV*- and *HAMP*-related) (74) (Table 3 and Figure 2). The implied dichotomy is misleading: These forms are merely two points on a phenotypic continuum. The underlying syndrome is the same and the target organs of iron damage are also the same, namely, liver, heart, endocrine glands, and joints. Iron is abundant (even excessive) in the plasma in HC, and its transport to the bone marrow by transferrin and incorporation into hemoglobin are

unaffected by the genetic defects that cause hemochromatosis. Consequently, anemia is not a feature of this iron-overload syndrome, and therapeutic phlebotomy is tolerated quite well.

Classic HFE Hemochromatosis

HFE-related hemochromatosis is a multifactorial disease characterized by stepwise progression from biochemical abnormality to organ toxicity (74). The altered HFE protein plays an essential role in this process, but its presence alone is insufficient to explain the broad spectrum of metabolic and pathologic consequences ascribed to the disease. Expressivity of the genetic defect may lead to biochemical abnormalities, symptoms, and signs, or to overt organ disease. Early diagnosis in hemochromatosis is especially important since treatment by venesection before irreversible end-organ damage has occurred can restore a normal life expectancy (6, 68, 95).

Hemochromatosis should be suspected in a middle-aged men presenting with cirrhosis of the liver, bronze skin, diabetes and other endocrine failure, or joint inflammation and heart disease. However, this classical syndromic presentation is rare. Today diagnosis is made at earlier stages as an effect of screening and enhanced case detection due to greater clinician awareness and higher index of suspicion. The most common presenting symptoms are now fatigue, malaise, and arthralgia, while hepatomegaly is one of the earliest physical signs. Elevated serum transferrin saturation with iron, which precedes increased serum ferritin, and moderately increased transaminase levels are common biochemical abnormalities. Increasing serum ferritin levels herald iron accumulation in tissues, and values above 1000 ng/ml may indicate underlying liver fibrosis in HFE-HC, even when transaminase levels are normal (35). Figure 3 proposes a diagnostic algorithm for patients presenting with unexplained hyperferritinemia. Once the diagnosis of HFE-HC is established, all family members, particularly siblings, should be subjected to a thorough biochemical and clinical evaluation, and genetic testing is advisable for adult first-degree relatives. Further details on HFE-HC are available elsewhere (78, 89).

Although all patients with overt HFE-related HC (i.e., with organ damage) carry the C282Y mutation on both HFE alleles, some C282Y homozygotes present no evidence of organ disease or biochemical abnormalities, although they should still be considered to be at increased risk. It is currently impossible to predict whether (and to what extent) a C282Y homozygote will express the disease phenotype. At present, we can only conclude that although the majority of C282Y homozygotes have laboratory evidence of plasma and tissue iron overload (i.e., high transferrin saturation and ferritin levels, respectively), organ disease requiring medical treatment is much less common today (2, 3, 5, 10, 70).

Although clinical descriptions of TfR2-related HC are currently limited, patients with TfR2 mutations almost invariably present signs of significant hepatic iron overload and express a systemic iron-loading syndrome almost indistinguishable from that of HFE hemochromatosis (11, 29, 37, 52, 75, 83).

Juvenile Hemochromatosis

The rather vague term "juvenile hemochromatosis" has been used to refer to a form of hereditary iron overload with a development pattern resembling that of adult HC but which is more rapidly progressive. Because of the higher rate of iron loading associated with this disorder (and possibly differential tissue sensitivities to this massive toxic insult), cardiomyopathy and endocrinopathy, including reduced glucose tolerance, appear earlier than they do in adult HC, and death before the age of 30 is not uncommon (13, 47). We now know that this syndrome is usually associated with HJV or, in rarer cases, HAMP mutations (Table 3). The commonest symptom at presentation is hypogonadism, which, at the end of the second decade, may be present in all cases. In sporadic cases, abdominal pain and cardiac disease also represent common findings; liver cirrhosis is recognized at later stages, although silent micronodular cirrhosis is part of the syndrome.

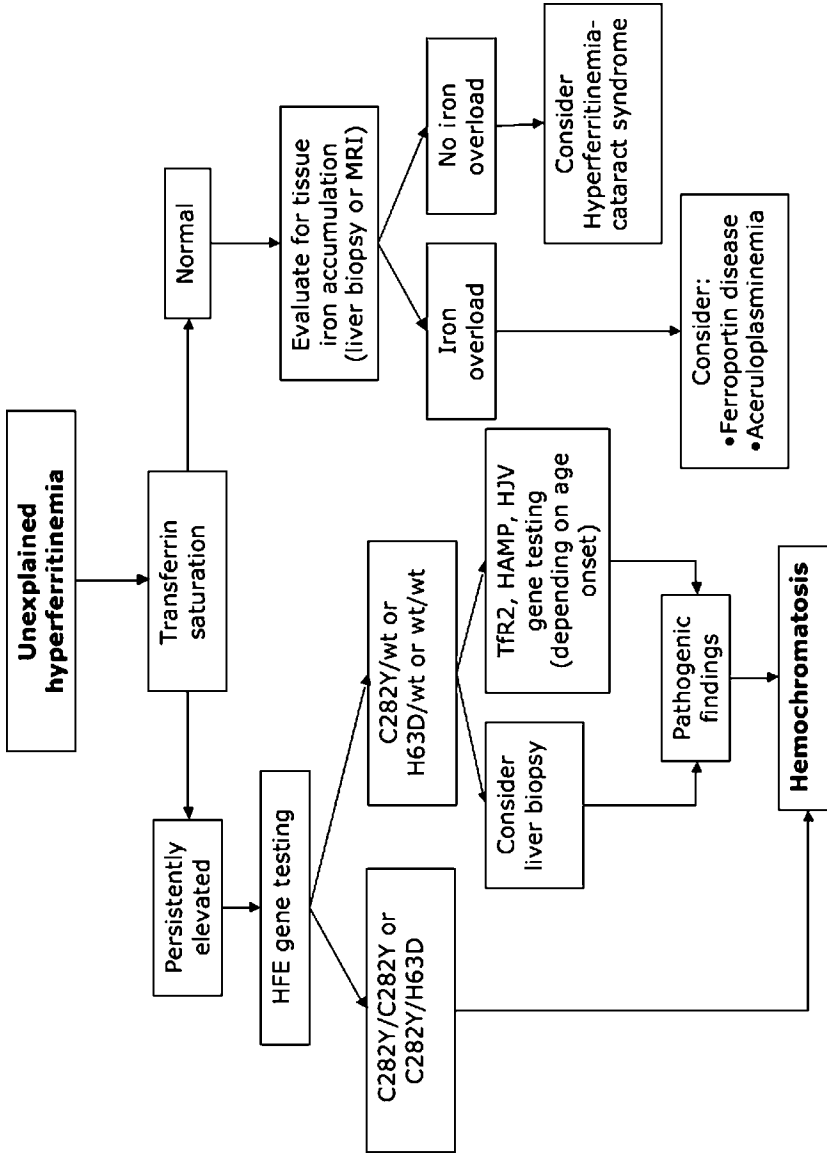
Increased risk of clinically expressed disease has already been documented in patients with heterozygous mutations of both *HFE* and *HAMP* (54). Reports of uncharacteristically severe disease in patients who apparently have TfR2 mutations alone, or in combination with HFE variants, might also be accounted for by undetected mutations of other hereditary hemochromatosis genes. The variety of genotypes that can produce a hereditary hemochromatosis phenotype highlights the importance of defining and classifying this disease as a unique clinicopathologic entity.

Therapy

Therapeutic phlebotomy is the safest, most effective, and most economical approach to treatment. It can normalize life expectancy if initiated before organ damage has occurred. One unit (400–500 ml) of blood (containing approximately 200–250 mg of iron) is removed weekly until serum ferritin is less than 20–50μg/L and transferrin saturation drops below 30%. Maintenance therapy, which typically involves removal of 2–4 units a year, can then be initiated and it must be continued for the duration of the patient's life to keep transferrin saturation and ferritin normal. As noted above, phlebotomy has little effect if started after organ impairment has already developed: The hypogonadism, cirrhosis, destructive arthritis, and insulin-dependent diabetes associated with HC are usually irreversible. Only if phlebotomy is contraindicated or nontolerated should other iron removal strategies (e.g., use of deferoxamine or other iron chelators) be considered.

FERROPORTIN DISEASE

Ferroportin disease (FD) (Tables 2 and 3) is a hereditary iron storage disease distinct from HC. It is an autosomal-dominant inherited disorder of iron metabolism (all affected patients carry a heterozygote pathogenic mutation of FPN) that causes progressive iron retention predominantly in reticuloendothelial cells of the spleen



and liver and is characterized by a steady increase of serum ferritin, inappropriately high as compared with the extent of serum transferrin saturation, marginal anemia, and mild organ disease (73).

The disorder was described clinically in 1999 (76) and was associated with the A77D mutation of FPN in 2001 (58, 69). The disorder has been now reported in many countries and, at variance with the distribution of the HFE gene mutations that appear to be restricted to Caucasians of northern European ancestry, it appears to be spread worldwide in different ethnic groups (73) (Table 3).

FPN is the main iron export protein in mammals. It is expressed in several cell types that play critical roles in mammalian iron metabolism, including placental syncytiotrophoblasts, duodenal enterocytes, hepatocytes, and reticuloendothelial macrophages (1, 22, 53). In vitro, as mentioned above, FPN has been found to be the cellular receptor for hepcidin (62) (Figure 1).

A current pathogenic model for FD is that loss-of-function mutations of FPN cause a mild but significant impairment of iron recycling, particularly by

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Figure 3 Diagnostic algorithm for hereditary hyperferritinemia. In the presence of unexplained hyperferritinemia (i.e., unrelated to inflammation, cancer, metabolic syndrome, or other secondary causes), transferrin saturation should be checked. Hereditary hemochromatosis should be suspected when fasting transferrin saturation levels are above 45%–50% (or 35% in premenopausal females) on at least two consecutive occasions. When other causes for elevated saturation levels (e.g., hepatic cytolysis causing high serum iron, liver failure causing low levels of transferrin) have been excluded, first-line genetic testing for C282Y and H63D mutations of HFE should be considered: A C282Y/C282Y or C282Y/H63D genotype confirms the diagnosis of hereditary hemochromatosis. Second-line genetic testing should be considered for patients with other *HFE* genotypes, also based on age of onset and clinical presentation. Adults with normal, i.e., wild-type (wt), HFE may have pathogenic mutations of *TfR2*; simple heterozygotes (C282Y/wt, H63D/wt) may have rarer *HFE* mutations or an additional heterozygous mutation of some other iron gene. A helpful addition is liver biopsy, which can also be performed if second-line genetic tests are negative. In the absence of other obvious causes of iron overload (e.g., iron-loading anemia with inefficient erythropoiesis), biopsy findings of parenchymal iron distribution with a periportal-to-central gradient, and a hepatic iron index (hepatic iron concentration in μM/gram dry weight divided by age in years) above 1.9 are strongly suggestive of hemochromatosis. For young adults with signs of juvenile-onset disease (hypogonadotropic hypogonadism and/or unexplained heart failure), the biochemical work-up is identical. First-line gene testing in these cases, however, consists of *HAMP* and *HJV* sequencing. Normal transferrin saturation in subjects with unexplained hyperferritinemia should not exclude a hereditary iron-loading disease. The presence of tissue iron overload, as detected by liver biopsy or magnetic resonance imaging, should prompt genetic testing for ferroportin disease. Other rarer disorders (i.e., aceruloplasminemia) can be also considered based on clinical findings.

reticuloendothelial macrophages (58), which normally must process and release a large quantity of iron derived from the lysis of senescent erythrocytes (Figure 1*D*). The FPN defect may not be limiting for iron transport in the enterocyte (Figure 1*C*), which handles a relatively low amount of iron on a daily basis; therefore, a sufficient iron transport may be still guaranteed by the residual PFN protein activity. In fact, enterocytes do not show excess iron deposits in FD (14). Consequently, iron retention by macrophages would lead to tissue iron accumulation (i.e., high serum ferritin) but decreased availability of iron for circulating transferrin (i.e., low transferrin saturation) and for bone marrow. At later stages, both iron retention in cells and activation of feedback mechanisms to increase intestinal absorption might contribute to more pronounced iron overload. This pathophysiologic model is consistent with the finding that patients with mutations in FPN have much larger reticuloendothelial iron stores than do patients with HC. Although the patients are not anemic in adulthood, indicating that adequate iron is available for normal erythropoiesis, they may show a reduced tolerance to phlebotomy and become anemic from therapy in spite of persistently elevated serum ferritin values (58, 76) (Table 3). It is possible that different mutations along the protein will differently affect the function of FPN and indirectly lead to variability in clinical expressivity. In this context, anecdotal evidence suggests that mutation of this gene can also be associated with parenchymal iron overload that closely resembles that of *HFE*-related hemochromatosis (86). In addition, recent in vitro studies suggest that a subgroup of ferroportin mutations might lead to hepcidin "resistance" and increased rather than diminished iron export (21, 23, 85). Therefore, a subgroup of patients with FD may carry gain-of-function mutations that lead to enhanced iron release from enterocytes and macrophages and a phenotype similar to classic HC. This hypothesis cannot be ruled out a priori, but it awaits validation from additional experimental data and more extensive clinical studies.

Although phlebotomy is an effective therapeutic tool, a weekly phlebotomy program is not tolerated in some individuals, and slight anemia and low transferrin saturation are rapidly reached despite a still elevated serum ferritin level. With a less aggressive phlebotomy regimen, they can also be iron depleted, although a therapeutic target of serum ferritin <30 ng/ml, adopted for classical hemochromatosis, should be avoided due to the risk of anemia. Adjuvant therapy with erythropoietin may be beneficial. Discontinuation of phlebotomy treatment is followed by a rapid rise of serum ferritin.

FD should be suspected in all cases of familial hyperferritinemia or in sporadic cases in the absence of known secondary causes (such as infection, dysmetabolism, inflammation, and malignancy) (Figure 3). Differential diagnosis should also consider the rare form of familial hyperferritinemia-congenital cataract syndrome, which is not associated with the tissue iron overload (4, 30), aceruloplasminemia (36, 96), and dysmetabolic hepatosiderosis (56) present in dyslipidemic individuals.

CONCLUSIONS

The basic features of the hereditary hemochromatosis syndrome, as we recognize it today, can be produced by pathogenic mutations of at least four different iron metabolism genes. Since the common pathogenic denominator of all forms of HC is the uncontrolled expansion of the plasma iron pool, mutations in other known or unknown genes affecting this iron compartment may very well lead to the same syndrome. Depending on the gene involved and its physiological role in iron homeostasis, the phenotype of HC varies, ranging from massive early-onset iron loading with severe organ disease (e.g., associated with homozygous mutations of HAMP or HJV) to the milder late-onset phenotype characterizing classic HFE- and TfR2-related forms. Phenotypes on the latter end of the spectrum are also particularly subject to the modifying effects of host-related and environmental factors, such as dietary iron, alcohol consumption, and viral hepatitis (74). "Intermediate" phenotypes could result from combined heterozygous or homozygous mutations of multiple hemochromatosis genes (Figure 2). In vitro and in vivo studies will be needed to dissect the biochemical consequences of each hereditary hemochromatosis allele and to increase our understanding of the precise contribution of each gene to the hereditary hemochromatosis phenotype.

In conclusion, except for hepcidin, the precise function for all other HC proteins is still unknown. Intriguingly, HFE, the most important HC protein, is unable to bind or transport iron, and likely has a marginal role in iron homeostasis, whereas all other HC genes, involved in very rare diseases, seem much more fundamental to iron traffic. Hepcidin, the iron hormone, holds a central role in iron homeostasis, similar to insulin in glucose metabolism. As in the case of insulin in diabetes, it appears now that genetic defect(s) leading to either lack of hepcidin (i.e., classic hemochromatosis) or hepcidin resistance (i.e., atypical ferroportin disease) results in disruption of the tendency for circulatory iron constancy and causes the disease known as hereditary hemochromatosis.

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LITERATURE CITED

1. Abboud S, Haile DJ. 2000. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. *J. Biol. Chem.* 275:19906–12
2. Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, et al. 2005. Hemochromatosis and iron-overload screening in a racially diverse population. *N. Engl. J. Med.* 352:1769–78
3. Asberg A, Hveem K, Thorstensen K, Ellekjter E, Kannelonning K, et al. 2001. Screening for hemochromatosis:

high prevalence and low morbidity in an unselected population of 65,238 persons. *Scand. J. Gastroenterol.* 36:1108–15

4. Beaumont C, Leneuve P, Devaux I, Scoazec JY, Berthier M, et al. 1995. Mutation in the iron responsive element of the L ferritin mRNA in a family with dominant hyperferritinaemia and cataract. *Nat. Genet.* 11:444–46
5. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. 2002. Penetrance of 845G → A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 359:211–18
6. Bomford A, Williams R. 1976. Long term results of venesection therapy in idiopathic haemochromatosis. *Q. J. Med.* 45:611–23
7. Bothwell TH. 1995. Overview and mechanisms of iron regulation. *Nutr. Rev.* 53:237–45
8. Bothwell TH, Abrahams C, Bradlow BA, Charlton RW. 1965. Idiopathic and Bantu hemochromatosis. *Arch. Pathol.* 79:163–68
9. Bridle KR, Frazer DM, Wilkins SJ, Dixon JL, Purdie DM, et al. 2003. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homoeostasis. *Lancet* 361:669–73
10. Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, et al. 2000. Disease-related conditions in relatives of patients with hemochromatosis. *N. Engl. J. Med.* 343:1529–35
11. Camaschella C, Roetto A, Cali A, De Gobbi M, Garozzo G, et al. 2000. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. *Nat. Genet.* 25:14–15
12. Carlson H, Zhang AS, Fleming WH, Enns CA. 2005. The hereditary hemochromatosis protein, HFE, lowers intracellular iron levels independently of transferrin receptor 1 in TRVb cells. *Blood* 105:2564–70
13. Cazzola M, Ascari E, Barosi G, Claudiani G, Dacco M, et al. 1983. Juvenile idiopathic haemochromatosis: a life-threatening disorder presenting as hypogonadotropic hypogonadism. *Hum. Genet.* 65:149–54
14. Corradini E, Montosi G, Ferrara F, Caleffi A, Pignatti E, et al. 2005. Lack of enterocyte iron accumulation in the ferroportin disease. *Blood Cells Mol. Dis.* 35:315–18
15. Courselaud B, Pigeon C, Inoue Y, Inoue J, Gonzalez FJ, et al. 2002. C/EBPalpha regulates hepatic transcription of hepcidin, an antimicrobial peptide and regulator of iron metabolism. Cross-talk between C/EBP pathway and iron metabolism. *J. Biol. Chem.* 277:41163–70
16. Cox TM, Halsall DJ. 2002. Hemochromatosis-neonatal and young subjects. *Blood Cells Mol. Dis.* 29:411–17
17. Crosby WH. 1963. The control of iron balance by the intestinal mucosa. *Blood* 22:441–49
18. Crosby WH. 1977. Hemochromatosis: the unsolved problems. *Semin. Hematol.* 14:135–43
19. Crosby WH, Conrad ME Jr, Wheby MS. 1963. The rate of iron accumulation in iron storage disease. *Blood* 22:429–40
20. Davies PS, Zhang AS, Anderson EL, Roy CN, Lampson MA, et al. 2003. Evidence for the interaction of the hereditary haemochromatosis protein, HFE, with the transferrin receptor in endocytic compartments. *Biochem. J.* 373:145–53
21. De Domenico I, Ward DM, Nemeth E, Vaughn MB, Musci G, et al. 2005. The molecular basis of ferroportin-linked hemochromatosis. *Proc. Natl. Acad. Sci. USA* 102:8955–60
22. Donovan A, Brownlie A, Zhou Y, Shepard J, Pratt SJ, et al. 2000. Positional cloning of zebrafish ferroportin1 identifies a conserved vertebrate iron exporter. *Nature* 403:776–81
23. Drakesmith H, Schimanski LM, Ormerod E, Merryweather-Clarke AT, Viprakasit V, et al. 2005. Resistance to hepcidin is conferred by hemochromatosis-associated mutations of ferroportin. *Blood* 106:1092–97
24. Edwards CQ, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner

JP. 1988. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N. Engl. J. Med.* 318:1355–62
25. Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, et al. 1996. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis *Nat. Genet.* 13:399–408
26. Finch S, Finch C. 1955. Idiopathic hemochromatosis, an iron storage disease: A. Iron metabolism in hemochromatosis. *Medicine* 34:381–430
27. Fleming RE, Ahmann JR, Migas MC, Waheed A, Koeffler HP, et al. 2002. Targeted mutagenesis of the murine transferrin receptor-2 gene produces hemochromatosis. *Proc. Natl. Acad. Sci. USA* 99:10653–58
28. Gehrke SG, Kulaksiz H, Herrmann T, Riedel HD, Bents K, et al. 2003. Expression of hepcidin in hereditary hemochromatosis: evidence for a regulation in response to serum transferrin saturation and non-transferrin-bound iron. *Blood* 102:371–76
29. Girelli D, Bozzini C, Roetto A, Alberti F, Daraio F, et al. 2002. Clinical and pathologic findings in hemochromatosis type 3 due to a novel mutation in transferrin receptor 2 gene. *Gastroenterology* 122:1295–302
30. Girelli D, Corrocher R, Bisceglia L, Olivieri O, De Franceschi L, et al. 1995. Molecular basis for the recently described hereditary hyperferritinemia-cataract syndrome: a mutation in the iron-responsive element of ferritin L-subunit gene (the "Verona mutation"). *Blood* 86:4050–53
31. Gochee PA, Powell LW, Cullen DJ, Du Sart D, Rossi E, Olynyk JK. 2002. A population-based study of the biochemical and clinical expression of the H63D hemochromatosis mutation. *Gastroenterology* 122:646–51
32. Gordeuk VR. 2002. African iron overload. *Semin. Hematol.* 39:263–69
33. Gordeuk VR, Caleffi A, Corradini E, Ferrara F, Jones RA, et al. 2003. Iron overload in Africans and African-Americans and a common mutation in the SCL40A1 (ferroportin 1) gene. *Blood Cells Mol. Dis.* 31:299–304
34. Gross CN, Irrinki A, Feder JN, Enns CA. 1998. Co-trafficking of HFE, a nonclassical major histocompatibility complex class I protein, with the transferrin receptor implies a role in intracellular iron regulation. *J. Biol. Chem.* 273:22068–74
35. Guyader D, Jacquelinet C, Moirand R, Turlin B, Mendler MH, et al. 1998. Non-invasive prediction of fibrosis in C282Y homozygous hemochromatosis. *Gastroenterology* 115:929–36
36. Harris ZL, Takahashi Y, Miyajima H, Serizawa M, MacGillivray RT, Gitlin JD. 1995. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. *Proc. Natl. Acad. Sci. USA* 92:2539–43
37. Hattori A, Wakusawa S, Hayashi H, Harashima A, Sanae F, et al. 2003. AVAQ 594–597 deletion of the TfR2 gene in a Japanese family with hemochromatosis. *Hepatol. Res.* 26:154–56
38. Hayashi A, Wada Y, Suzuki T, Shimizu A. 1993. Studies on familial hypotransferrinemia—unique clinical course and molecular pathology. *Am. J. Hum. Genet.* 53:201–13
39. Huang FW, Pinkus JL, Pinkus GS, Fleming MD, Andrews NC. 2005. A mouse model of juvenile hemochromatosis. *J. Clin. Invest.* 115:2187–91
40. Hunter HN, Fulton DB, Ganz T, Vogel HJ. 2002. The solution structure of human hepcidin, a peptide-hormone with antimicrobial activity that is involved in iron uptake and hereditary hemochromatosis. *J. Biol. Chem.* 40:37597–603
41. Kato J, Fujikawa K, Kanda M, Fukuda N, Sasaki K, et al. 2001. A mutation, in the iron-responsive element of H ferritin mRNA, causing autosomal dominant iron overload. *Am. J. Hum. Genet.* 69:191–97
42. Kawabata H, Fleming RE, Gui D, Moon SY, Saitoh T, et al. 2005. Expression of hepcidin is down-regulated in TfR2 mutant

mice manifesting a phenotype of hereditary hemochromatosis. *Blood* 105:376–81
43. Kawabata H, Germain RS, Vuong PT, Nakamaki T, Said JW, Koeffler HP. 2000. Transferrin receptor 2-alpha supports cell growth both in iron-chelated cultured cells and in vivo. *J. Biol. Chem.* 275:16618–25
44. Kawabata H, Yang R, Hirama T, Vuong PT, Kawano S, et al. 1999. Molecular cloning of transferrin receptor 2. A new member of the transferrin receptor-like family. *J. Biol. Chem.* 274:20826–32
45. Krause A, Neitz S, Magert HJ, Schulz A, Forssmann WG, et al. 2000. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. *FEBS Lett.* 480:147–50
46. Laftah AH, Ramesh B, Simpson RJ, Solanky N, Bahram S, et al. 2004. Effect of hepcidin on intestinal iron absorption in mice. *Blood* 103:3940–44
47. Lamon JM, Marynick SP, Roseblatt R, Donnelly S. 1979. Idiopathic hemochromatosis in a young female. A case study and review of the syndrome in young people. *Gastroenterology* 76:178–83
48. Lebron JA, Bennett MJ, Vaughn DE, Chirino AJ, Snow PM, et al. 1998. Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor. *Cell* 93:111–23
49. Lin L, Goldberg YP, Ganz T. 2005. Competitive regulation of hepcidin mRNA by soluble and cell-associated hemojuvelin. *Blood* 106:2884–89
50. Lou DQ, Lesbordes JC, Nicolas G, Viatte L, Bennoun M, et al. 2005. Iron- and inflammation-induced hepcidin gene expression in mice is not mediated by Kupffer cells in vivo. *Hepatology* 41:1056–64
51. Lynch SR, Skikne BS, Cook JD. 1989. Food iron absorption in idiopathic hemochromatosis. *Blood* 74:2187–93
52. Mattman A, Huntsman D, Lockitch G, Langlois S, Buskard N, et al. 2002. Transferrin receptor 2 (TfR2) and HFE mutational analysis in non-C282Y iron overload: identification of a novel TfR2 mutation. *Blood* 100:1075–77
53. McKie AT, Marciani P, Rolfs A, Brennan K, Wehr K, et al. 2000. A novel duodenal iron-regulated transporter, IREG1, implicated in the basolateral transfer of iron to the circulation. *Mol. Cell* 5:299–309
54. Merryweather-Clarke AT, Cadet E, Bomford A, Capron D, Viprakasit V, et al. 2003. Digenic inheritance of mutations in HAMP and HFE results in different types of haemochromatosis. *Hum. Mol. Genet.* 12:2241–47
55. Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJH. 1997. Global prevalence of putative haemochromatosis mutations. *J. Med. Genet.* 34(4):275–78
56. Moirand R, Mortaji AM, Loreal O, Paillard F, Brissot P, Deugnier Y. 1997. A new syndrome of liver iron overload with normal transferrin saturation. *Lancet* 349(9045):95–97
57. Montosi G, Corradini E, Garuti C, Barelli S, Recalcati S, et al. 2005. Kupffer cells and macrophages are not required for hepatic hepcidin activation during iron overload. *Hepatology* 41:545–52
58. Montosi G, Donovan A, Totaro A, Garuti C, Pignatti E, et al. 2001. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. *J. Clin. Invest.* 108:619–23
59. Moyo VM, Mandishona E, Hasstedt SJ, Gangaidzo IT, Gomo ZA, et al. 1998. Evidence of genetic transmission in African iron overload. *Blood* 91:1076–82
60. Muckenthaler M, Roy CN, Custodio AO, Minana B, de Graaf J, et al. 2003. Regulatory defects in liver and intestine implicate abnormal hepcidin and Cybrd1 expression in mouse hemochromatosis. *Nat. Genet.* 34:102–7
61. Nemeth E, Roetto A, Garozzo G, Ganz T, Camaschella C. 2005. Hepcidin is decreased in TFR2 hemochromatosis. *Blood* 105:1803–6
62. Nemeth E, Tuttle MS, Powelson J, Vaughn

MB, Donovan A, et al. 2004. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 306:2090–93

63. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. 2003. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood* 101:2461–63
64. Nicolas G, Bennoun M, Devaux I, Beaumont C, Grandchamp B, et al. 2001. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proc. Natl. Acad. Sci. USA* 98:8780–85
65. Nicolas G, Bennoun M, Porteu A, Mativet S, Beaumont C, et al. 2002. Severe iron deficiency anemia in transgenic mice expressing liver hepcidin. *Proc. Natl. Acad. Sci. USA* 99:4596–601
66. Nicolas G, Chauvet C, Viatte L, Danan JL, Bigard X, et al. 2002. The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J. Clin. Invest.* 110:1037–44
67. Nicolas G, Viatte L, Lou DQ, Bennoun M, Beaumont C, et al. 2003. Constitutive hepcidin expression prevents iron overload in a mouse model of hemochromatosis. *Nat. Genet.* 34:97–101
68. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. 1985. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N. Engl. J. Med.* 313:1256–62
69. Njajou OT, Vaessen N, Joosse M, Berghuis B, van Dongen JW, et al. 2001. A mutation in SLC11A3 is associated with autosomal dominant hemochromatosis. *Nat. Genet.* 28:213–14
70. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. 1999. A population-based study of the clinical expression of the hemochromatosis gene. *N. Engl. J. Med.* 341:718–24
71. Papanikolaou G, Samuels ME, Ludwig EH, MacDonald ML, Franchini PL, et al. 2004. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. *Nat. Genet.* 36:77–82
72. Park CH, Valore EV, Waring AJ, Ganz T. 2001. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J. Biol. Chem.* 276:7806–10
73. Pietrangelo A. 2004. The ferroportin disease. *Blood Cells Mol. Dis.* 32:131–38
74. Pietrangelo A. 2004. Hereditary hemochromatosis—a new look at an old disease. *N. Engl. J. Med.* 350:2383–97
75. Pietrangelo A, Caleffi A, Henrion J, Ferrara F, Corradini E, et al. 2005. Juvenile hemochromatosis associated with pathogenic mutations of adult hemochromatosis genes. *Gastroenterology* 128:470–79
76. Pietrangelo A, Montosi G, Totaro A, Garuti C, Conte D, et al. 1999. Hereditary hemochromatosis in adults without pathogenic mutations in the hemochromatosis gene. *N. Engl. J. Med.* 341:725–32
77. Pigeon C, Ilyin G, Courselaud B, Leroyer P, Turlin B, et al. 2001. A new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J. Biol. Chem.* 276:7811–19
78. Powell LW. 2002. Diagnosis of hemochromatosis. *Semin. Gastrointest. Dis.* 13:80–88
79. Powell LW, Bassett ML, Halliday JW. 1980. Hemochromatosis: 1980 update. *Gastroenterology* 78:374–81
80. Rivera S, Nemeth E, Gabayan V, Lopez MA, Farshidi D, Ganz T. 2005. Synthetic hepcidin causes rapid dose-dependent hypoferremia and is concentrated in ferroportin-containing organs. *Blood* 106:2196–99
81. Rochette J, Pointon JJ, Fisher CA, Perera G, Arambepola M, et al. 1999. Multicentric origin of hemochromatosis gene (HFE) mutations. *Am. J. Hum. Genet.* 64:1056–62; erratum 64:1491
82. Roetto A, Papanikolaou G, Politou M, Alberti F, Girelli D, et al. 2003. Mutant

antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis. *Nat. Genet.* 33:21–22
83. Roetto A, Totaro A, Piperno A, Piga A, Longo F, et al. 2001. New mutations inactivating transferrin receptor 2 in hemochromatosis type 3. *Blood* 97:2555–60
84. Rohrlich PS, Fazilleau N, Ginhoux F, Firat H, Michel F, et al. 2005. Direct recognition by alphabeta cytolytic T cells of Hfe, a MHC class Ib molecule without antigen-presenting function. *Proc. Natl. Acad. Sci. USA* 102:12855–60
85. Schimanski LM, Drakesmith H, Merryweather-Clarke AT, Viprakasit V, Edwards JP, et al. 2005. In vitro functional analysis of human ferroportin (FPN) and hemochromatosis-associated FPN mutations. *Blood* 105:4096–102
86. Sham RL, Phatak PD, West C, Lee P, Andrews C, Beutler E. 2005. Autosomal dominant hereditary hemochromatosis associated with a novel ferroportin mutation and unique clinical features. *Blood Cells Mol. Dis.* 34:157–61
87. Sheldon J. 1935. *Haemochromatosis*. London: Oxford Univ. Press
88. Smith PM, Godfrey BE, Williams R. 1969. Iron absorption in idiopathic haemochromatosis and its measurement using a whole-body counter. *Clin. Sci.* 37:519–31
89. Tavill AS. 2001. Diagnosis and management of hemochromatosis. *Hepatology* 33:1321–28
90. von Recklinghausen FD. 1889. Über hämochromatose. *Taggeblatt der Versammlung deutscher Naturforscher und Aerzte, Heidelberg* 62:324–25
91. Waheed A, Parkkila S, Zhou XY, Tomatsu S, Tsuchihashi Z, et al. 1997. Hereditary hemochromatosis: effects of C282Y and H63D mutations on association with beta(2)-microglobulin, intracellular processing, and cell surface expression of the HFE protein in COS-7 cells. *Proc. Natl. Acad. Sci. USA* 94:12384–89
92. Wang RH, Li C, Xu X, Zheng Y, Xiao C, et al. 2005. A role of SMAD4 in iron metabolism through the positive regulation of hepcidin expression. *Cell. Metab.* 6:399–409
93. West AP Jr, Bennett MJ, Sellers VM, Andrews NC, Enns CA, Bjorkman PJ. 2000. Comparison of the interactions of transferrin receptor and transferrin receptor 2 with transferrin and the hereditary hemochromatosis protein HFE. *J. Biol. Chem.* 275:38135–38
94. Whitington PF, Malladi P. 2005. Neonatal hemochromatosis: Is it an alloimmune disease? *J. Pediatr. Gastroenterol. Nutr.* 40:544–49
95. Wojcik JP, Speechley MR, Kertesz AE, Chakrabarti S, Adams PC. 2002. Natural history of C282Y homozygotes for hemochromatosis. *Can. J. Gastroenterol.* 16:297–302
96. Yoshida K, Furihata K, Takeda S, Nakamura A, Yamamoto K, et al. 1995. A mutation in the ceruloplasmin gene is associated with systemic hemosiderosis in humans. *Nat. Genet.* 9:267–72
97. Zhang AS, Davies PS, Carlson HL, Enns CA. 2003. Mechanisms of HFE-induced regulation of iron homeostasis: insights from the W81A HFE mutation. *Proc. Natl. Acad. Sci. USA* 100:9500–5

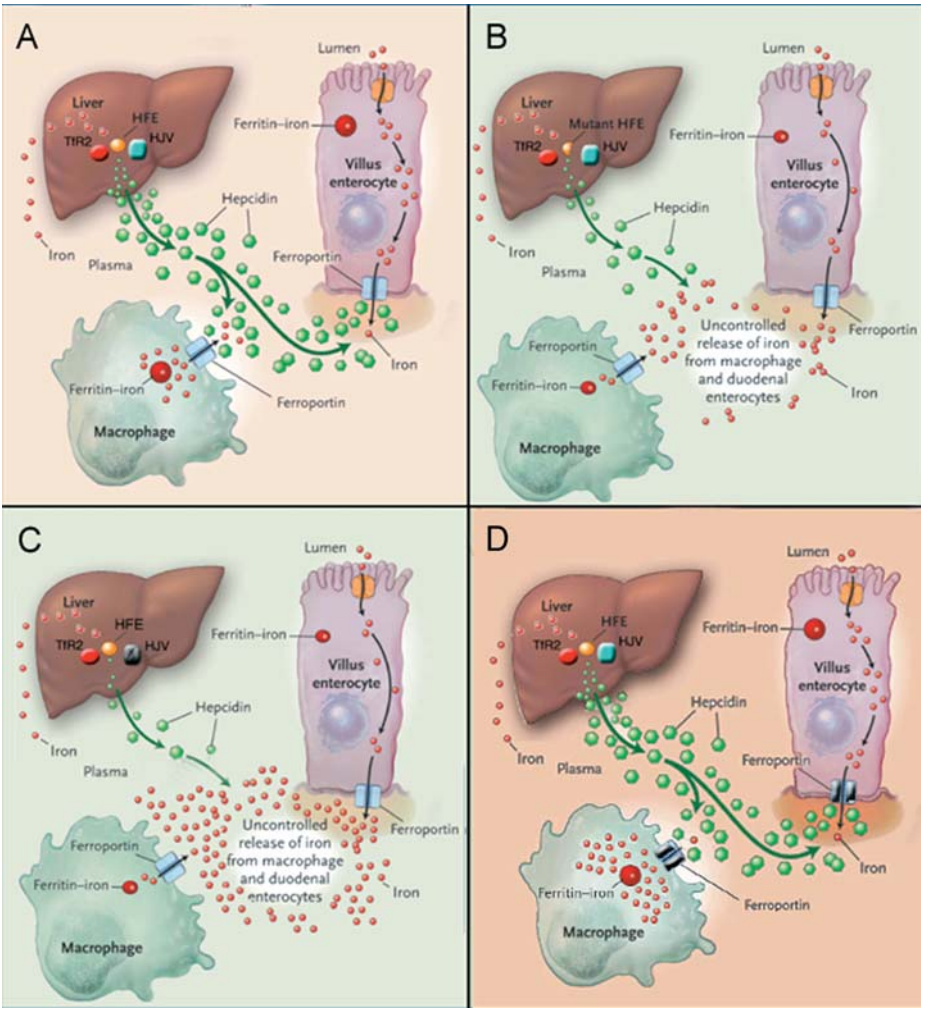

Figure 1 The hepcidin-ferroportin functional axis in the control of circulatory iron and consequences of its genetic disruption. (Panel *A*) In normal subjects, hepcidin secreted by the liver modulates the extent and rate of iron release from macrophages and enterocytes. HFE, TfR2, and HJV are likely required for hepcidin activation in response to the circulatory iron signal. Lack of one of the hepcidin regulators will lead to unrestricted release of iron from macrophages and enterocytes followed by progressive expansion of the plasma iron pool, tissue iron overload, and organ damage (see text for details). Depending on the role of the regulators in the control of hepcidin expression, the extent of circulatory iron overload will be marginal (HFE-HC; panel *B*) or massive (HJV-HC; panel *C*). When the genetic defects lie at the other end of the hepcidin-ferroportin functional axis, impaired iron egress from cells, particularly macrophages, will cause tissue iron overload with relative circulatory iron deficiency, the pathologic hallmark of ferroportin disease (panel *D*). Abbreviations: HC, hemochromatosis; HJV, hemojuvelin; TfR2, transferrin receptor 2. Modified from Reference 74 with permission.

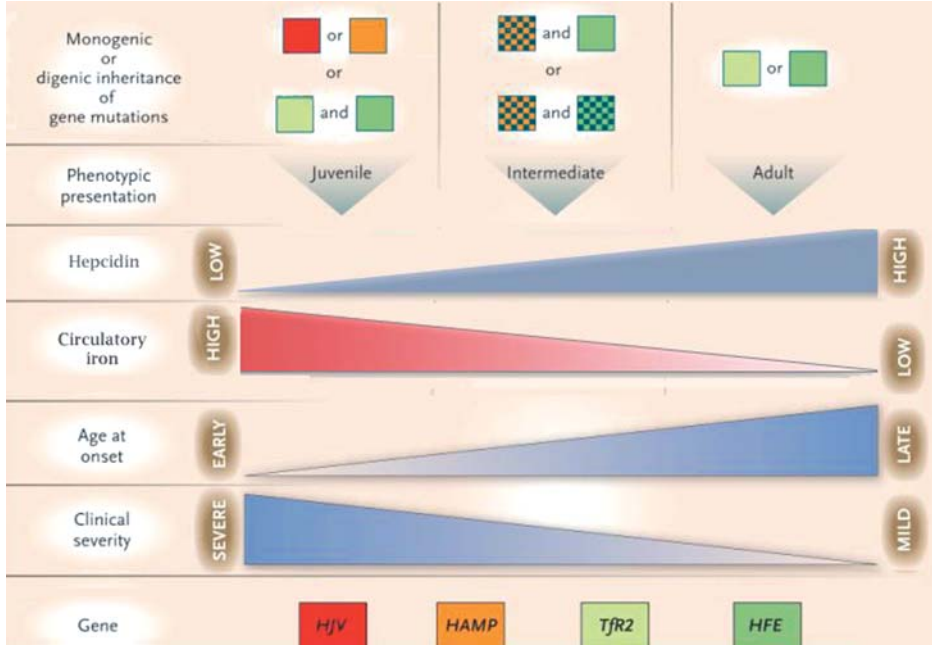

Figure 2 The multigenic nature of hemochromatosis. Hereditary hemochromatosis can be caused by pathogenic homozygous mutations of at least four different iron metabolism genes (*colored boxes* at bottom of figure). Depending on the gene involved and its role in controlling hepatic hepcidin expression, the hereditary hemochromatosis phenotype varies, ranging from massive early-onset circulatory iron loading with severe organ disease (e.g., associated with homozygous mutations of *HAMP* or *HJV* or combined pathogenic mutations of *HFE* and *TfR2*) to the milder late-onset phenotype characterizing classic *HFE* and *TfR2*-related forms. "Intermediate phenotypes" could result from combined heterozygous (*checked squares*) or homozygous (*solid-colored squares*) mutations of multiple hemochromatosis genes (see text for details). HAMP, hepcidin; HJV, hemojuvelin; TfR2, transferrin receptor 2. Modified from Reference 74 with permission.

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