The mechanisms of systemic iron homeostasis and etiology, diagnosis, and treatment of hereditary hemochromatosis

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Abstract

Hereditary hemochromatosis (HH) is a group of genetic iron overload disorders that manifest with various symptoms, including hepatic dysfunction, diabetes, and cardiomyopathy. Classic HH type 1, which is common in Caucasians, is caused by bi-allelic mutations of *HFE*. Severe types of HH are caused by either bi-allelic mutations of *HFE2* that encodes hemojuvelin (type 2A) or *HAMP* that encodes hepcidin (type 2B). HH type 3, which is of intermediate severity, is caused by bi-allelic mutations of *TFR2* that encodes transferrin receptor 2. Mutations of *SLC40A1* that encodes ferroportin, the only cellular iron exporter, causes either HH type 4A (loss-of-function mutations) or HH type 4B (gain-of-function mutations). Studies on these gene products uncovered a part of the mechanisms of the systemic iron regulation; *HFE*, hemojuvelin, and *TFR2* are involved in iron sensing and stimulating hepcidin expression, and hepcidin downregulates the expression of ferroportin of the target cells. Phlebotomy is the standard treatment for HH, and early initiation of the treatment is essential for preventing irreversible organ damage. However, because of the rarity and difficulty in making the genetic diagnosis, a large proportion of patients with non-*HFE* HH might have been undiagnosed; therefore, awareness of this disorder is important.

Keywords Hepcidin · Transferrin receptor 2 · Ferroportin · Hemojuvelin · *HFE*

Introduction

Iron is essential for numerous cellular processes, but in excess it can damage various important organs through the production of reactive oxygen species [1]. In healthy individuals, the amount of iron in the body is strictly controlled by sophisticated systems [2, 3]. If these systems are disrupted, either systemic iron deficiency or iron overload occur [1, 4]. Hereditary hemochromatosis (HH) is the most common genetic iron overload disorder among Caucasians [5]. Since it was first described by Dr. Armand Trousseau in 1865 as diabetes with bronze-colored skin, researchers have been searching the etiologies and pathophysiology of this disorder [6]. Finally, its responsible gene named *HFE* (chromosomal location: 6p21) was identified by Feder et al. in 1996

[7]. The product of this gene turned out to be a membrane protein belonging to the major histocompatibility complex class I family that hetero-dimerizes with β 2-microglobulin. A pathogenic mutation of this gene causing amino acid substitution of C282Y is quite common in Caucasians in the USA and Europe, especially in the Irish population [8]. After the discovery of *HFE*, researchers discovered several other gene mutations that also cause different types of HH [9–12]. Unsurprisingly, products of these genes had important roles in maintaining systemic iron homeostasis, and investigations of these genes contributed to our current understanding of the mechanisms of systemic iron homeostasis [13]. This review summarizes the mechanisms of systemic iron homeostasis and the etiology, diagnosis, and treatment of HH.

Iron absorption from the intestine

Throughout the evolution of life, iron has been an essential and precious nutrient for all organisms. Consequently, active mechanisms for excreting iron from the body do not exist in humans, and the amount of iron in the body is controlled at

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the entrance, i.e., the duodenal enterocytes. In the duodenum, dietary iron is absorbed as at least 3 forms: inorganic non-heme iron, heme-bound iron, and iron incorporated in ferritin [14]. Among them, the main form is inorganic non-heme iron [15]. In the duodenum, the inorganic non-heme Fe^{3+} is reduced to Fe^{2+} by the duodenal cytochrome B reductase [16] and imported by the divalent metal transporter 1 (DMT1), which is expressed in the apical membrane of the enterocytes, into the cytoplasm (Fig. 1) [17, 18]. To maintain systemic iron homeostasis, intestinal iron absorption increases in response to iron deficiency and decreases

in iron overload. In the enterocytes, cell surface expression of DMT1 is regulated at both transcriptional and post-transcriptional levels. In the promoters of *SLC11A2* gene which encodes DMT1, a hypoxia-responsive element (HRE) exists [19–22]. In the situations of hypoxia or iron deficiency, expression of hypoxia-inducible factors (HIF1 α and HIF2 α), which interact with the HRE, increases and thereby activates transcription of *SLC11A2*. After transcription, the stability of the DMT1 messenger RNA is controlled by a mechanism in which interactions of an iron-responsive element (IRE), a stem loop-like structure in the 3'-untranslated

Fig. 1 Iron absorption by enterocytes. In the duodenum, the inorganic non-heme Fe^{3+} is reduced to Fe^{2+} by the duodenal cytochrome B reductase (DCYTB) and imported by the divalent metal transporter 1 (DMT1) into the cytoplasm. Then the imported Fe^{2+} is transported to iron exporter ferroportin (FPN) located in the basolateral membrane of the enterocyte by a chaperone protein poly(rC)-binding protein 2 (PCBP2). After transportation to the portal vein by FPN, Fe^{2+} is oxidized to Fe^{3+} by ferroxidases, i.e., hephaestin (HEPH) and ceruloplasmin (CP), and then carried by transferrin (Tf) into the blood stream

region (UTR), and the iron-regulatory proteins (IRP1 and IRP2), the cytoplasmic iron sensors, play crucial roles [23]. In iron deficiency, IRPs bind to the IRE and stabilize the transcript, resulting in upregulation of translation of DMT1; on the other hand, in iron repletion, IRP1 dissociates from the IRE and IRP2 is degraded after ubiquitination, resulting in destabilization and degradation of the DMT1 transcript [24]. Thus, intestinal expression of iron transporter DMT1 is regulated by these transcriptional and post-transcriptional mechanisms upon intracellular iron status.

Then the imported Fe^{2+} into the cytosol is transported to the iron exporter ferroportin (FPN) located in the basolateral membrane of the enterocyte by a chaperone protein, poly(rC)-binding protein 2 [25] (Fig. 1). FPN, which is encoded by the *SLC40A1* gene, is the only known iron exporter in vertebrate cells [26, 27]. Although the expression of FPN is partially regulated by HRE at the transcriptional level and by the IRP/IRE system at the post-transcriptional level [20, 27, 28], the main regulator of expression of this

protein is hepcidin, the central actor in the systemic iron homeostasis described later. After being transported to the portal vein by FPN, Fe^{2+} is oxidized to Fe^{3+} by ferroxidases, i.e., hephaestin and ceruloplasmin, and then carried by transferrin in the blood stream (Fig. 1).

Regulation of systemic iron homeostasis by hepcidin

The central regulator of systemic iron homeostasis is hepcidin, a peptide hormone mainly produced by hepatocytes. Hepcidin was discovered by a couple of research groups by means of different approaches [29–32]. Among them, Ganz's group originally discovered it as an anti-microbial peptide in the urine [31]. It is transcribed as a proprotein consisting of 84 amino acids, and the peptides of 20–25 amino acids of its carboxyl terminus are cleaved off by furin-like convertases to become mature peptides (Fig. 2).

Fig. 2 Regulation of hepcidin expression in the liver. Bone morphogenetic protein 6 (BMP6) secreted by the liver sinusoidal endothelial cells stimulates hepcidin expression through binding to the BMP receptors (BMPRs)/hemojuvelin (HJV) complex and phosphorylates SMAD proteins. The HFE protein/transferrin receptor 2 (TFR2) complex is also involved in iron sensing. The expression of transmembrane protease, serine 6 (TMPRSS6, matriptase 2) increases upon iron deficiency, and it cleaves off the iron-sensing complexes to reduce the expression of hepcidin. *Fe-Tf* iron-bound transferrin, *TFR1* transferrin receptor 1, *DMT1* divalent metal transporter 1

The main form of mature hepcidin consists of 25 amino acids. This active form of hepcidin-25 binds to FPN on the target cells such as enterocytes, macrophages, and hepatocytes, and induces endocytosis and degradation of this iron exporter, thereby reducing iron supply from these cells to the blood stream (Fig. 3) [33]. The expression of hepcidin is regulated by various factors including transferrin-bound iron, iron status of the body, inflammation, hypoxia/anemia, and erythropoietic activity [13]. In iron deficiency, hepcidin expression decreases, which enhances the expression of intestinal expression of FPN, resulting in an increase of iron absorption from the intestine (Fig. 3). In iron-replete conditions, hepcidin expression increases, which downregulates intestinal FPN expression, resulting in a decrease of intestinal iron absorption (Fig. 3). The mechanism by which iron regulates hepcidin expression seems very complex and has not been fully clarified yet, but at least products of HH-responsive genes, HFE, transferrin receptor 2 (TFR2) [9], and hemojuvelin (HJV) [10] are involved in sensing body iron status (Figs. 2, 3).

TFR2 is a low-affinity transferrin receptor mainly expressed in the hepatocytes and erythroid precursors [34]. HFE can form a complex with TFR2 in the cell membrane (Figs. 2, 3) [35]. This complex probably plays an important role in sensing transferrin-bound iron. Disruption of either the *HFE* or *TFR2* gene causes downregulation of hepcidin expression [36–38]. HJV is a glycosylphosphatidylinositol-anchored membrane protein and a co-receptor for bone morphogenetic proteins (BMPs), which belong to the transforming growth factor- β superfamily [39]. BMP2, 4, 6, and 9 have been shown to induce hepcidin expression [40, 41]. Interaction of BMPs to the BMP receptors causes activation of the promoter of *HAMP*, the gene encoding hepcidin, through

activation of the SMAD phosphorylation pathway (Fig. 2) [41, 42]. In iron-replete mice, hepatic expression of BMP6 increases [43]. In the liver, BMP6 is mainly expressed in the sinusoidal endothelial cells [42, 44] and induces hepcidin expression upon iron loading in a paracrine manner (Fig. 2).

Not only iron, but also other factors regulate hepatic expression of hepcidin. Inflammatory stimuli, e.g., interleukin-6, upregulate hepcidin expression [45]. This regulation is evolutionally developed probably for biological defense, by reducing available iron for the pathogens in the situations of infectious diseases; ironically, this causes iron-restricted anemia observed in chronic inflammation in various clinical settings [46–49]. In contrast, hypoxia, anemia, and erythropoietic activity downregulate hepcidin expression, thereby increasing iron absorption from the intestine and iron supply from the stored iron in the macrophages [50]. In severe types of thalassemia syndromes and congenital dyserythropoietic anemias, serum levels of hepcidin are inappropriately low (Table 1) and frequently manifest as iron overload even if red blood cell transfusions are not administered [51–53]. It is likely that increased erythroblasts in the dyserythropoietic bone marrow secrete a factor that inhibits hepcidin expression. In mice, erythroferrone (FAM132b), a tumor necrosis factor superfamily molecule, was shown to be expressed by erythroblasts and suppress hepcidin expression [54–58].

Various types of HH

The classic type of HH (type 1), caused by mutations of *HFE*, is common in Caucasians. Common mutations of *HFE* observed in HH type 1 are H63D, C282Y, and S65C; among them, C282Y is clearly pathogenic [59, 60]. Typically,

Fig. 3 Systemic regulation of iron homeostasis. The central regulator of the systemic iron homeostasis is hepcidin which is mainly produced by hepatocytes. There is an iron-sensing complex consisting of bone morphogenetic protein (BMP) receptors (BMPRs), hemojuvelin (HJV), transferrin receptor 2 (TFR2), and HFE protein in the hepatocytes. Upon iron loading, BMP6 and iron-bound transferrin (Fe-Tf) stimulate the promoter of *HAMP*, the hepcidin gene. Hepcidin downregulates FPN expression, resulting in decreases of intestinal iron absorption and iron release from macrophages

Table 1 Hereditary iron overload disorders with hyperferritinemia

Disorder	Responsible gene and inheritance	TSAT	Serum hepcidin	Anemia	Neurologic symptoms
HH type 1	<i>HFE</i> , AR	High	Low	—	—
HH type 2a	<i>HJV</i> (<i>HFE2</i>), AR	High	Low	—	—
HH type 2b	<i>HAMP</i> , AR	High	Absent	—	—
HH type 3	<i>TFR2</i> , AR	High	Low	—	—
HH type 4A	<i>SLC40A1</i> , AD	Normal	High	Variable	—
HH type 4B	<i>SLC40A1</i> , AD	High	High	—	—
Thalassemia	<i>HBB</i> , AR <i>HBA</i> , AR	High	Low	+	—
CDA	<i>CDAN1</i> , AR <i>SEC23B</i> , AR <i>KIF23</i> , AD	High	Low	+	—
CSA	<i>ALAS2</i> , XL <i>SLC25A38</i> , AR <i>GLRX5</i> , AR <i>ABCB7</i> , XL	High	Low	+	<i>ALAS2</i> , — <i>SLC25A38</i> , — <i>GLRX5</i> , + <i>ABCB7</i> , +
Aceruloplasminemia	<i>CP</i> , AR	Low	Low	+	+
Atransferrinemia	<i>TF</i> , AR	High	Low	+	—
HX/DHS	<i>PIEZO1</i> , AD	High	Low	+	—

HH hereditary hemochromatosis, *HJV* hemojuvelin, *TFR2* transferrin receptor 2, *CDA* congenital dyserythropoietic anemia, *CSA* congenital sideroblastic anemia, *HX/DHS* hereditary xerocytosis/dehydrated hereditary stomatocytosis, *AD* autosomal dominant, *AR* autosomal recessive, *XL* X-linked, *TSAT* transferrin saturation

hepatic dysfunction and diabetes develop in middle-aged individuals, but the disease penetrance is low and only a small proportion of homozygote *HFE* C282Y mutation manifests symptomatic HH [61]. Men are more susceptible to symptomatic disease than women; the disease penetrance of homozygotes is estimated to be 24–43% in men and 1–14% in women [62]. Genetic background other than *HFE* and lifestyle habits, such as alcoholic consumption and dietary behavior, can affect susceptibility to HH. Mutation of this gene in humans and disruption of this gene in mice cause iron overload through the reduction of hepcidin expression [37]. *HFE* protein can interact with TFR1 and TFR2 [35, 63], and it is probably involved in iron sensing in the hepatocytes (Fig. 2).

In contrast to the adult-onset classic type of HH, patients with juvenile types of HH which manifested as systemic iron overload in their early life, although very rare, have been reported [64–66]. Manifestations of this type of HH are severe and include hypogonadism, diabetes, and cardiomyopathy [67]. In 1999, a locus of a responsible gene was mapped to 1q21, which was distinct from the locus of *HFE* [68], and finally a responsible gene, *HFE2*, was identified in 2004 (HH type 2A, Table 1) [10]. The product of this gene was *HJV*, which was the co-receptor for BMPs as mentioned previously. Disruption of this gene in mice caused decreased expression of hepcidin and severe iron overload [69], and urine hepcidin levels were low or undetectable in patients with this type of HH despite total body iron excess

[70]. Moreover, another type of very severe juvenile HH caused by mutations of *HAMP* which encodes hepcidin was reported (HH type 2B, Table 1) [11].

In 2000, Camaschella et al. described 6 patients who met the diagnostic criteria for HH but were not linked to *HFE* from 2 families of Sicilian origin, and identified homozygous Y250X mutation in *TFR2* in these patients [9]. Since this discovery, a number of cases with HH harboring various *TFR2* mutations have been reported, and this condition is classified as HH type 3 [71, 72]. The Y245X mutation of this gene in mice, equivalent to Y250X in humans, causes downregulation of hepcidin expression and iron accumulation in the liver [36]. Disease severity of this type of HH is moderate.

In patients with HH types 1, 2A, 2B, and 3, the serum hepcidin concentration is inappropriately low despite iron overload, and the diseases are inherited in the autosomal recessive pattern. In contrast, germline mutations of *SLC40A1*, which encodes FPN, the only cellular iron exporter and target of hepcidin, cause different types of iron overload disorders with appropriately elevated serum hepcidin levels in response to iron excess (Table 1) [73]. Phenotypes of mutations of this gene depend on the positions of mutations [74]; loss-of-function mutations cause HH type 4A (so called “ferroportin disease”) with iron accumulation predominantly in reticuloendothelial cells [75, 76], and gain-of-function mutations cause HH type 4B with accumulation of iron in parenchymal cells [77, 78], similar to HH types 1,

2A, 2B, and 3. In HH type 4A and type 4B, the inheritance pattern is autosomal dominant. The heterozygous mutation of *SLC40A1* Q248H is frequently observed in African populations and is associated with mild microcytic anemia and the tendency to iron overload [79, 80].

Recently, families of HH harboring mutations in the propeptide of the *BMP6* gene have been reported [81, 82]. According to these studies, serum hepcidin levels of patients with heterozygous mutations of this gene were markedly low or inappropriately low for the iron overload. In addition, Kato et al. described patients with systemic iron overload harboring a heterozygous mutation in the IRE in the 5'-UTR of *FTH* gene that encodes the ferritin-H subunit from a Japanese family [83]. The proband had iron deposition in hepatocytes and Kupffer cells/macrophages in the liver and spleen. According to their report, expression of the ferritin-H subunit was downregulated and that of ferritin-L subunit was upregulated in the liver of an affected family member, and transfection of the *FTH* gene with the same mutation caused upregulation of the expression of endogenous ferritin-L subunit in COS-1 cells [83]. Heterozygous *FTH* knockout mice manifested with hyperferritinemia, but unlike the human cases the mice did not show any sign of iron overload [84].

The prevalence of *HFE* C282Y mutation is extremely low in Asians [85]. In the literature, I could find only one Japanese hemochromatosis case harboring the homozygous *HFE* C282Y mutation [86]. However, a Japanese family with a homozygous mutation of *HFE* (c. 691_693del) responsible for the loss of a tyrosine at the position 231 (p. Y231del) of the *HFE* protein has been reported [87]. The same mutation was found in the Huh-7 hepatoma cell line and was shown to prevent the translocation of *HFE* to the cell surface [88]. In addition, families with various types of HH were sporadically reported from Asian countries, including Japan, China, and Pakistan [67, 87, 89–104]. In Japan, mutations in *HFE2* (type 2A), *TFR2* (type 3), and *SLC40A1* (type 4) seem relatively common causes of HH [97].

Hereditary disorders that should be differentiated from HH

Hereditary hyperferritinemia cataract syndrome is caused by mutations of the IRE in the 5'-UTR of the *FTL* gene, which encodes the ferritin-L subunit. This is an autosomal dominant disorder associated with high serum ferritin levels and the development of cataracts in young individuals without the manifestation of systemic iron overload throughout their lifetime. Dozens of cases have been reported since it was first described in 1995 [105]. Unbalanced formation of ferritin-L and its precipitation in lens was shown to be responsible for the cataracts [106].

Aceruloplasminemia is another rare inherited disorder that should be differentiated from HH. Ceruloplasmin is a serum ferroxidase that converts Fe^{2+} to Fe^{3+} ion (Fig. 1). Defects of this enzyme causes iron accumulation in the brain, liver, and pancreas, leading to neurological symptoms, retinal degeneration, diabetes, and anemia [107, 108]. Patients with this disease show low serum copper and iron levels, high serum ferritin levels, and undetectable serum ceruloplasmin. According to the report by Kaneko et al., serum hepcidin levels in patients with this disease were relatively low despite the elevated serum ferritin levels [96].

Hereditary diseases with ineffective erythropoiesis such as thalassemia syndromes, congenital dyserythropoietic anemias, congenital sideroblastic anemias, and hereditary xerocytosis/dehydrated hereditary stomatocytosis also manifest as systemic iron overload due to downregulation of hepcidin expression, and they may need to be differentiated from HH in clinical settings (Table 1) [51, 53, 109–111].

Manifestations of HH

Skin pigmentation, liver dysfunction, diabetes, and cardiomyopathy are common manifestations of HH, which are caused by iron accumulation in the skin, liver, pancreas and heart, respectively (Fig. 4) [112–114]. Hepatic dysfunction indicated by elevations of serum alanine aminotransferase levels is often observed in the relatively early stages of this disease. Hepatic dysfunction may progress to cirrhosis and can cause hepatocellular carcinomas [115, 116]. Cardiomyopathy is observed in severe iron overload, and it can cause arrhythmia and heart failure leading to mortality [117]. Iron also accumulates in various endocrine organs and may cause hypothyroidism and hypogonadism [118]. Arthropathy or joint pain is another common but sometimes overlooked symptom of HH [119]. Arthropathy in HH may involve the metacarpophalangeal and proximal interphalangeal joints, wrists, knees, hips, feet, and shoulders, and can be misdiagnosed as rheumatoid arthritis [120, 121]. HH type 4A has distinctive clinical features such as a low transferrin saturation and marginal anemia with low tolerance to phlebotomy [76]. We previously described a Japanese family with HH type 4B and juvenile cataract, though the mechanism of the development of early-onset cataract in this family was undetermined [122].

Diagnostic tests

In clinical practice, the most useful biomarker for estimating systemic iron storage is serum ferritin [123]. Ferritin is a cytoplasmic storage protein composed of 24 of ferritin-H and ferritin-L subunits in various ratios, and macrophages

Fig. 4 Symptoms observed in hereditary hemochromatosis

actively secrete the ferritin heteropolymer into the blood through a non-classical pathway [124]. If serum ferritin exceeds 300 ng/mL, systemic iron overload is suspected. Caution should be taken to ensure that the expression of ferritin is controlled not only by iron, but also by inflammatory cytokines, hormones, and oxidative stress at both transcriptional and post-transcriptional levels [125]. Therefore, serum ferritin should be evaluated together with C-reactive protein as an inflammatory marker. Remarkable elevation of serum ferritin levels is observed in adult Still's disease and hemophagocytic syndrome [126, 127].

Transferrin saturation (TSAT), which is calculated by dividing the serum iron level by the total iron binding capacity, is another biomarker for systemic iron status. Iron overload is suspected if TSAT exceeds 50%, and its values over 80% suggests an increase of highly toxic

non-transferrin-bound iron (NTBI), which causes organ damage [128]. TSAT does not increase in HH type 4A, so if the serum ferritin level is high and TSAT is low, HH type 4A can be suspected (Table 1).

Imaging tests also help in diagnosing HH. The hepatic density increases on a computed tomography image when excess iron is accumulated. Magnetic resonance imaging (MRI) is another non-invasive way of evaluating iron accumulation in organs. On a T2-intensified MRI scan, the intensity decreases with iron accumulation [129, 130]. For quantification of cardiac iron contents, the T2* method seems more accurate, but this method is not widely available [131]. Liver biopsy is an old and standard method to directly demonstrate iron deposition in the liver, but this procedure is invasive and not routinely performed to make a diagnosis of HH.

In healthy individuals, the serum hepcidin level increases upon iron loading and inflammation and decreases in iron deficiency, hypoxia, and increased erythropoiesis. Therefore, serum levels of hepcidin-25 are positively correlated with the levels of serum ferritin [132, 133]. The serum hepcidin-25 level is abnormally low in types 1, 2A, 2B, and 3 HH for the high serum ferritin levels, and it can be a useful marker for suspecting these types of HH (Table 1). Unfortunately, only selected institutions currently offer this test. A genetic test is necessary for diagnosing HH, and it is widely used for diagnosing HH type 1 [134]. However, examining all the genes known to be responsible for HH requires considerable time and costs. If HH is strongly suspected based on the patient's clinical features, family history, blood test results, and imaging results, physicians should consult specialists of HH to make a genetic diagnosis [135].

Treatment and management of patients with HH

Early diagnosis and prompt initiation of appropriate treatments are essential for preventing irreversible organ damage [135]. Hepatic function, glucose tolerance, cardiac function, thyroid function, and gonadal function should be evaluated once HH is diagnosed, and symptoms secondary to iron overload, such as diabetes, cardiomyopathy, hypothyroidism, and hypogonadism, should be appropriately treated by consultation with the specialists of these disorders [116]. Phlebotomy is the standard treatment for HH. It should be repeated at appropriate intervals for at least 1 week [116]. Each time before phlebotomy, the hemoglobin (Hb) level should be monitored to avoid inducing anemia. The standard volume of phlebotomy is 400–500 mL, and it should be modified according to the patient's age, body weight, Hb levels, and comorbidities [116]. The target value of the serum ferritin level is between 50 and 100 ng/mL [136]. Mild liver disease due to iron overload is reversible, but once liver cirrhosis develops it may be irreversible [137]. Improvement of diabetes is often difficult, because once the islet cells are damaged, impaired insulin secretion is rarely recovered [137, 138]. In many patients, insulin therapy is required for treating diabetes. Cardiomyopathy may be reversible by phlebotomy in some patients, but it can be fatal in others [112, 139]. Phlebotomy removes not only iron, but also other factors and nutrients; hence, treatment with erythrocytapheresis in combination with erythropoiesis-stimulating agents experimentally has been reported [140]. In patients with both iron overload and anemia, phlebotomy is inappropriate. In such cases, iron chelation therapy using desferrioxamine, deferasirox, or deferiprone may be considered. Physicians should recommend the patients not to take iron-containing supplements and to avoid alcohol consumption.

Evolutional benefits of HFE mutations

The very high incidences of mutations in the *HFE* gene among Caucasians evoke the idea that these mutations might have offered advantages to their carriers [114]. For instance, increased iron uptake might have offered advantages to people with a grain-based diet and especially to women of reproductive ages in their survival and reproduction. Unlike C282Y homozygote women who might have hypogonadism, heterozygote women may have a reproducible advantage [141]. Interestingly, a recent study demonstrated that 80% of the French athletes who won international competitions in rowing, Nordic skiing, and judo display mutations in one allele of *HFE* [142], suggesting that the enhanced iron supply by these mutations might have contributed to their superior physical performance. Mutations of *HFE* may also modulate the immune system by upregulating expression of FPN and reducing intracellular iron of macrophages, which makes them less susceptible to bacteria and parasites that require iron for their growth [143, 144]. A meta-analysis revealed that a mutation of *HFE* H63D plays a protective role for Alzheimer disease risk [145]. Large-scale epidemiological studies of Sicilian and Sardinian populations demonstrated that female *HFE* C282Y heterozygotes had significantly increased life expectancy compared to controls [146, 147]. Taken together, carriers of heterozygous *HFE* mutations might have some advantages over the wild-type *HFE* carriers, and these mutations have been inherited in high frequencies.

Conclusions

Hereditary iron overload disorders such as HH and thalassemia syndromes are very common in the world [148–150]. Since the discoveries of *HFE* and hepcidin as the priming pumps in the research field of iron metabolism, a lot of new knowledge about systemic iron regulation have been provided by numerous investigations worldwide. Since the serum ferritin level is not routinely evaluated in clinical practice and because the genetic tests for HH, especially for the non-*HFE* types, can be performed at only select institutions, a great number of patients with HH with hepatic dysfunction, diabetes, cardiomyopathy, endocrinopathy, and arthropathy might have been undiagnosed and inappropriately treated. If the diagnosis was made in the early stage of the disease, such complications could have been prevented by appropriate treatments, including phlebotomy. Awareness of this disorder is important not only for hematologists, but also for endocrinologists, cardiologists, hepatologists, and especially family physicians.

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Compliance with ethical standards

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