Non-\textit{HFE} Hepatic Iron Overload

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\textbf{ABSTRACT}

Numerous clinical entities have now been identified to cause pathologic iron accumulation in the liver. Some are well described and have a verified hereditary basis; in others the genetic basis is still speculative, while in several cases nongenetic iron-loading factors are apparent. The non-\textit{HFE} hemochromatosis syndromes identifies a subgroup of hereditary iron loading disorders that share with classic \textit{HFE}-hemochromatosis, the autosomal recessive trait, the pathogenic basis (i.e., lack of hepcidin synthesis or activity), and key clinical features. Yet, they are caused by pathogenic mutations in other genes, such as transferrin receptor 2 (\textit{TFR2}), hepcidin (\textit{HAMP}), hemojuvelin (\textit{HJV}), and ferroportin (\textit{FPN}), and, unlike \textit{HFE}-hemochromatosis, are not restricted to Caucasians. Ferroportin disease, the most common non-\textit{HFE} hereditary iron-loading disorder, is caused by a loss of iron export function of FPN resulting in early and preferential iron accumulation in Kupffer cells and macrophages with high ferritin levels and low-to-normal transferrin saturation. This autosomal dominant disorder has milder expressivity than hemochromatosis. Other much rarer genetic disorders are associated with hepatic iron load, but the clinical picture is usually dominated by symptoms and signs due to failure of other organs (e.g., anemia in atransferrinemia or neurologic defects in aceruloplasminemia). Finally, in the context of various necro-inflammatory or disease processes (i.e., chronic viral or metabolic liver diseases), regional or local iron accumulation may occur that aggravates the clinical course of the underlying disease or limits efficacy of therapy.

\textbf{KEYWORDS:} Iron overload, non-\textit{HFE} hemochromatosis, transferrin receptor 2, hepcidin, ferroportin, hemojuvelin

The liver is the main source of the iron-regulatory hormone hepcidin and plays a central role in the homeostatic control of iron traffic in the body. Although intestinal iron absorption is tightly regulated to sustain hemoglobin synthesis and critical cell functions, there is no active mechanism for iron excretion from the body.\textsuperscript{1} This exposes humans to a substantial risk for iron overload and iron-driven toxicity, particularly in the liver, the principal iron storage site in the body. Excess iron, in solution with oxygen, may generate free radical formation via Fenton and Haber-Weiss chemistry, with hydrogen peroxide (\textit{H}_2\textit{O}_2), being changed into its noxious hydroxyl radical (\textit{HO}_\textit{C} \textit{O}_\textit{O})\textsuperscript{2}. This leads to consequent damage to DNA, proteins, and membranes.\textsuperscript{2} The classic example of iron overload in human pathology is \textit{HFE}-hereditary hemochromatosis (HC), but numerous other entities are now identified to cause pathologic iron accumulation in the liver\textsuperscript{3} (Table 1). Some are well described and have a verified hereditary basis, whereas in others the genetic and hereditary basis is still speculative. A large percentage...
reflect systemic iron overload, others, in the context of a necro-inflammatory, or in as yet unknown disease processes, results in regional or local iron accumulation (e.g., chronic liver diseases) (Table 1). Finally, an increasingly recognized class of iron disorders is due to disrupted intracellular (e.g., Friedreich ataxia) or body iron traffic (e.g., anemia of chronic diseases) leading to iron misdistribution despite a normal total body iron content (Table 1). Here we will discuss causes and consequences of most common hereditary or acquired disorders associated with hepatic iron overload beyond \( HFE \)-hemochromatosis.

**HEREDITARY DISORDERS**

**Non-\( HFE \) Hereditary Hemochromatosis**

Hemochromatosis, or hereditary hemochromatosis, has been historically considered a unique clinicopathologic entity likely due to a single gene defect. This view seemed to be confirmed in 1996 when a single-gene polymorphism was found in most hemochromatotic patients worldwide (see also Olynyk et al elsewhere in this issue). However, as genetic testing for \( HFE \) became more widespread and nearly one-fifth of HC patients turned out to lack the pathogenic p.Cys282Tyr change, it rapidly became clear that the situation was more complicated than previously thought. Other iron genes whose mutations were associated with hereditary iron overload syndromes with some, or many, or apparently even all of the phenotypic features of classic HC, were reported: transferrin receptor-2 (\( TFR2 \)), hepcidin (\( HAMP \)), hemojuvelin (\( HJV \)), and ferroportin (\( FPN \)) (Table 1).

Today, the term non-\( HFE \) hereditary hemochromatosis embraces all forms of HC nonlinked to the common \( HFE \) p.Cys282Tyr polymorphism, and thus far associated with pathogenic mutations of \( TFR2 \), \( HJV \), \( HAMP \), and in rare cases, the \( FPN \) gene. These non-\( HFE \) hemochromatosis syndromes share with classic \( HFE \)-HC key features, namely (1) early and progressive expansion of the plasma iron compartment (increasing

**Table 1  Common Causes of Non-\( HFE \) Iron Overload or Mis-Distribution in Humans**

| Hereditary Disorder/Cause | Pattern of Iron Accumulation | Acquired Disorder/Cause | Pattern of Iron Accumulation |
|--------------------------|------------------------------|-------------------------|-----------------------------|
| Hereditary | Iron Overload | Iron Mis-Distribution |
| Non-\( HFE \) hereditary hemochromatosis (TFR2-, HJV-, HAMP-, FPN-related) | Systemic | X-linked sideroblastic anemias | Systemic (mitochondria) |
| Ferroportin disease (classic form) | Systemic | Friedreich ataxia | Systemic (mitochondria) |
| Aceruloplasminemia | Systemic | | |
| Atransferrinemia | Systemic | | |
| DMT-1 deficiency | Regional (mainly liver) | | |
| H-ferritin related iron overload with inefficient erythropoiesis | Systemic (early hepatic iron load due to increased iron absorption) | | |
| Hereditary iron-loading anemias | | | |

**Acquired**

| Disorder/Cause | Pattern of Iron Accumulation |
|---------------|-----------------------------|
| Oral | Systemic |
| Parenteral | Systemic |
| Posttransfusion | Systemic (preferential iron accumulation in macrophages) |
| Chronic liver diseases (viral- and alcohol-related; NASH) | Regional (liver) |
| Neurodegenerative disorders | Regional (brain) |

**Miscellaneous**

| Disorder/Cause | Pattern of Iron Accumulation |
|---------------|-----------------------------|
| Porphyria cutanea tarda | Systemic (mainly liver) |
| African siderosis | Systemic |
| Alloimmune (neonatal) hemochromatosis | Systemic |

\( TFR2 \), transferrin receptor-2; \( HAMP \), hepcidin; \( HJV \), hemojuvelin; \( FPN \), ferroportin; NASH, nonalcoholic steatohepatitis.
transferrin saturation [TS]), which precedes tissue iron overload (increasing serum ferritin [SF]); (2) progressive and preferential iron deposits in parenchymal cells with potential for severe damage and disease that may involve liver, endocrine glands, heart, and joints; (3) nonimpaired erythropoiesis and optimal response to therapeutic phlebotomy; and (4) inadequate hepcidin synthesis or activity. These similarities with HFE-HC stem from the fact that—beyond their genetic diversities—all known hemochromatoses belong to the same clinicopathologic entity, as they all originate from the failure to prevent unneeded iron from entering the circulatory pool due to hepcidin deficiency (see also, Babitt and Lin, this issue; and below). Depending on the gene involved and its role in hepcidin regulation, the phenotype of HC varies, ranging from the severe HVJ- and HAMP-juvenile forms, to the relatively milder adult-onset TFR2 and FPN phenotypes.

EPIDEMIOLOGY
Unlike HFE, none of the non-HFE-HC genes appears to be restricted to northern European descent. Most cases of TFR2-HC represent largely inbred families of Italian extraction with high consanguinity.11–15 However, pathogenic mutations of TFR2 have also been identified in other ethnicities, including Asian populations.16–21 In Asians, where HFE-HC is almost nonexistent, TFR2-HC seems a common form of hereditary HC. Reported TFR2 mutations include missense and nonsense, deletions, and frameshifts, followed by a premature stop codon and alternative splicing mutations (Table 2).

Although most FPN mutations give rise to a distinct form of hereditary iron overload called ferroportin disease28 (see below), unusual FPN mutations are believed to cause rare forms of HC similar to HFE-HC.28–31,33,35,36,38 Most cases of so-called juvenile HC (JHC) are due to mutations of HVJ, formerly HFE2.8 Many HVJ pathogenic mutations have been reported,42,54,55,57 one, p.Gly320Val, seems more common than others as it has been found in most reported pedigrees worldwide (Table 2).3,5,42,43,46,47,51,53–61

The study of additional cases with JHC identified a cohort demonstrating mutations in HAMP, the gene encoding hepcidin, on chromosome 19q13.7 HAMP-HC is much rarer than HVJ-HC, and only few cases have been reported so far.34,64–66,69–71 The concept and spectrum of JHC has been further extended by the identification of patients with combined mutations for HFE and TFR2 presenting with a severe hemochromatotic syndrome identical to JHC.24

In addition, there is evidence that selected HVJ and HAMP mutations, when carried simultaneously with mutant HFE, may aggravate and accelerate the course of classic HC (Table 2).45,48,53,67,68

PATHOGENESIS
The first biochemical manifestation of all forms of HC, regardless of the pathogenic gene involved, is an increase of TS that reflects an uncontrolled influx of iron into the bloodstream from enterocytes and macrophages.73 As the body has no effective means of significantly reducing plasma iron levels, without therapeutic intervention, overload in the plasma compartment will lead to the progressive accumulation of iron in the parenchymal cells of key organs, creating a distinct risk for oxidative damage. The time of onset and pattern of organ involvement in HC vary depending on the rate and magnitude of plasma iron overloading, which depends in turn on the underlying genetic mutation. The latter determines the extent of hepcidin deficiency and eventually the rate and magnitude of body iron loading. For this reason, milder adult-onset forms (e.g., TFR2- and FPN-related) and more severe juvenile-onset forms (e.g., HVJ- and HAMP-related) of HC are recognized. Iron release from enterocytes and macrophages into the bloodstream in humans is under the control of the hepcidin–ferroportin axis. It now seems that most non-HFE HC genes play a role in conveying the iron signal to hepcidin, although the details of this process are not fully uncovered (see Babitt and Lin, this issue). In the rare cases of FPN-HC, instead FPN mutations are thought to impair hepcidin-triggered FPN degradation and/or FPN internalization/degradation (see De Domenico, Ward, and Kaplan, this issue).74

CLINICAL ASPECTS
In view of the genetic and pathogenic considerations expressed above, HC can be seen as a genetically heterogeneous disease that results from the complex interaction between genetic and acquired factors. If the altered gene plays a dominant role in hepcidin synthesis/activity (e.g., HAMP itself or HVJ), circulatory iron overload occurs rapidly and reaches high levels. In these cases, the modifying effects of acquired environmental and lifestyle factors will be negligible and the clinical presentation will invariably be dramatic, with early onset (first to second decade) of a full-blown organ disease.3 In contrast, p.Cys282Tyr HFE homozygosity results in a genetic predisposition that requires the concurrence of host-related or environmental factors to produce disease (see also, Gan, Powell, and Olynyk, this issue). As mentioned, co-inherited mutations in other HC genes, such as HAMP and HVJ, may have a role in disease penetrance of HFE-HC, but they are rare.45,48,53,67,68

The clinical appearance of TFR2-HC patients mimics that of HFE-hereditary HC, namely patients with high TS and SF and low penetrance in premenopausal women.13 Age range is somewhat younger, but
Table 2  Non-\textit{HFE} Hemochromatosis: Reported Gene Mutations

| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|-------------------|-------------------|-------------------|-----------|------------|
| **TFR2** (RefSeq NM_003227.3, NP_003218.2) | | | | |
| 1 | c.64G>A | p.Val22Ile | Missense (heterozygous) | Postulated effect on iron status | 22 |
| 2 | c.88_89insC | p.Arg30ProfsX31 | Frameshift (homozygous) | Hemochromatosis | 12 |
| 3 | c.313C>T | p.Arg105X | Nonsense (homozygous) | Hemochromatosis | 18 |
| 4 | c.515T>A | p.Met172Lys | Missense (homozygous) | Hemochromatosis | 12, 14 |
| 5 | c.614+4A>G | | Splicing (homozygous) | Hemochromatosis | 23 |
| 6 | c.750C>G | p.Tyr250X | Nonsense (homozygous) | Hemochromatosis | 6, 11 |
| 7 | c.949C>T | p.Gln317X | Nonsense (homozygous) | Hemochromatosis | 24 |
| 8 | c.1186C>T | p.Arg396X | Nonsense (compound heterozygous with p.Gly792Arg or c.1538–2A>G) | Hemochromatosis | |
| 9 | c.1231_1233del3 | p.Asn411del | Deletion (compound heterozygous with p.Ala444Thr) | Hemochromatosis | 25 |
| 10 | c.1330G>A | p.Ala444Thr | Missense (compound heterozygous with p.Asn411del) | Hemochromatosis | 25 |
| 11 | c.1364G>A | p.Arg455Gln | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous | 26 |
| 12 | c.1403G>A | p.Arg468His | Missense (homozygous) | Hemochromatosis | 21 |
| 13 | c.1469T>G | p.Leu490Arg | Missense (homozygous) | Hemochromatosis | 19 |
| 14 | c.1538–2A>G | | Splicing (compound heterozygous with p.Arg396X) | Hemochromatosis | 15 |
| 15 | c.1665delC | p.Ser556AlafsX6 | Frameshift (homozygous) | Hemochromatosis | 19 |
| 16 | c.1861_1872del12 | p.Ala621_Gln624del | Deletion (homozygous) | Hemochromatosis | 13, 17 |
| 17 | c.2069A>C | p.Gln690Pro | Missense (homozygous) | Hemochromatosis | 16 |
| 18 | c.2137–1G>A | | Splicing (homozygous) | Hemochromatosis | 25 |
| 19 | c.2374G>A | p.Gly792Arg | Missense (compound heterozygous with p.Arg396X) | Hemochromatosis | 20 |

**SLC40A1** (RefSeq NM_014585.5, NP_055400.1)

| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|-------------------|-------------------|-------------------|-----------|------------|
| 1 | c.-59_-45del15 | | Deletion (heterozygous) | Hemochromatosis* | 27 |
| 2 | c.190T>A | p.Tyr64Asn | Missense (heterozygous) | Hemochromatosis | 28 |
| 3 | c.430A>C | p.Asn144His | Missense (heterozygous) | Hemochromatosis | 29 |
| 4 | c.430A>G | p.Asn144Asp | Missense (heterozygous) | Hemochromatosis | 30 |
| 5 | c.431A>C | p.Asn144Thr | Missense (heterozygous) | Hemochromatosis | 31 |
| 6 | c.718A>G | p.Lys240Glu | Missense (heterozygous) | Hemochromatosis* | 32 |
| 7 | c.977G>A | p.Cys326Tyr | Missense (heterozygous) | Hemochromatosis* | 33, 34 |
| 8 | c.977G>C | p.Cys326Ser | Missense (heterozygous) | Hemochromatosis | 35 |
| 9 | c.1014T>G | p.Ser338Arg | Missense (heterozygous) | Hemochromatosis | 36 |
| 10 | c.1502A>G | p.Tyr501Cys | Missense (heterozygous) | Hemochromatosis* | 37 |
| 11 | c.1520A>G | p.His507Arg | Missense (heterozygous) | Hemochromatosis | 38 |

**HJV** (RefSeq NM_213653.3, NP_998818.1)

| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|-------------------|-------------------|-------------------|-----------|------------|
| 1 | c.81delG | p.Leu28SerfsX24 | Frameshift (homozygous) | Juvenile hemochromatosis | 39 |
| 2 | c.160A>T | p.Arg54X | Nonsense (homozygous) | Juvenile hemochromatosis | 40 |
| 3 | c.196G>T | p.Gly66X | Nonsense (homozygous) | Juvenile hemochromatosis | 41 |
| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|-------------------|-------------------|-------------------|-----------|------------|
| 4 c.220delG | p.Val74TrpsX40 | Frameshift (compound heterozygous with p.Asn269LysfsX43) | Juvenile hemochromatosis | 42 |
| 5 c.238T>C | p.Cys80Arg | Missense (compound heterozygous with p.Leu101Pro or p.Arg326X) | Juvenile hemochromatosis | 43,44 |
| 6 c.239G>A | p.Cys80Tyr | Missense (compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 34 |
| 7 c.253T>C | p.Ser85Pro | Missense (homozygous) | Juvenile hemochromatosis | 42 |
| 8 c.295G>A | p.Gly99Arg | Missense (homozygous or compound heterozygous with p.Leu101Pro) | Juvenile hemochromatosis | 34,42 |
| 9 c.296G>T | p.Gly99Val | Missense | Juvenile hemochromatosis | 8 |
| 10 c.302T>C | p.Leu101Pro | Missense (homozygous or compound heterozygous with p.Cys80Arg or p.Gly99Arg; heterozygous) | Juvenile hemochromatosis | 42,43,45 |
| 11 c.314C>T | p.Ser105Leu | Missense (heterozygous) | Juvenile hemochromatosis | 45 |
| 12 c.346C>T | p.Gln116X | Nonsense (compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 46 |
| 13 c.356G>T | p.Cys119Phe | Missense (homozygous) | Juvenile hemochromatosis | 47 |
| 14 c.391_403del13 | p.Arg131PhefsX115 | Frameshift (homozygous) | Juvenile hemochromatosis | 42,48 |
| 15 c.404T>G | p.Leu135Arg | Missense (heterozygous) | Juvenile hemochromatosis | 48 |
| 16 c.445delG | p.Asp149ThrfsX97 | Frameshift (homozygous) | Juvenile hemochromatosis | 42 |
| 17 c.494T>A | p.Leu165X | Nonsense (homozygous) | Juvenile hemochromatosis | 49 |
| 18 c.503C>A | p.Ala168Asp | Missense (homozygous) | Juvenile hemochromatosis | 42 |
| 19 c.509T>C | p.Phe170Ser | Missense (homozygous) | Juvenile hemochromatosis | 42 |
| 20 c.512G>T | p.Gly171Val | Missense (homozygous) | Juvenile hemochromatosis | 50 |
| 21 c.516C>G | p.Asp172Glu | Missense (compound heterozygous with p.Cys321ValfsX21) | Juvenile hemochromatosis | 42 |
| 22 c.526C>T | p.Arg176Cys | Missense (homozygous or compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 51,52 |
| 23 c.573G>T | p.Trp191Cys | Missense (homozygous) | Juvenile hemochromatosis | 42 |
| 24 c.575C>T | p.Pro192Leu | Missense (homozygous) | Juvenile hemochromatosis | 34 |
| 25 c.581T>C | p.Leu194Pro | Missense (homozygous) | Juvenile hemochromatosis | 34 |
| 26 c.588T>G | p.Asn196Lys | Missense (heterozygous) | Juvenile hemochromatosis | 53 |
| 27 c.615C>G | p.Ser205Arg | Missense (compound heterozygous with p.Gly250Val) | Juvenile hemochromatosis | 42 |
| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|------------------|------------------|------------------|-----------|------------|
| c.665T>A        | p.Ile222Asn      | Missense (compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 8,43 |
| c.745G>C        | p.Asp249His      | Missense (homozygous) | | |
| c.749G>T        | p.Gly250Val      | Missense (compound heterozygous with p.Ser205Arg) | Juvenile hemochromatosis | 42 |
| .806_807insA    | p.Asn269LysfsX43 | Frameshift (compound heterozygous with p.Val74TrpfsX40) | Juvenile hemochromatosis | 42 |
| c.842T>C        | p.Ile281Thr      | Missense (homozygous or compound heterozygous with p.Cys321X) | Juvenile hemochromatosis | 8,55 |
| c.862C>T        | p.Arg288Trp      | Missense (homozygous) | Juvenile hemochromatosis | 42,56 |
| c.904G>A        | p.Glu302Lys      | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous | 45 |
| c.934C>T        | p.Gln312X        | Nonsense (homozygous) | Juvenile hemochromatosis | 54,57 |
| c.959G>T        | p.Gly320Val      | Missense (homozygous or compound heterozygous; heterozygous) | Juvenile hemochromatosis | 8,44,42–44,46,47,51,58–61 |
| .960_961insG    | p.Cys321ValfsX21 | Frameshift (homozygous) | Juvenile hemochromatosis | 42 |
| c.963C>G        | p.Cys321Trp      | Missense (compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 43 |
| c.963C>A        | p.Cys321X        | Nonsense (compound heterozygous with p.Ile281Thr) | Juvenile hemochromatosis | 55 |
| c.976C>T        | p.Arg326X        | Nonsense (compound heterozygous with p.Cys80Arg or p.Gly320Val) | Juvenile hemochromatosis | 8,44 |
| .982_985del4    | p.Ser328AspfsX10 | Frameshift (compound heterozygous with p.Gly320Val) | Juvenile hemochromatosis | 47 |
| c.985C>T        | p.Arg329X        | Nonsense (homozygous) | Juvenile hemochromatosis | 62 |
| c.1004G>A       | p.Arg335Gln      | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous | 45 |
| c.1026delT      | p.Ala343ProfsX24 | Frameshift (homozygous) | Juvenile hemochromatosis | 34 |
| c.1080delC      | p.Cys361ValfsX6  | Frameshift (homozygous) | Juvenile hemochromatosis | 8 |
| c.1114A>G       | p.Asn372Asp      | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous | 45 |
| c.1153C>T       | p.Arg385X        | Nonsense (homozygous) | Juvenile hemochromatosis | 42 |

**HAMP (RefSeq NM_021175.2, NP_066998.1)**

| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|------------------|------------------|------------------|-----------|------------|
| c.153C>T        | p.Ala43Thr       | Promoter mutation (heterozygous) | Juvenile hemochromatosis | 62 |
| c.25G>A         | p.Ala43Thr       | Promoter mutation (homozygous) | Juvenile hemochromatosis | 64–66 |
| c.95delG        | p.Gly32Aspsfs    | Frameshift (homozygous) | Juvenile hemochromatosis | 7 |
| c.126,127del2   | p.Arg42Serfs     | Frameshift (homozygous) | Juvenile hemochromatosis | 34 |
with slower progression of iron overload than in JHC. Although relatively few cases have been documented, the liver pathology is again described as strongly resembling HFE-hereditary HC with early iron deposition in periportal hepatocytes (see Deugnier and Turlin, this issue). Most demonstrate a milder degree of iron overload than those with HFE-HC, although there is progression to cirrhosis in some published cases. The variability in clinical expressivity may also depend on the underlying TFR2 defect that may have different effects on hepcidin expression and the resulting iron-loading phenotype. The diagnosis is made by clinical presentation, serum iron indices, and exclusion of the HFE genotype. The leading diagnostic clue is usually, as in the case of the other non-HFE HC syndromes, unexplained hypoferritinemia (Fig. 1). Treatment, as in the case of classic hereditary HC, is by venesection.

Most reported cases of FPN-HC refer to patients with clinical manifestations identical to HFE- (or TFR2-) HC with high TF and SF levels, predominant hepatic parenchymal iron overload, and cirrhosis and organ failure in advanced cases. As in the other forms of HC, phlebotomy appears to be well tolerated and effective.

**HJV-HC** accounts for almost all cases of JHC, the most severe form of human HC, known for decades as a distinct clinicopathologic entity. The first reports date back to the 1950s. Lamon first reviewed all published cases and described the main clinical features of JHC. The syndrome differs considerably from HFE-HC with respect to age, an almost equal ratio between sexes, greater frequency of cardiac and endocrine disturbances. The patient usually presents in the second decade, typically with hypogonadism that manifests as primary infertility in the female. A dilated cardiomyopathy that often becomes refractory to treatment is a common complication; the untreated patient usually dies of cardiac disease by the 30th year. The hepatic complications of iron overload in JHC may seem not as common as in the case of adult forms of HC (HFE-, TFR2, and FPN-HC), but this may be simply because the clinical picture is dominated by the endocrine and cardiac failure. In fact, the hepatic pathology may be profound, with histologically diagnosed cirrhosis developing even at a young age in up to 40% of patients. However, the clinical diagnosis of JHC is often coincidental, relating to investigation of endocrine or cardiac abnormalities including cardiac

### Table 2 (Continued)

| Nucleotide Change | Amino Acid Change | Type of Variation | Phenotype | References |
|-------------------|-------------------|-------------------|-----------|------------|
| 5 c.148_150+1del4 | p.Met50del        | Frameshift (heterozygous) | Putative modifier in p.Cys282Tyr HFE heterozygous | 67 |
| 6 c.166C>T        | p.Arg56X          | Nonsense (homozygous; heterozygous) | Juvenile hemochromatosis Putative modifier in p.Cys282Tyr HFE homozygous when heterozygous | 7,68 |
| 7 c.175C>G        | p.Arg59Gly        | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous and heterozygous | 68 |
| 8 c.208T>C        | p.Cys70Arg        | Missense (homozygous) | Juvenile hemochromatosis or hemochromatosis | 69,70 |
| 9 c.212G>A        | p.Gly71Asp        | Missense (heterozygous) | Putative modifier in p.Cys282Tyr HFE homozygous | 67,68 |
| 10 c.233G>A       | p.Cys78Tyr        | Missense (homozygous) | Juvenile hemochromatosis | 71 |

**Gene TFR2 + HFE**

1 HFE: c.187C>G/ c.845G>A
    HFE: p.His63Asp/ p.Cys282Tyr
    TFR2: c.949C>T
    TFR2: p.Gln317X
    HFE missense and TFR2 nonsense (digenic inheritance: HFE compound heterozygous and TFR2 homozygous)
    Juvenile hemochromatosis | 24 |

TFR2, transferrin receptor-2; SLC40A1, ferroportin; HJV, hemojuvelin; HAMP, hepcidin.

*Reports of patients with a classic hemochromatosis phenotype but lacking confirmatory liver histopathology.

HJV-HC accounts for almost all cases of JHC, the most severe form of human HC, known for decades as a distinct clinicopathologic entity. The first reports date back to the 1950s. Lamon first reviewed all published cases and described the main clinical features of JHC. The syndrome differs considerably from HFE-HC with respect to age, an almost equal ratio between sexes, greater frequency of cardiac and endocrine disturbances. The patient usually presents in the second decade, typically with hypogonadism that manifests as primary infertility in the female. A dilated cardiomyopathy that often becomes refractory to treatment is a common complication; the untreated patient usually dies of cardiac disease by the 30th year. The hepatic complications of iron overload in JHC may seem not as common as in the case of adult forms of HC (HFE-, TFR2, and FPN-HC), but this may be simply because the clinical picture is dominated by the endocrine and cardiac failure. In fact, the hepatic pathology may be profound, with histologically diagnosed cirrhosis developing even at a young age in up to 40% of patients. However, the clinical diagnosis of JHC is often coincidental, relating to investigation of endocrine or cardiac abnormalities including cardiac
shock. Glucose intolerance is manifest in almost two-thirds of patients and there may be presentation due to arthropathy or skin changes. Iron liver pathology in JHC are similar to those of hereditary HC in that there is progressive iron loading of parenchymal cells with typical sparing of the reticuloendothelial system (see Deugnier and Turlin, this issue). As in other forms of HC, aggressive venesection remains the cornerstone of therapy. Depending on the extent of progression of the disease, there may be a place for chelating therapy and cardiac transplant.\(^78\)

**Ferroportin Disease**

In 1999, when only one HC gene (i.e., \textit{HFE}) was known, a non-\textit{HFE} hereditary iron-overload condition with typical reticuloendothelial iron deposits was described in a large family from Italy.\(^10\) In the wake of the discovery of ferroportin, genome-wide screening procedures confirmed that the disease gene was \textit{SLC40A1}, coding for ferroportin, on chromosome 2q32.\(^9\) All patients were heterozygous for a c.230C—a substitution resulting in the replacement of alanine 77 with aspartate. This was subsequently referred to as ferroportin disease or other much rarer hereditary iron loading diseases can be considered (see text for details). TS, transferrin saturation.

**Figure 1** In patients with unexplained hyperferritinemia, regardless of the level of serum iron, cofactors and comorbidities associated with increased serum ferritin (SF) (e.g., chronic alcohol consumption, metabolic disturbances, obesity, inflammation, etc.) should be considered first. In the absence of these comorbidities, or if the iron abnormalities persist after these conditions have been effectively treated. If transferrin saturation (TS) is persistently elevated, \textit{HFE}-hemochromatosis (HC) should be excluded by genetic testing. If \textit{HFE} test is not diagnostic, parenchymal iron overload must be confirmed, ideally by liver biopsy (LB), before considering non-\textit{HFE}-HC. Parenchymal iron overload in adults, in the absence of thalassemia intermedia/nontransfused hereditary anemias with inefficient erythropoiesis or advanced cirrhosis, is typical of \textit{TFR2}-hemochromatosis, or more rarely, ferroportin-(\textit{FPN}) related forms. In young patients with severe cardiomyopathy and hypogonadism, juvenile HC should be considered and hemojulvin-(\textit{HJV}) and hepcidin-(\textit{HAMP}) gene sequencing performed. If available. In patients with increased SF levels and normal-low TS, in the absence of common causes of hyperferritinemia (see above), the workup should focus on documenting an iron-overload state by LB or magnetic resonance imaging (MRI). If so, depending on the pattern of iron distribution (e.g., preferential Kupffer cells, iron overload) and/or accompanying symptoms (e.g., severe anemia and/or neurologic disorders) ferroportin disease or other much rarer hereditary iron loading diseases can be considered (see text for details). TS, transferrin saturation.

**Epidemiology**

As opposed to \textit{HFE} and non-\textit{HFE}-HC, the pattern of inheritance of FD is autosomal dominant. Therefore, either parent carries the pathogenic mutation of \textit{FPN} and presents with unexplained hyperferritinemia. Numerous mutations of the \textit{FPN}
gene have been identified so far in families with primary hyperferritinemia, with divergent findings with respect to the pattern of ferritin/transferrin dissociation in probands of French–Canadian, Melanesian, Thai, Asian, and European heritage (Table 3). Yet, a few common FPN mutations have been independently reported in different countries (e.g., p.Val162del; p.Ala77Asp; p.Gly80Ser) (Table 3).

Overall, these figures make ferroportin disease the most common form of hereditary iron overload beyond HFE-HC.

**PATHOGENESIS**

The pathogenesis is quite different from hereditary HC and is discussed in this issue by De Domenico, Ward, and Kaplan. As originally hypothesized, the disorder is due to a loss of iron-export function of FPN: the

| Nucleotide Change | Amino Acid Change | Type of Variation* | Phenotype | Reference |
|-------------------|-------------------|--------------------|-----------|-----------|
| 1 c.134C>T        | p.Ala45Glu        | Missense           | Ferroportin disease | 98       |
| 2 c.206C>T        | p.Ala69Val        | Missense           | Ferroportin disease | 98       |
| 3 c.212C>T        | p.Ser71Phe        | Missense           | Ferroportin disease | 94       |
| 4 c.214G>T        | p.Val72Phe        | Missense           | Ferroportin disease | 98,99,99 |
| 5 c.230C>A        | p.Ala77Asp        | Missense           | Ferroportin disease | 94,96,98,100,101 |
| 6 c.238G>A        | p.Gly80Ser        | Missense           | Ferroportin disease | 88       |
| 7 c.239G>T        | p.Gly80Val        | Missense           | Ferroportin disease | 27,98    |
| 8 c.262A>G        | p.Arg88Gly        | Missense           | Ferroportin disease | 91       |
| 9 c.263G>C        | p.Arg88Thr        | Missense           | Ferroportin disease | 93       |
| 10 c.454A>T       | p.Ile152Phe       | Missense           | Ferroportin disease | 94       |
| 11 c.469G>A       | p.Asp157Asn       | Missense           | Ferroportin disease | 97       |
| 12 c.470A>C       | p.Asp157Ala       | Missense           | Ferroportin disease | 85,98    |
| 13 c.470A>G       | p.Asp157Gly       | Missense           | Ferroportin disease | 98       |
| 14 c.473G>T       | p.Trp158Leu       | Missense           | Ferroportin disease | 38       |
| 15 c.474G>T       | p.Trp158Cys       | Missense           | Ferroportin disease | 38       |
| 16 c.484_486del3  | p.Val162del       | Deletion           | Ferroportin disease | 81–84,87,98,99,102,103 |
| 17 c.521A>T       | p.Asn174Ile       | Missense           | Ferroportin disease | 100      |
| 18 c.532C>G       | p.Arg178Gly       | Missense           | Ferroportin disease | 102      |
| 19 c.533G>A       | p.Arg178Gln       | Missense           | Ferroportin disease | 27,98    |
| 20 c.539T>C       | p.Ile180Thr       | Missense           | Ferroportin disease | 91       |
| 21 c.542A>T       | p.Asp181Val       | Missense           | Ferroportin disease | 88,98    |
| 22 c.546G>T       | p.Gln182His       | Missense           | Ferroportin disease | 85,98    |
| 23 c.553A>G       | p.Asn185Asp       | Missense           | Ferroportin disease | 98,104   |
| 24 c.554A>C       | p.Asn185Thr       | Missense           | Ferroportin disease | 98       |
| 25 c.610G>A       | p.Gly204Ser       | Missense           | Ferroportin disease | 105      |
| 26 c.695C>A       | p.Ala232Asp       | Missense           | Ferroportin disease | 93,98    |
| 27 c.698T>C       | p.Leu233Pro       | Missense           | Ferroportin disease | 106,107  |
| 28 c.744G>T       | p.Gln248His       | Missense           | Ferroportin disease | 88       |
| 29 c.800G>A       | p.Gly267Asp       | Missense           | Ferroportin disease | 108      |
| 30 c.809A>T       | p.Asp270Val       | Missense           | Ferroportin disease | 85       |
| 31 c.968G>T       | p.Gly323Val       | Missense           | Ferroportin disease | 98       |
| 32 c.1111C>T      | p.Arg371Trp       | Missense           | Ferroportin disease | 98       |
| 33 c.1112G>A      | p.Arg371Gln       | Missense           | Ferroportin disease | 109      |
| 34 c.1402G>A      | p.Gly468Ser       | Missense           | Ferroportin disease | 110      |
| 35 c.1466G>A      | p.Arg499Lys       | Missense           | Ferroportin disease | 90       |
| 36 c.1467A>C      | p.Arg499Ser       | Missense           | Ferroportin disease | 27,98    |
| 37 c.1468G>A      | p.Gly490Ser       | Missense           | Ferroportin disease | 86       |
| 38 c.1469G>A      | p.Gly490Asp       | Missense           | Ferroportin disease | 86       |

*All reported ferroportin mutations are at the heterozygous state, according to the autosomal dominant trait.

Reported data do not allow to conclusively assign a classic ferroportin diseases phenotype.
resultant reduction in iron efflux causes a bottleneck in macrophages, which generate the largest iron flows, resulting in iron accumulation in Kupffer cells (KC) and macrophages with high SF levels and low to normal TS until late in the disease when TS also rises. The low-normal TS despite high SF is the biochemical hallmark of the disease, and along with the early and preferential accumulation of iron in hepatic KC (see Deugnier and Turlin, this issue) is central in the diagnostic workup of the disorder (Fig. 1). Although KC iron load is an early feature of FD and essential in the differential diagnosis with HFE-HC, discrete hepatocytic iron deposits are also appreciable in the classic FD, due to defective FPN activity in hepatocytes, even at early stages.10

**CLINICAL ASPECTS**

Clinical presentation appears heterogeneous, but overall, expressivity is milder than classic HC and the associated liver disease is usually not as severe. Hypochromic anemia is common in young females, and may require iron supplementation, which may further exacerbate the iron overload. Although venesection is again the cornerstone of therapy, it may not be tolerated equally in all patients and low TS with anemia may be rapidly established despite SF still being elevated.72 If phlebotomy is discontinued, there is a rapid rise in the ferritin level and both oral chelation and erythropoietin may be of some benefit. The disease must be suspected in any individual with unexplained hyperferritinemia, and investigated with arterial magnetic resonance imaging (MRI) is a useful noninvasive diagnostic tool to categorize and diagnose the disorder. Brain MRI with typical iron accumulation in basal ganglia and thalamus may help confirm the diagnosis. Iron chelators have been used with beneficial effects.120,121

**Aceruloplasminemia**

This is an extremely rare autosomal recessive disease, first reported by Miyajima,112 described mainly in Japanese patients and due to loss of function mutations in ceruloplasmin (CP) and resulting in iron overload in the liver and pancreas and progressive neurodegeneration.113–115 Ceruloplasmin is a copper-containing ferroxidase synthesized by hepatocytes that catalyzes the oxidation of ferrous to ferric iron, necessary for the release of iron to plasma transferrin.116,117 This activity may involve the stabilization of membrane FPN.118 Patients develop diabetes mellitus, retinal degeneration, ataxia, and dementia late in life.119 A mild-to-moderate degree of anemia with low serum iron and elevated SF is a constant feature and the pattern of hepatic iron overload is reminiscent of hereditary HC, but fibrosis or cirrhosis is uncommon. The disease should be suspected in cases presenting with anemia, high SF, and neurologic involvement. Brain MRI with typical iron accumulation in basal ganglia and thalamus may help confirm the diagnosis. Iron chelators have been used with beneficial effects.

**A transferrinemia/Hypotransferrinemia**

An extremely rare autosomal recessive hereditary disorder, at transferrinemia, was first described in a young girl with severe hypochromic anemia, and marked generalized iron overload122 it, has since been described in very few families worldwide.122,124–128 Transferrin delivers iron to the erythroid precursors and the defect leads to decreased hemoglobin synthesis resulting in a severe microcytic hypochromic anemia. However, this in turn leads to increased intestinal absorption that, although inefficiently handled in the plasma, is efficiently imported by parenchymal cells leading to often severe parenchymal iron overload at sites including the liver, myocardium, pancreas, and thyroid. Clinical presentation and features include pallor and fatigue with high SF, serum iron, and decreased total iron-binding capacity (TIBC). Treatment may be relatively effective, at least in some patients, via combined infusion of fresh frozen plasma, and subsequent phlebotomy or chelation therapy.

**DMT-1 Deficiency**

Divalent metal transporter 1 (DMT1) is the protein at the apical membrane of the duodenal enterocyte that transports iron (and other divalent ions) upon reduction to its ferrous state by the brush border ferrireductase DcytB.129 DMT1 also allows the iron exit from the acidified endosomes. Autosomal recessive mutations of DMT1 have been recently reported.130–135 All patients with DMT1 deficiency present with severe hypochromic microcytic anemia at birth, increased TS with normal TIBC, and slightly elevated SF, increased soluble transferrin receptor. All reported cases except one,135 unlike the DMT1 mutant animal models, present with marked hepatic iron overload. Patients appear to respond to erythropoietin.136,137

**H-Ferritin-Related Iron Overload**

Hyperferritinemia and concomitant hepatic iron overload have been described in four of seven members of a Japanese family carrying a heterozygous single point mutation (A49U) of the IRE motif in the
5′-untranslated region (5′UTR) of H-ferritin mRNA (+ 49A>T)\textsuperscript{138}. No further cases have been reported since the original series. However, an elegant animal study has recently showed that mice with an intestinal ferritin H gene deletion develop hemochromatosis,\textsuperscript{139} indicating that intestinal ferritin H is also required to limit iron efflux from intestinal cells, and that ferritin is an iron-loading gene, at least in mice.

**Hereditary Iron-Loading Anemias with Inefficient Erythropoiesis or Altered Intracellular Iron Traffic**

Within the spectrum of hereditary anemias, variable iron overload in the liver may be identified not only due to transfusional iron, but also to primary abnormalities of iron metabolism (see also, Deugnier and Turlin, this issue). The thalassemias, due to inherited maladies of iron metabolism (see also, Deugnier and Turlin, this issue). The thalassemias, due to inherited defects of either the α− or β− globin chains of hemoglobin, represent the most common single gene inherited disorder in the world.\textsuperscript{140} Although transfusions may largely account for the iron-overload states found in these patients (see below), the characteristic ineffective erythropoietic drive likely induces excess iron absorption via inhibition of hepcidin synthesis (see Babitt and Lin, this issue) and leads to hepatic iron overload. This is especially evident in patients with thalassemia intermedia who present marked parenchymal iron overload that mimics HFE-HC (see also, Deugnier and Turlin, this issue). Similar mechanistic phenomena may occur in the sideroblastic hereditary (and acquired) anemias characterized by anemia with ringed sideroblasts in the bone marrow and iron overload.\textsuperscript{141}

Liver disease, due to iron-driven oxidative damage but also to concomitant viral hepatitis, is common in β-thalassemia, the more severe and clinically important hemoglobinopathy. Standard pegylated interferon/ribavirin therapy can be successfully used in these patients\textsuperscript{142}: the aggravation of the underlying anemic state due to the hemolytic activity of ribavirin can be managed by using erythropoiesis-stimulating agents and blood transfusions. Thalassemic patients with chronic liver disease need close hepatic ultrasound surveillance for hepatocellular carcinoma (HCC).

In X-linked sideroblastic anemia, due to mutations of delta-aminolevulinic acid synthetase 2, the primary pathogenic event is excessive deposition of mitochondrial iron (Table 1). Seemingly, in Friedreich ataxia,\textsuperscript{143} an autosomal recessive, degenerative disease that involves the central and peripheral nervous systems and the heart, a defect in iron-sulfur cluster assembly interferes with iron export from mitochondria. These conditions represent the paradigm of a new class of iron-loading disorders due to iron mis-distribution within the cell (Table 1), and seem to benefit from the use of iron chelators.\textsuperscript{144}

**ACQUIRED DISORDERS**

**Enteral/Parenteral Iron Overload**

Iron overload may arise from excessive iron introduction through the enteral or parenteral route (Table 1). Usually, it is the long-term blood transfusion for hereditary anemias or various causes of bone marrow failure (e.g., aplastic anemia, myelodysplastic syndrome, etc.), which may cause a clinically apparent iron-loading disorder. This may also be the case in transfusion-dependent anemic patients with chronic kidney disease and long-term dialysis. The iron excess, in all these cases, is derived from senescent red blood cells and will thus preferentially accumulate in KC and macrophages; it is usually associated with some architectural disturbance in the liver, whereas endocrine glands and the heart are the preferential targets of toxicity and failure. Iron chelators are the mainstay of treatment in posttransfusion iron overload.\textsuperscript{145} The reporting of responses to chelation therapies has typically focused on average changes in serum ferritin in patient populations. This approach has limitations. Changes in serum ferritin may not reflect trends in iron balance equally in all patients or for all chelation regimens and provide no useful information about the proportion of responder patients. For example, this gives insufficient information about iron trends in tissues such as the heart. Recently, monitoring of iron overload and response to therapy has advanced with the increasing use of MRI techniques to estimate iron balance (changes in liver iron concentration) and extra-hepatic iron distribution (myocardial T2*).\textsuperscript{146} A patient’s lack of a response may result from inadequate dosing, high transfusion requirement, poor treatment adherence, or unfavorable pharmacology of the chelation regime. In fact, despite therapeutic improvements with the use of new and potent iron chelators, it is still cardiac iron overload that causes most deaths in posttransfusion iron-loading anemias.\textsuperscript{145} The efficacy of iron chelation in patients with chronic kidney disease is often complicated by the presence of a chronic inflammatory state that leads to iron sequestration in the reticuloendothelial system and prevents iron redistribution.\textsuperscript{147}

**Chronic Liver Diseases**

Common chronic liver diseases, including viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, and HCC, are often associated with varying degrees of iron loading.\textsuperscript{148} This may be of low grade, but is sometimes sufficiently severe as to mistakenly identify hereditary HC, although this is less of a problem after the introduction of genotyping. Important questions still
have to be answered, however. These include the relationship between iron and the primary disease as well as its possible association with the various types of hereditary HC. Recent advances in the understanding of the iron regulatory genes and in particular hepcidin increasingly support a direct relationship between disease progression and a pathogenic role for iron. Pathologic and diagnostic aspects and the role of liver biopsy in hepatic iron overload found in the course of various liver diseases is discussed by Deugnier and Turlin (this issue).

**MISCELLANEOUS DISORDERS**

Several human diseases due to both hereditary (clearly identified or suspected) and acquired disorders are characterized by iron accumulation in the liver.

**Porphyria Cutanea Tarda**

Porphyria cutanea tarda (PCT), the most common porphyria, is caused by a deficiency of uroporphyrinogen decarboxylase activity (UROD). In the sporadic subtype (75% of cases), UROD activity is deficient only in the liver, whereas in the familial subtype (25% of cases), an autosomal dominant disorder at early-onset disorder affecting both sexes, the defect leads to a constitutive 50% UROD deficiency also in the erythrocytes. Porphyria cutanea tarda is a complex disease in which both a multigenic predisposition and environmental risk factors are needed for clinical expressivity. The risk factors that contribute to inactivation or inhibition of this enzyme are mainly alcohol abuse, estrogens, hepatitis C, and to a lesser extent, HIV infections and inheritance of one or more HFE genotypes. Symptoms develop when residual, hepatic UROD decreases below a threshold of ~25%. Clinical features include photosensitive skin lesions, hepatic accumulation and urinary excretion of uroporphyrins, altered iron indices, and hepatic iron overload. Iron removal by phlebotomy is part of the current therapeutic strategy in PCT: It improves the clinical outcome and biochemical signs of the disease.

**African Siderosis**

African iron overload, formerly called Bantu siderosis, is still an important pathology in rural society where up to 15% of adult males may be affected. It was originally described by Strachan in individuals from several parts of southern and central Africa in the 1920s. Originally, iron overload was attributed to consumption of food, or more significantly to large quantities of traditional beer prepared in iron pots. Later, a genetic modifier was postulated, and a polymorphism of the ferroportin gene (p.Gln248His) restricted to Africans and African Americans has been considered a candidate modifier, but no conclusive evidence has been provided so far. Regardless of a predisposing genetic trait, alcoholic beverages are a main factor leading to iron overload and liver disease in southern Africa’s rural adult population. They may develop cirrhosis and HCC and liver iron concentration may reach the level found in HFE-HC and beyond.

**Alloimmune (Neonatal) Hemochromatosis**

Neonatal hemochromatosis (NH) is a severe neonatal disease characterized by stillbirth or neonatal liver failure in the antenatal or early neonatal period, usually within a period of hours to days postdelivery. Intrauterine growth retardation, and associated placental edema and either oligohydramnios or polyhydramnios are common. The prevailing presentation is jaundice with coagulopathy, hypoglycemia, and hypoalbuminemia and high SF. Thus, diagnosis is made after exclusion of other causes of liver failure and may be confirmed by (1) salivary gland biopsy, which demonstrates excess iron; and (2) MRI, which typically shows iron deposition in liver, pancreas, and heart, but with sparing of the spleen. Various theories have been put forth to explain the etiology of NH, including fetal liver injury causing abnormalities of iron handling, or alternatively, abnormalities of iron handling by the maternofetal unit, with the possibility existing that they are not mutually exclusive. There is a high rate of recurrence if a mother has a previous pregnancy complicated by NH; occasionally, it has been also documented in consanguineous families, which has been considered support that NH is a genetic disease. However, a candidate gene has not yet being identified. On the contrary, recently, an alloimmune mechanism for the disease has been postulated. Neonatal hemochromatosis may represent the phenotypic expression of gestational alloimmune foetal liver disease induced by the placental passage of specific reactive immunoglobulin G and involving the activation of fetal complement by the classical pathway leading to the formation of membrane attack complex as the effector of cell injury. Recently, Pan et al found that the percentage of hepatocytes containing antiterminal complement cascade neoantigens involved in membrane attack complex formation in NH was much greater than that in non-NH liver disease. In this vein, high-dose intravenous immunoglobulin therapy (IVIG) to the mother appears to significantly increase survival of newborns, high-dose IVIG, with or without exchange transfusions, to newborns achieved 75% good outcome compared with 17% in historical controls not treated with IVIG. The prognosis of NH is extremely poor. Antioxidant therapy and chelation appear to be of limited value, and although liver transplantation has been identified as a viable therapeutic option, there may be reaccumulation of hepatic iron.
ABBREVIATIONS

CP ceruloplasmin
DMTI divalent metal transporter-1
FD ferroportin disease
FPN ferroportin
HAMP hepcidin
HC hemochromatosis
HCC hepatocellular carcinoma
HJV hemojuvelin
IVIG intravenous immunoglobulin
JHC juvenile hemochromatosis
KC Kupffer cells
MRI magnetic resonance imaging
NH neonatal hemochromatosis
PCT porphyria cutanea tarda
SF serum ferritin
TFR2 transferrin receptor 2
TIBC total iron binding capacity
TS transferrin saturation
UROD uroporphyrinogen decarboxylase

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