Non-*HFE* Hepatic Iron Overload

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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-*HFE* hemochromatosis syndromes identifies a subgroup of hereditary iron loading disorders that share with classic *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 (*TFR2*), hepcidin (*HAMP*), hemojuvelin (*HJV*), and ferroportin (*FPN*), and, unlike *HFE*-hemochromatosis, are not restricted to Caucasians. Ferroportin disease, the most common non-*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.

KEYWORDS: Iron overload, non-*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.[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 (H_2O_2), being changed into its noxious hydroxyl radical (HO·). This leads to consequent damage to DNA, proteins, and membranes.[2] The classic example of iron overload in human pathology is *HFE*-hereditary hemochromatosis (HC), but numerous other entities are now identified to cause pathologic iron accumulation in the liver[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

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

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

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[4](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.[5] 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*),[6] hepcidin (*HAMP*),[7] hemojuvelin (*HJV*),[8] and ferroportin (*FPN*) (Table 1).[9,10]

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

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.[3] 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 *HJV*- 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 disease[72] (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 *HJV,* formerly *HFE2*.[8] Many *HJV* 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).[8,34,42,43,46,47,51,58–61]

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 *HJV*-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 *HJV* 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., *HJV*- 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 *HJV*), 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 *HJV*, 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-*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	15,20
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)**					
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)					
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

Table 2 (*Continued*)

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
4	c.220delG	p.Val74TrpfsX40	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 Putative modifier in p.Cys282Tyr *HFE* homozygous when heterozygous	42,43,45
11	c.314C>T	p.Ser105Leu	Missense (heterozygous)	Putative modifier in p.Cys282Tyr *HFE* homozygous	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
15	c.404T>G	p.Leu135Arg	Missense (heterozygous)	Putative modifier in p.His63Asp *HFE* homozygous	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)	Putative modifier in p.Cys282Tyr/p.His63Asp *HFE* compound heterozygous	53
27	c.615C>G	p.Ser205Arg	Missense (compound heterozygous with p.Gly250Val)	Juvenile hemochromatosis	42

Table 2 (*Continued*)

	Nucleotide Change	Amino Acid Change	Type of Variation	Phenotype	References
28	c.665T>A	p.Ile222Asn	Missense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	8,43
29	c.745G>C	p.Asp249His	Missense (homozygous)	Hemochromatosis in middle age	54
30	c.749G>T	p.Gly250Val	Missense (compound heterozygous with p.Ser205Arg)	Juvenile hemochromatosis	42
31	c.806_807insA	p.Asn269LysfsX43	Frameshift (compound heterozygous with p.Val74TrpfsX40)	Juvenile hemochromatosis	42
32	c.842T>C	p.Ile281Thr	Missense (homozygous or compound heterozygous with p.Cys321X)	Juvenile hemochromatosis	8,55
33	c.862C>T	p.Arg288Trp	Missense (homozygous)	Juvenile hemochromatosis	42,56
34	c.904G>A	p.Glu302Lys	Missense (heterozygous)	Putative modifier in p.Cys282Tyr *HFE* homozygous	45
35	c.934C>T	p.Gln312X	Nonsense (homozygous)	Juvenile hemochromatosis	54,57
36	c.959G>T	p.Gly320Val	Missense (homozygous or compound heterozygous; heterozygous)	Juvenile hemochromatosis	8,34,42–44,46, 47,51,58–61
				Putative modifier in p.Cys282Tyr *HFE* homozygous when heterozygous	45
37	c.960_961insG	p.Cys321ValfsX21	Frameshift (homozygous)	Juvenile hemochromatosis	42
38	c.963C>G	p.Cys321Trp	Missense (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	43
39	c.963C>A	p.Cys321X	Nonsense (compound heterozygous with p.Ile281Thr)	Juvenile hemochromatosis	55
40	c.976C>T	p.Arg326X	Nonsense (compound heterozygous with p.Cys80Arg or p.Gly320Val)	Juvenile hemochromatosis	8,44
41	c.982_985del4	p.Ser328AspfsX10	Frameshift (compound heterozygous with p.Gly320Val)	Juvenile hemochromatosis	47
42	c.985C>T	p.Arg329X	Nonsense (homozygous)	Juvenile hemochromatosis	62
43	c.1004G>A	p.Arg335Gln	Missense (heterozygous)	Putative modifier in p.Cys282Tyr *HFE* homozygous	45
44	c.1026delT	p.Ala343ProfsX24	Frameshift (homozygous)	Juvenile hemochromatosis	34
45	c.1080delC	p.Cys361ValfsX6	Frameshift (homozygous)	Juvenile hemochromatosis	8
46	c.1114A>G	p.Asn372Asp	Missense (heterozygous)	Putative modifier in p.Cys282Tyr *HFE* homozygous	45
47	c.1153C>T	p.Arg385X	Nonsense (homozygous)	Juvenile hemochromatosis	42
***HAMP* (RefSeq NM_021175.2, NP_066998.1)**					
1	c.-153C>T		Promoter mutation (heterozygous)	Putative modifier in p.Cys282Tyr *HFE* homozygous	63
2	c.-25G>A		Promoter mutation (homozygous)	Juvenile hemochromatosis	64–66
3	c.95delG	p.Gly32Aspfs	Frameshift (homozygous)	Juvenile hemochromatosis	7
4	c.126_127del2	p.Arg42Serfs	Frameshift (homozygous)	Juvenile hemochromatosis	34

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 *TFR2:* c.949C > T	*HFE:* p.His63Asp/ p.Cys282Tyr *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.

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 hyperferritinemia (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.[29–31,35] 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.[75] Lamon[76] 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.[77–80] 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

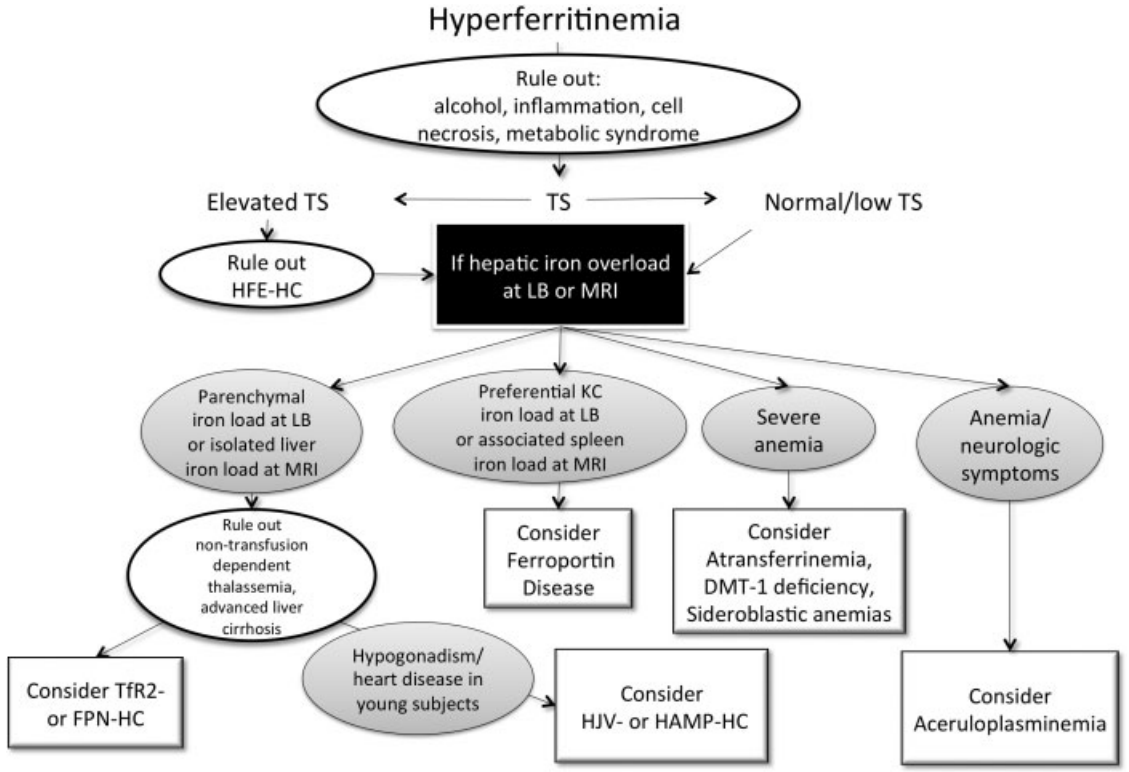

Figure 1 In patients with unexplained hyperferritinemia, regardless of the level of serum iron, cofactors and comorbidities associated with increased serum ferritin (SF) (e.g., chronic alcohol consumption, metabolic disturbances, obesity, inflammation, etc.) should be considered first. In the absence of these comorbidities, or if the iron abnormalities persist after these conditions have been effectively treated. If transferrin saturation (TS) is persistently elevated, *HFE*-hemochromatosis (HC) should be excluded by genetic testing. If *HFE* test is not diagnostic, parenchymal iron overload must be confirmed, ideally by liver biopsy (LB), before considering non-*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 *TFR2*-hemochromatosis, or more rarely, ferroportin-(*FPN*-) related forms. In young patients with severe cardiomyopathy and hypogonadism, juvenile HC should be considered and hemojuvelin-(*HJV*-) and hepcidin-(*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.

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., *HFE*) was known, a non-*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 *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 (FD).[72]

EPIDEMIOLOGY

As opposed to *HFE*- and non-*HFE*-HC, the pattern of inheritance of FD is autosomal dominant. Therefore, either parent carries the pathogenic mutation of *FPN* and presents with unexplained hyperferritinemia. Numerous mutations of the *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).[9,28,34,37,38,81–98] 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,[9] the disorder is due to a loss of iron-export function of FPN: the

Table 3 Ferroportin Disease: Reported Mutations

	SLC40A1 (RefSeq NM_014585.5, NP_055400.1)				
	Nucleotide Change	**Amino Acid Change**	**Type of Variation***	**Phenotype**	**Reference**
1	c.134C>A	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†	98
4	c.214G>T	p.Val72Phe	Missense	Ferroportin disease	94
5	c.230C>A	p.Ala77Asp	Missense	Ferroportin disease	9,89,99
6	c.238G>A	p.Gly80Ser	Missense	Ferroportin disease	92,96,98,100,101
7	c.239G>T	p.Gly80Val	Missense	Ferroportin disease	88
8	c.262A>G	p.Arg88Gly	Missense	Ferroportin disease	27,98
9	c.263G>C	p.Arg88Thr	Missense	Ferroportin disease	91
10	c.454A>T	p.Ile152Phe	Missense	Ferroportin disease	93
11	c.469G>A	p.Asp157Asn	Missense	Ferroportin disease	94
12	c.470A>C	p.Asp157Ala	Missense	Ferroportin disease	97
13	c.470A>G	p.Asp157Gly	Missense	Ferroportin disease	85,98
14	c.473G>T	p.Trp158Leu	Missense	Ferroportin disease	98
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†	98
26	c.695C>A	p.Ala232Asp	Missense	Ferroportin disease	105
27	c.698T>C	p.Leu233Pro	Missense	Ferroportin disease	93,98
28	c.744G>T	p.Gln248His	Missense	Ferroportin disease†	106,107
29	c.800G>A	p.Gly267Asp	Missense	Ferroportin disease	88
30	c.809A>T	p.Asp270Val	Missense	Ferroportin disease	108
31	c.968G>T	p.Gly323Val	Missense	Ferroportin disease	85
32	c.1111C>T	p.Arg371Trp	Missense	Ferroportin disease†	98
33	c.1112G>A	p.Arg371Gln	Missense	Ferroportin disease†	98
34	c.1402G>A	p.Gly468Ser	Missense	Ferroportin disease†	109
35	c.1466G>A	p.Arg489Lys	Missense	Ferroportin disease	110
36	c.1467A>C	p.Arg489Ser	Missense	Ferroportin disease	90
37	c.1468G>A	p.Gly490Ser	Missense	Ferroportin disease	27,98
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 serum iron studies and genetic testing, if available, of the immediate family (Fig. 1). Abdominal magnetic resonance imaging (MRI) is a useful noninvasive diagnostic tool to categorize and diagnose the disorder, as it can differentiate patients with classic FD, characterized by liver, spleen, and bone marrow iron retention, from the rarer nonclassic form of FPN-related iron load (i.e., *FPN*-HC), associated with liver iron overload, but normal spleen and bone marrow iron content.[111]

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.[120,121]

Atransferrinemia/Hypotransferrinemia

An extremely rare autosomal recessive hereditary disorder, atransferrinemia, was first described in a young girl with severe hypochromic anemia, and marked generalized iron overload[122] 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)[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,[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 defects of either the α− or β− globin chains of hemoglobin, represent the most common single gene inherited disorder in the world.[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.[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[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,[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.[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.[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 extrahepatic iron distribution (myocardial T2*).[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.[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.[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.[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).[149] 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.[150] 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.[151–153] 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.[154]

African Siderosis

African iron overload, formerly called Bantu siderosis,[155] 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.[156] Originally, iron overload was attributed to consumption of food, or more significantly to large quantities of traditional beer prepared in iron pots.[157] Later, a genetic modifier was postulated,[158] and a polymorphism of the ferroportin gene (p.Gln248His) restricted to Africans and African Americans has been considered a candidate modifier,[106,107] 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.[159]

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.[160] 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.[161] 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.[160] 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.[161] 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[162] 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[163]; high-dose IVIG, with or without exchange transfusions, to newborns achieved 75% good outcome compared with 17% in historical controls not treated with IVIG.[164] 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.[165]

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

REFERENCES

1. Bothwell TH. The control of iron absorption. Br J Haematol 1968;14(5):453–456
2. Pietrangelo A. Metals, oxidative stress, and hepatic fibrogenesis. Semin Liver Dis 1996;16(1):13–30
3. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology 2010;139(2):393–408, 408; e1–e2
4. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet 1996;13(4):399–408
5. Pietrangelo A. Hemochromatosis 1998: is one gene enough? J Hepatol 1998;29(3):502–509
6. Camaschella C, Roetto A, Calì A, et al. The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. Nat Genet 2000;25(1):14–15
7. Roetto A, Papanikolaou G, Politou M, et al. Mutant antimicrobial peptide hepcidin is associated with severe juvenile hemochromatosis. Nat Genet 2003;33(1):21–22
8. Papanikolaou G, Samuels ME, Ludwig EH, et al. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. Nat Genet 2004; 36(1):77–82
9. Montosi G, Donovan A, Totaro A, et al. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. J Clin Invest 2001;108(4): 619–623
10. Pietrangelo A, Montosi G, Totaro A, et al. Hereditary hemochromatosis in adults without pathogenic mutations in the hemochromatosis gene. N Engl J Med 1999;341(10): 725–732
11. De Gobbi M, Barilaro MR, Garozzo G, Sbaiz L, Alberti F, Camaschella C. TFR2 Y250X mutation in Italy. Br J Haematol 2001;114(1):243–244
12. Roetto A, Totaro A, Piperno A, et al. New mutations inactivating transferrin receptor 2 in hemochromatosis type 3. Blood 2001;97(9):2555–2560
13. Girelli D, Bozzini C, Roetto A, et al. Clinical and pathologic findings in hemochromatosis type 3 due to a novel mutation in transferrin receptor 2 gene. Gastroenterology 2002;122(5):1295–1302
14. Majore S, Milano F, Binni F, et al. Homozygous p.M172K mutation of the TFR2 gene in an Italian family with type 3 hereditary hemochromatosis and early onset iron overload. Haematologica 2006;91(8, Suppl):ECR33
15. Gérolami V, Le Gac G, Mercier L, Nezri M, Bergé-Lefranc JL, Férec C. Early-onset haemochromatosis caused by a novel combination of TFR2 mutations(p.R396X/c.1538-2 A> G) in a woman of Italian descent. Haematologica 2008;93(5):e45–e46
16. Mattman A, Huntsman D, Lockitch G, et al. Transferrin receptor 2 (TfR2) and HFE mutational analysis in non-C282Y iron overload: identification of a novel TfR2 mutation. Blood 2002;100(3):1075–1077
17. Hattori A, Wakusawa S, Hayashi H, et al. AVAQ_594-597 deletion of the TfR2 gene in a Japanese family with hemochromatosis. Hepatol Res 2003;26(2):154–156
18. Le Gac G, Mons F, Jacolot S, Scotet V, Férec C, Frébourg T. Early onset hereditary hemochromatosis resulting from a novel TFR2 gene nonsense mutation (R105X) in two siblings of north French descent. Br J Haematol 2004;125(5):674–678
19. Koyama C, Wakusawa S, Hayashi H, et al. Two novel mutations, L490R and V561X, of the transferrin receptor 2 gene in Japanese patients with hemochromatosis. Haematologica 2005;90(3):302–307
20. Lee PL, Barton JC. Hemochromatosis and severe iron overload associated with compound heterozygosity for TFR2 R455Q and two novel mutations TFR2 R396X and G792R. Acta Haematol 2006;115(1–2):102–105
21. Hsiao PJ, Tsai KB, Shin SJ, et al. A novel mutation of transferrin receptor 2 in a Taiwanese woman with type 3 hemochromatosis. J Hepatol 2007;47(2):303–306
22. Biasiotto G, Belloli S, Ruggeri G, et al. Identification of new mutations of the HFE, hepcidin, and transferrin receptor 2 genes by denaturing HPLC analysis of individuals with biochemical indications of iron overload. Clin Chem 2003;49(12):1981–1988
23. Pelucchi S, Mariani R, Trombini P, et al. Expression of hepcidin and other iron-related genes in type 3 hemochromatosis due to a novel mutation in transferrin receptor-2. Haematologica 2009;94(2):276–279
24. Pietrangelo A, Caleffi A, Henrion J, et al. Juvenile hemochromatosis associated with pathogenic mutations of adult hemochromatosis genes. Gastroenterology 2005;128(2): 470–479
25. Biasiotto G, Camaschella C, Forni GL, Polotti A, Zecchina G, Arosio P. New TFR2 mutations in young Italian patients with hemochromatosis. Haematologica 2008;93(2):309–310
26. Hofmann WK, Tong XJ, Ajioka RS, Kushner JP, Koeffler HP. Mutation analysis of transferrin-receptor 2 in patients with atypical hemochromatosis. Blood 2002;100(3):1099–1100
27. Cunat S, Giansily-Blaizot M, Bismuth M, et al; CHU Montpellier AOI 2004 Working Group. Global sequencing approach for characterizing the molecular background of hereditary iron disorders. Clin Chem 2007;53(12):2060–2069
28. Rivard SR, Lanzara C, Grimard D, et al. Autosomal dominant reticuloendothelial iron overload (HFE type 4) due to a new missense mutation in the FERROPORTIN 1

gene (SLC11A3) in a large French-Canadian family. Haematologica 2003;88(7):824–826
29. Njajou OT, Vaessen N, Joosse M, et al. A mutation in SLC11A3 is associated with autosomal dominant hemochromatosis. Nat Genet 2001;28(3):213–214
30. Wallace DF, Clark RM, Harley HA, Subramaniam VN. Autosomal dominant iron overload due to a novel mutation of ferroportin1 associated with parenchymal iron loading and cirrhosis. J Hepatol 2004;40(4):710–713
31. Arden KE, Wallace DF, Dixon JL, et al. A novel mutation in ferroportin1 is associated with haemochromatosis in a Solomon Islands patient. Gut 2003;52(8):1215–1217
32. Del-Castillo-Rueda A, Moreno-Carralero MI, Alvarez-Sala-Walther LA, et al. Two novel mutations in the SLC40A1 and HFE genes implicated in iron overload in a Spanish man. Eur J Haematol 2011;86(3):260–264
33. Viprakasit V, Merryweather-Clarke AT, Chinthammitr Y, et al. Molecular diagnosis of the first ferroportin mutation (C326Y) in the Far East causing a dominant form of inherited iron overload. Blood 2004;104(11):3204(ASH Annual Meeting Abstracts)
34. Lok CY, Merryweather-Clarke AT, Viprakasit V, et al. Iron overload in the Asian community. Blood 2009;114(1): 20–25
35. Sham RL, Phatak PD, West C, Lee P, Andrews C, Beutler E. Autosomal dominant hereditary hemochromatosis associated with a novel ferroportin mutation and unique clinical features. Blood Cells Mol Dis 2005;34(2):157–161
36. Wallace DF, Dixon JL, Ramm GA, Anderson GJ, Powell LW, Subramaniam VN. A novel mutation in ferroportin implicated in iron overload. J Hepatol 2007;46(5):921–926
37. Létocart E, Le Gac G, Majore S, et al. A novel missense mutation in SLC40A1 results in resistance to hepcidin and confirms the existence of two ferroportin-associated iron overload diseases. Br J Haematol 2009;147(3):379–385
38. Mayr R, Griffiths WJ, Hermann M, et al. Identification of mutations in SLC40A1 that affect ferroportin function and phenotype of human ferroportin iron overload. Gastroenterology 2011;140(7):2056–2063, e1
39. Lee P, Promrat K, Mallette C, Flynn M, Beutler E. A juvenile hemochromatosis patient homozygous for a novel deletion of cDNA nucleotide 81 of hemojuvelin. Acta Haematol 2006;115(1–2):123–127
40. Murugan RC, Lee PL, Kalavar MR, Barton JC. Early age-of-onset iron overload and homozygosity for the novel hemojuvelin mutation HJV R54X (exon 3; c.160A—> T) in an African American male of West Indies descent. Clin Genet 2008;74(1):88–92
41. Jánosi A, Andrikovics H, Vas K, et al. Homozygosity for a novel nonsense mutation (G66X) of the HJV gene causes severe juvenile hemochromatosis with fatal cardiomyopathy. Blood 2005;105(1):432
42. Lanzara C, Roetto A, Daraio F, et al. Spectrum of hemojuvelin gene mutations in 1q-linked juvenile hemochromatosis. Blood 2004;103(11):4317–4321
43. Lee PL, Beutler E, Rao SV, Barton JC. Genetic abnormalities and juvenile hemochromatosis: mutations of the HJV gene encoding hemojuvelin. Blood 2004;103(12):4669–4671
44. Wallace DF, Dixon JL, Ramm GA, Anderson GJ, Powell LW, Subramaniam N. Hemojuvelin (HJV)-associated hemochromatosis: analysis of HJV and HFE mutations and iron overload in three families. Haematologica 2005;90(2): 254–255
45. Le Gac G, Scotet V, Ka C, et al. The recently identified type 2A juvenile haemochromatosis gene (HJV), a second candidate modifier of the C282Y homozygous phenotype. Hum Mol Genet 2004;13(17):1913–1918
46. Daraio F, Ryan E, Gleeson F, Roetto A, Crowe J, Camaschella C. Juvenile hemochromatosis due to G320V/Q116X compound heterozygosity of hemojuvelin in an Irish patient. Blood Cells Mol Dis 2005;35(2):174–176
47. Gehrke SG, Pietrangelo A, Kascák M, et al. HJV gene mutations in European patients with juvenile hemochromatosis. Clin Genet 2005;67(5):425–428
48. de Diego C, Opazo S, Sánchez-Castaño A, Martínez-Castro P. New HJV mutation in a patient with hyperferritinemia and H63D homozygosity for the HFE gene. Int J Hematol 2007;86(4):379–380
49. van Dijk BA, Kemna EH, Tjalsma H, et al. Effect of the new HJV-L165X mutation on penetrance of HFE. Blood 2007;109(12):5525–5526
50. Klomp C, Abbes AP, Engel H. Gene symbol: HFE2a (HJV). Disease: juvenile hemochromatosis. Hum Genet 2005;118(3–4):545–546
51. Aguilar-Martinez P, Lok CY, Cunat S, Cadet E, Robson K, Rochette J. Juvenile hemochromatosis caused by a novel combination of hemojuvelin G320V/R176C mutations in a 5-year old girl. Haematologica 2007;92(3):421–422
52. Ka C, Le Gac G, Letocart E, Gourlaouen I, Martin B, Férec C. Phenotypic and functional data confirm causality of the recently identified hemojuvelin p.r176c missense mutation. Haematologica 2007;92(9):1262–1263
53. Biasiotto G, Roetto A, Daraio F, et al. Identification of new mutations of hepcidin and hemojuvelin in patients with HFE C282Y allele. Blood Cells Mol Dis 2004;33(3): 338–343
54. Koyama C, Hayashi H, Wakusawa S, et al. Three patients with middle-age-onset hemochromatosis caused by novel mutations in the hemojuvelin gene. J Hepatol 2005;43(4): 740–742
55. Huang FW, Rubio-Aliaga I, Kushner JP, Andrews NC, Fleming MD. Identification of a novel mutation (C321X) in HJV. Blood 2004;104(7):2176–2177
56. Filali M, Le Jeunne C, Durand E, et al. Juvenile hemochromatosis HJV-related revealed by cardiogenic shock. Blood Cells Mol Dis 2004;33(2):120–124
57. Nagayoshi Y, Nakayama M, Suzuki S, et al. A Q312X mutation in the hemojuvelin gene is associated with cardiomyopathy due to juvenile haemochromatosis. Eur J Heart Fail 2008;10(10):1001–1006
58. Militaru MS, Popp RA, Trifa AP. Homozygous G320V mutation in the HJV gene causing juvenile hereditary haemochromatosis type A. A case report. J Gastrointestin Liver Dis 2010;19(2):191–193
59. Brakensiek K, Fegbeutel C, Mälzer M, Strüber M, Kreipe H, Stuhrmann M. Juvenile hemochromatosis due to homozygosity for the G320V mutation in the HJV gene with fatal outcome. Clin Genet 2009;76(5):493–495
60. Santos PC, Cançado RD, Pereira AC, et al. Hereditary hemochromatosis: mutations in genes involved in iron homeostasis in Brazilian patients. Blood Cells Mol Dis 2011;46(4):302–307
61. Várkonyi J, Lueff S, Szucs N, et al. Hemochromatosis and hemojuvelin G320V homozygosity in a Hungarian woman. Acta Haematol 2010;123(3):191–193

62. Zhou R-F, Ouyang J, Guo X, et al. Novel homozygous mutation (R329X) in the hemojuvelin gene is associated with hypogonadotrophic hypogonadism, diabetes mellitus and heart failure due to juvenile hemochromatosis. Blood 2009;114(22):5102(ASH Annual Meeting Abstracts)
63. Island ML, Jouanolle AM, Mosser A, et al. A new mutation in the hepcidin promoter impairs its BMP response and contributes to a severe phenotype in HFE related hemochromatosis. Haematologica 2009;94(5):720–724
64. Matthes T, Aguilar-Martinez P, Pizzi-Bosman L, et al. Severe hemochromatosis in a Portuguese family associated with a new mutation in the 5′-UTR of the HAMP gene. Blood 2004;104(7):2181–2183
65. Porto G, Roetto A, Daraio F, et al. A Portuguese patient homozygous for the -25G>A mutation of the HAMP promoter shows evidence of steady-state transcription but fails to up-regulate hepcidin levels by iron. Blood 2005;106(8):2922–2923
66. Mendes AI, Ferro A, Martins R, et al. Non-classical hereditary hemochromatosis in Portugal: novel mutations identified in iron metabolism-related genes. Ann Hematol 2009;88(3):229–234
67. Merryweather-Clarke AT, Cadet E, Bomford A, et al. Digenic inheritance of mutations in HAMP and HFE results in different types of haemochromatosis. Hum Mol Genet 2003;12(17):2241–2247
68. Jacolot S, Le Gac G, Scotet V, Quere I, Mura C, Ferec C. HAMP as a modifier gene that increases the phenotypic expression of the HFE pC282Y homozygous genotype. Blood 2004;103(7):2835–2840
69. Roetto A, Daraio F, Porporato P, et al. Screening hepcidin for mutations in juvenile hemochromatosis: identification of a new mutation (C70R). Blood 2004; 103(6): 2407–2409
70. Majore S, Binni F, Pennese A, De Santis A, Crisi A, Grammatico P. HAMP gene mutation c.208T>C (p.C70R) identified in an Italian patient with severe hereditary hemochromatosis. Hum Mutat 2004;23(4):400
71. Delatycki MB, Allen KJ, Gow P, et al. A homozygous HAMP mutation in a multiply consanguineous family with pseudo-dominant juvenile hemochromatosis. Clin Genet 2004;65(5):378–383
72. Pietrangelo A. The ferroportin disease. Blood Cells Mol Dis 2004;32(1):131–138
73. Pietrangelo A. Hereditary hemochromatosis—a new look at an old disease. N Engl J Med 2004;350(23):2383–2397
74. De Domenico I, Ward DM, Langelier C, et al. The molecular mechanism of hepcidin-mediated ferroportin down-regulation. Mol Biol Cell 2007;18(7):2569–2578
75. Plattner HC, Nussbaumer T, Rywlin A. [Juvenile and familial hemochromatosis with endocrinomyocardiac syndrome]Helv Med Acta 1951;18(4-5):499–502
76. Lamon JM, Marynick SP, Roseblatt R, Donnelly S. Idiopathic hemochromatosis in a young female. A case study and review of the syndrome in young people. Gastroenterology 1979;76(1):178–183
77. Cazzola M, Ascari E, Barosi G, et al. Juvenile idiopathic haemochromatosis: a life-threatening disorder presenting as hypogonadotropic hypogonadism. Hum Genet 1983;65(2): 149–154
78. Kelly AL, Rhodes DA, Roland JM, Schofield P, Cox TM. Hereditary juvenile haemochromatosis: a genetically heterogeneous life-threatening iron-storage disease. QJM 1998; 91(9):607–618
79. Rivard SR, Mura C, Simard H, et al. Clinical and molecular aspects of juvenile hemochromatosis in Saguenay-Lac-Saint-Jean (Quebec, Canada). Blood Cells Mol Dis 2000; 26(1):10–14
80. De Gobbi M, Roetto A, Piperno A, et al. Natural history of juvenile haemochromatosis. Br J Haematol 2002;117(4): 973–979
81. Devalia V, Carter K, Walker AP, et al. Autosomal dominant reticuloendothelial iron overload associated with a 3-base pair deletion in the ferroportin 1 gene (SLC11A3). Blood 2002;100(2):695–697
82. Wallace DF, Pedersen P, Dixon JL, et al. Novel mutation in ferroportin1 is associated with autosomal dominant hemochromatosis. Blood 2002;100(2):692–694
83. Roetto A, Merryweather-Clarke AT, Daraio F, et al. A valine deletion of ferroportin 1: a common mutation in hemochromastosis type 4. Blood 2002;100(2):733–734
84. Cazzola M, Cremonesi L, Papaioannou M, et al. Genetic hyperferritinaemia and reticuloendothelial iron overload associated with a three base pair deletion in the coding region of the ferroportin gene (SLC11A3). Br J Haematol 2002;119(2):539–546
85. Hetet G, Devaux I, Soufir N, Grandchamp B, Beaumont C. Molecular analyses of patients with hyperferritinemia and normal serum iron values reveal both L ferritin IRE and 3 new ferroportin (SLC11A3) mutations. Blood 2003;102(5): 1904–1910
86. Jouanolle AM, Douabin-Gicquel V, Halimi C, et al. Novel mutation in ferroportin 1 gene is associated with autosomal dominant iron overload. J Hepatol 2003;39(2): 286–289
87. Zoller H, McFarlane I, Theurl I, et al. Primary iron overload with inappropriate hepcidin expression in V162del ferroportin disease. Hepatology 2005;42(2):466–472
88. Cremonesi L, Forni GL, Soriani N, et al. Genetic and clinical heterogeneity of ferroportin disease. Br J Haematol 2005;131(5):663–670
89. Subramaniam VN, Wallace DF, Dixon JL, Fletcher LM, Crawford DH. Ferroportin disease due to the A77D mutation in Australia. Gut 2005;54(7):1048–1049
90. Koyama C, Wakusawa S, Hayashi H, et al. A Japanese family with ferroportin disease caused by a novel mutation of SLC40A1 gene: hyperferritinemia associated with a relatively low transferrin saturation of iron. Intern Med 2005;44(9):990–993
91. Bach V, Remacha A, Altés A, Barceló MJ, Molina MA, Baiget M. Autosomal dominant hereditary hemochromatosis associated with two novel ferroportin 1 mutations in Spain. Blood Cells Mol Dis 2006;36(1):41–45
92. De Domenico I, McVey Ward D, Nemeth E, et al. Molecular and clinical correlates in iron overload associated with mutations in ferroportin. Haematologica 2006;91(8):1092–1095
93. Girelli D, De Domenico I, Bozzini C, et al. Clinical, pathological, and molecular correlates in ferroportin disease: a study of two novel mutations. J Hepatol 2008;49(4):664–671
94. Pelucchi S, Mariani R, Salvioni A, et al. Novel mutations of the ferroportin gene (SLC40A1): analysis of 56 consecutive patients with unexplained iron overload. Clin Genet 2008; 73(2):171–178

95. Mayr R, Janecke AR, Schranz M, et al. Ferroportin disease: a systematic meta-analysis of clinical and molecular findings. J Hepatol 2010;53(5):941–949
96. McDonald CJ, Wallace DF, Ostini L, Bell SJ, Demediuk B, Subramaniam VN. G80S-linked ferroportin disease: classical ferroportin disease in an Asian family and reclassification of the mutant as iron transport defective. J Hepatol 2011; 54(3):538–544
97. Saja K, Bignell P, Robson K, Provan D. A novel missense mutation c.470 A> C (p.D157A) in the SLC40A1 gene as a cause of ferroportin disease in a family with hyperferritinaemia. Br J Haematol 2010;149(6):914–916
98. Le Lan C, Mosser A, Ropert M, et al. Sex and acquired cofactors determine phenotypes of ferroportin disease. Gastroenterology 2011;140(4):1199–1207; e1–e2
99. Lim FL, Dooley JS, Roques AW, Grellier L, Dhillon AP, Walker AP. Hepatic iron concentration, fibrosis and response to venesection associated with the A77D and V162del "loss of function" mutations in ferroportin disease. Blood Cells Mol Dis 2008;40(3):328–333
100. Corradini E, Montosi G, Ferrara F, et al. Lack of enterocyte iron accumulation in the ferroportin disease. Blood Cells Mol Dis 2005;35(3):315–318
101. Mougiou A, Pietrangelo A, Caleffi A, Kourakli A, Karakantza M, Zoumbos N. G80S-linked ferroportin disease: the first clinical description in a Greek family. Blood Cells Mol Dis 2008;41(1):138–139
102. Speletas M, Kioumi A, Loules G, et al. Analysis of SLC40A1 gene at the mRNA level reveals rapidly the causative mutations in patients with hereditary hemochromatosis type IV. Blood Cells Mol Dis 2008;40(3):353–359
103. Wallace DF, Browett P, Wong P, Kua H, Ameratunga R, Subramaniam VN. Identification of ferroportin disease in the Indian subcontinent. Gut 2005;54(4):567–568
104. Morris TJ, Litvinova MM, Ralston D, Mattman A, Holmes D, Lockitch G. A novel ferroportin mutation in a Canadian family with autosomal dominant hemochromatosis. Blood Cells Mol Dis 2005;35(3):309–314
105. Relvas L, Claro MT, Bento MC, Ribeiro ML. Novel human pathological mutations. Gene symbol: SLC40A1. Disease: haemochromatosis, type 4. Hum Genet 2009; 125(3):338
106. Gordeuk VR, Caleffi A, Corradini E, et al. Iron overload in Africans and African-Americans and a common mutation in the SCL40A1 (ferroportin 1) gene. Blood Cells Mol Dis 2003;31(3):299–304
107. Beutler E, Barton JC, Felitti VJ, et al. Ferroportin 1 (SCL40A1) variant associated with iron overload in African-Americans. Blood Cells Mol Dis 2003;31(3):305–309
108. Zaahl MG, Merryweather-Clarke AT, Kotze MJ, van der Merwe S, Warnich L, Robson KJ. Analysis of genes implicated in iron regulation in individuals presenting with primary iron overload. Hum Genet 2004;115(5): 409–417
109. Lee PL, Gelbart T, West C, Barton JC. SLC40A1 c.1402G—> a results in aberrant splicing, ferroportin truncation after glycine 330, and an autosomal dominant hemochromatosis phenotype. Acta Haematol 2007;118(4): 237–241
110. Griffiths WJ, Mayr R, McFarlane I, et al. Clinical presentation and molecular pathophysiology of autosomal dominant hemochromatosis caused by a novel ferroportin mutation. Hepatology 2010;51(3):788–795
111. Pietrangelo A, Corradini E, Ferrara F, et al. Magnetic resonance imaging to identify classic and nonclassic forms of ferroportin disease. Blood Cells Mol Dis 2006;37(3):192–196
112. Miyajima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. Neurology 1987;37(5):761–767
113. Yoshida K, Furihata K, Takeda S, et al. A mutation in the ceruloplasmin gene is associated with systemic hemosiderosis in humans. Nat Genet 1995;9(3):267–272
114. Harris ZL, Takahashi Y, Miyajima H, Serizawa M, MacGillivray RT, Gitlin JD. Aceruloplasminemia: molecular characterization of this disorder of iron metabolism. Proc Natl Acad Sci U S A 1995;92(7):2539–2543
115. Kono S, Suzuki H, Takahashi K, et al. Hepatic iron overload associated with a decreased serum ceruloplasmin level in a novel clinical type of aceruloplasminemia. Gastroenterology 2006;131(1):240–245
116. Yang F, Naylor SL, Lum JB, et al. Characterization, mapping, and expression of the human ceruloplasmin gene. Proc Natl Acad Sci U S A 1986;83(10):3257–3261
117. Harris ZL, Durley AP, Man TK, Gitlin JD. Targeted gene disruption reveals an essential role for ceruloplasmin in cellular iron efflux. Proc Natl Acad Sci U S A 1999;96(19): 10812–10817
118. De Domenico I, Ward DM, di Patti MC, et al. Ferroxidase activity is required for the stability of cell surface ferroportin in cells expressing GPI-ceruloplasmin. EMBO J 2007; 26(12):2823–2831
119. Miyajima H. Aceruloplasminemia. In: Pagon RA, Bird TD, Dolan CR, Stephens K, eds. Seattle, WA: GeneReviews; 1993
120. Miyajima H, Takahashi Y, Kamata T, Shimizu H, Sakai N, Gitlin JD. Use of desferrioxamine in the treatment of aceruloplasminemia. Ann Neurol 1997;41(3):404–407
121. Finkenstedt A, Wolf E, Höfner E, et al. Hepatic but not brain iron is rapidly chelated by deferasirox in aceruloplasminemia due to a novel gene mutation. J Hepatol 2010;53(6):1101–1107
122. Heilmeyer L, Keller W, Vivell O, et al. [Congenital atransferrinemia in a 7-year-old girl]. Dtsch Med Wochenschr 1961;86:1745–1751
123. Hayashi A, Wada Y, Suzuki T, Shimizu A. Studies on familial hypotransferrinemia: unique clinical course and molecular pathology. Am J Hum Genet 1993;53(1):201–213
124. Beutler E, Gelbart T, Lee P, Trevino R, Fernandez MA, Fairbanks VF. Molecular characterization of a case of atransferrinemia. Blood 2000;96(13):4071–4074
125. Knisely AS, Gelbart T, Beutler E. Molecular characterization of a third case of human atransferrinemia. Blood 2004;104(8):2607
126. Aslan D, Crain K, Beutler E. A new case of human atransferrinemia with a previously undescribed mutation in the transferrin gene. Acta Haematol 2007;118(4):244–247
127. Chen C, Wen S, Tan X. Molecular analysis of a novel case of congenital atransferrinemia. Acta Haematol 2009;122(1): 27–28
128. Shamsian BS, Rezaei N, Arzanian MT, Alavi S, Khojasteh O, Eghbali A. Severe hypochromic microcytic anemia in a patient with congenital atransferrinemia. Pediatr Hematol Oncol 2009;26(5):356–362

129. Andrews NC. The iron transporter DMT1. Int J Biochem Cell Biol 1999;31(10):991–994
130. Mims MP, Guan Y, Pospisilova D, et al. Identification of a human mutation of DMT1 in a patient with microcytic anemia and iron overload. Blood 2005;105(3):1337–1342
131. Lam-Yuk-Tseung S, Camaschella C, Iolascon A, Gros P. A novel R416C mutation in human DMT1 (SLC11A2) displays pleiotropic effects on function and causes microcytic anemia and hepatic iron overload. Blood Cells Mol Dis 2006;36(3):347–354
132. Beaumont C, Delaunay J, Hetet G, Grandchamp B, de Montalembert M, Tchernia G. Two new human DMT1 gene mutations in a patient with microcytic anemia, low ferritinemia, and liver iron overload. Blood 2006;107(10): 4168–4170
133. Iolascon A, d'Apolito M, Servedio V, Cimmino F, Piga A, Camaschella C. Microcytic anemia and hepatic iron overload in a child with compound heterozygous mutations in DMT1 (SCL11A2). Blood 2006;107(1):349–354
134. Iolascon A, Camaschella C, Pospisilova D, Piscopo C, Tchernia G, Beaumont C. Natural history of recessive inheritance of DMT1 mutations. J Pediatr 2008;152(1): 136–139
135. Blanco E, Kannengiesser C, Grandchamp B, Tasso M, Beaumont C. Not all DMT1 mutations lead to iron overload. Blood Cells Mol Dis 2009;43(2):199–201
136. Pospisilova D, Mims MP, Nemeth E, Ganz T, Prchal JT. DMT1 mutation: response of anemia to darbepoetin administration and implications for iron homeostasis. Blood 2006;108(1):404–405
137. Iolascon A, De Falco L. Mutations in the gene encoding DMT1: clinical presentation and treatment. Semin Hematol 2009;46(4):358–370
138. Kato J, Fujikawa K, Kanda M, et al. A mutation, in the iron-responsive element of H ferritin mRNA, causing autosomal dominant iron overload. Am J Hum Genet 2001;69(1):191–197
139. Vanoaica L, Darshan D, Richman L, Schümann K, Kühn LC. Intestinal ferritin H is required for an accurate control of iron absorption. Cell Metab 2010;12(3):273–282
140. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med 2005;353(11):1135–1146
141. Cazzola M, Barosi G, Gobbi PG, Invernizzi R, Riccardi A, Ascari E. Natural history of idiopathic refractory sideroblastic anemia. Blood 1988;71(2):305–312
142. Di Marco V, Capra M, Angelucci E, et al; Italian Society for the Study of Thalassemia and Haemoglobinopathies; Italian Association for the Study of the Liver. Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel. Blood 2010; 116(16):2875–2883
143. Campuzano V, Montermini L, Moltò MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271(5254):1423–1427
144. Boddaert N, Le Quan Sang KH, Rötig A, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood 2007;110(1):401–408
145. Porter JB, Shah FT. Iron overload in thalassemia and related conditions: therapeutic goals and assessment of response to chelation therapies. Hematol Oncol Clin North Am 2010; 24(6):1109–1130
146. Wood JC, Noetzli L. Cardiovascular MRI in thalassemia major. Ann N Y Acad Sci 2010;1202:173–179
147. Babitt JL, Lin HY. Molecular mechanisms of hepcidin regulation: implications for the anemia of CKD. Am J Kidney Dis 2010;55(4):726–741
148. Pietrangelo A. Iron in NASH, chronic liver diseases and HCC: how much iron is too much? J Hepatol 2009;50(2): 249–251
149. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet 2010; 375(9718):924–937
150. Elder GH, Lee GB, Tovey JA. Decreased activity of hepatic uroporphyrinogen decarboxylase in sporadic porphyria cutanea tarda. N Engl J Med 1978;299(6):274–278
151. Sampietro M, Piperno A, Lupica L, et al. High prevalence of the His63Asp HFE mutation in Italian patients with porphyria cutanea tarda. Hepatology 1998; 27(1):181–184
152. Fargion S, Fracanzani AL. Prevalence of hepatitis C virus infection in porphyria cutanea tarda. J Hepatol 2003;39(4): 635–638
153. Chemmanur AT, Bonkovsky HL. Hepatic porphyrias: diagnosis and management. Clin Liver Dis 2004;8(4):807–838; viii–viii
154. Epstein JH, Redeker AG. Porphyria cutanea tarda. A study of the effect of phlebotomy. N Engl J Med 1968;279(24): 1301–1304
155. Walker AR, Arvidsson UB. Iron intake and haemochromatosis in the Bantu. Nature 1950;166(4219):438–439
156. Gordeuk VR, McLaren CE, MacPhail AP, Deichsel G, Bothwell TH. Associations of iron overload in Africa with hepatocellular carcinoma and tuberculosis: Strachan's 1929 thesis revisited. Blood 1996;87(8):3470–3476
157. Bothwell TH, Seftel HC, Jacobs P, Torrance JD, Baumslag N. Iron overload in Bantu subjects. Studies on the availability of iron in Bantu beer. Am J Clin Nutr 1964; 14:47–51
158. Gordeuk V, Mukiibi J, Hasstedt SJ, et al. Iron overload in Africa. Interaction between a gene and dietary iron content. N Engl J Med 1992;326(2):95–100
159. Mandishona E, MacPhail AP, Gordeuk VR, et al. Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. Hepatology 1998;27(6):1563–1566
160. Knisely AS, Mieli-Vergani G, Whitington PF. Neonatal hemochromatosis. Gastroenterol Clin North Am 2003; 32(3):877–889; vi–vii
161. Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet 2004;364(9446):1690–1698
162. Pan X, Kelly S, Melin-Aldana H, Malladi P, Whitington PF. Novel mechanism of fetal hepatocyte injury in congenital alloimmune hepatitis involves the terminal complement cascade. Hepatology 2010;51(6):2061–2068
163. Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. Pediatrics 2008; 121(6):e1615–e1621
164. Rand EB, Karpen SJ, Kelly S, et al. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. J Pediatr 2009;155(4):566–571
165. Whitington PF. Neonatal hemochromatosis: a congenital alloimmune hepatitis. Semin Liver Dis 2007;27(3):243–250