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Hepatology Snapshot: Hemochromatoses

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Definition — BOX 1

Iron overload of genetic origin and related to relative hepcidin deficiency with regard to iron status or, rarely, to hepcidin resistance.

Causative gene mutations — BOX 2

HFE (Frequent) — Hepcidin deficiency

- *C828Y/C282Y* genotype High prevalence
- *C282Y*/other HFE private mutations*

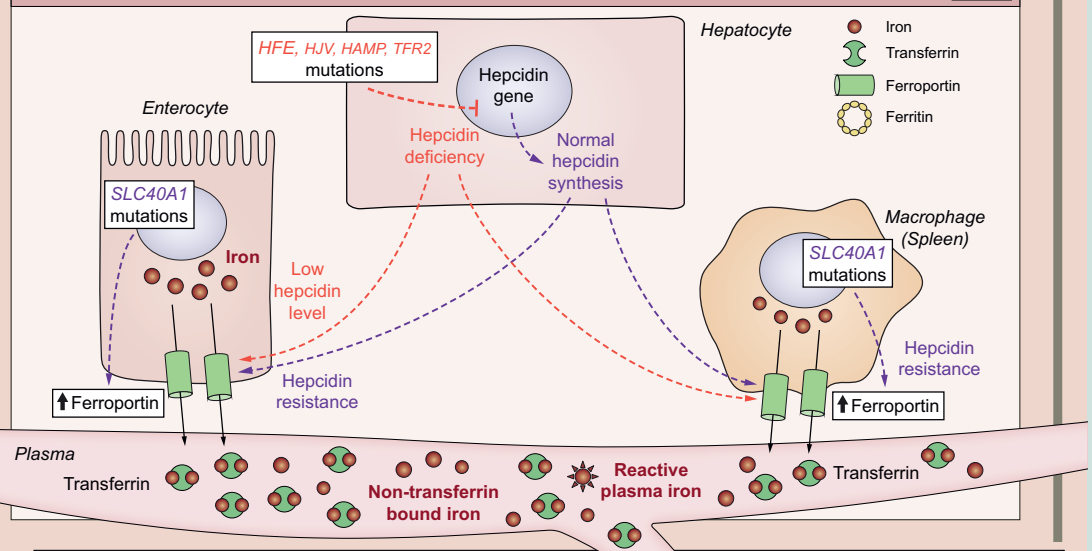
* The *C282Y/H63D* genotype alone does not cause clinically significant iron overload.

Non-HFE (Rare)

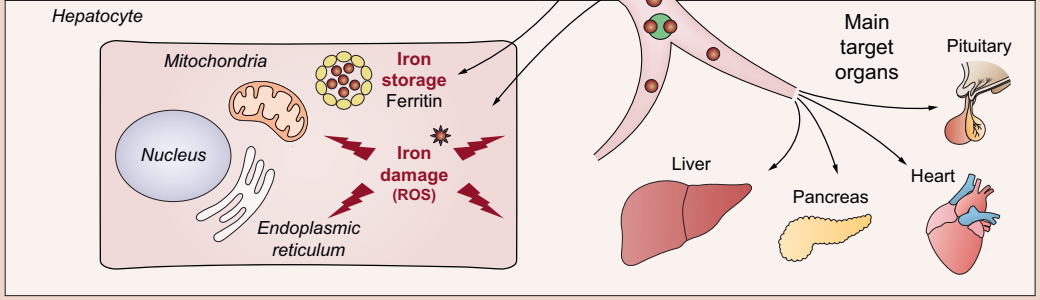
- *HJV (Hemojuvelin)* — Hepcidin deficiency
- *HAMP (Hepcidin)* — Hepcidin deficiency
- * *TFR2 (Transferrin receptor 2)* — Hepcidin deficiency
- *SLC40A1 (Ferroportin)* *(Loss of hepcidin receptor function)* — Hepcidin resistance

Pathophysiology

From gene to hepcidin deficiency/resistance syndromes — BOX 3



Iron overload, toxicity and tissue damage — BOX 4



Hemochromatosis

Clinical features and non-invasive diagnosis — BOX 5

HFE clinical findings

(Variable penetrance)

- Adult (>30 yrs)
- Caucasian
- Fatigue/impotence
- Arthropathy
- Bronze skin
- Liver disease (see text)
- Diabetes mellitus

Laboratory data

↑ Transferrin saturation
↑ Serum ferritin

(In case of confounding factors of increased serum ferritin)

Imaging data *(MRI-T2)*

"Black" liver

"White" spleen

Non-HFE clinical findings

- Rare but not limited to Caucasians
- Younger (<30 yrs)
- Enhanced "classical" HFE signs
  - Cirrhosis (see text)
  - Cardiac failure
  - Endocrine dysfunction (pituitary)
- Massive iron overload

Genetic testing

Homozygosity for *HFE C282Y* mutation?

YES → HFE hemochromatosis

NO → **Genetic testing** (by expert center)

- Private *HFE* mutations → HFE hemochromatosis
- Non-HFE mutations → Non-HFE hemochromatosis

Differential diagnosis — BOX 6

Iron overload with high transferrin saturation

Context of chronic anemia:

- Transfusional iron overload
- Excessive parenteral iron supplementation
- Dyserythropoiesis

Iron overload with normal or low transferrin saturation*

Ferroportin disease:

- Rare (dominant inheritance)
- Mild disease
- MRI: "Black" spleen (= iron overload)
- *SLC40A1* mutation (loss of iron export function)

Hereditary aceruloplasminemia:

- Very rare
- Anemia
- Early diabetes
- Potentially severe neurological signs
- Aceruloplasminemia
- Ceruloplasmin gene mutations

* If mild iron excess: consider possible dysmetabolic syndrome

Iron overload management — BOX 7

Iron depletion therapy

Phlebotomy

- Mainstay of treatment
- Targets:
  - Serum ferritin ~ 50 ng/ml (key target)
  - Transferrin saturation ~ 50%? (see text)

Oral iron chelation

- Rarely used
- Off-label drug

Disease prevention

- Family screening
- Increased awareness in medical profession and general population
- Population screening (?)

Treatments in development

- Hepcidin supplementation
- Intestinal inhibition of ferroportin iron transport activity

Keywords: Iron overload; Hepcidin; Ferroportin; Non-transferrin bound iron; HFE; TFR2; HJV; SLC40A1; Aceruloplasminemia; Magnetic resonance imaging
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Hemochromatoses definition

In the field of chronic iron overload diseases, hemochromatoses are genetic diseases where iron overload is caused by hepcidin deficiency and, much more rarely, by hepcidin resistance. These disorders are related to mutations of *HFE* or *non-HFE* genes that are involved in the control of hepcidin expression or bioactivity, which tunes systemic iron homeostasis.[1]

Pathophysiology

Mutations in proteins, including HFE, transferrin receptor 2 (TFR2) and hemojuvelin (HJV), that are located at the cell membrane of hepatocytes, are responsible for defective iron status sensing. These mutations lead to an abnormally low transduction signal for the synthesis of hepcidin, despite increasing iron levels. The reduced circulating hepcidin means that the iron transport function of the ferroportin protein (normally under hepcidin control) is not appropriately reduced, especially in enterocytes and macrophages. As a result, plasma iron and transferrin saturation increase. In turn, non-transferrin bound iron (NTBI) forms appear and "rush" into hepatocytes causing cellular iron excess. Whenever transferrin saturation exceeds 75%, a component of this plasma NTBI (reactive plasma iron) can exert cellular and tissue toxicity. When mutations of the ferroportin gene (*SLC40A1*) affect its normal interaction with hepcidin, there is hepcidin "resistance", the metabolic consequences of which are similar to those of hepcidin deficiency.

Diagnostic aspects

Hemochromatoses can now be diagnosed non-invasively (without liver biopsy). The diagnostic approach combines: a) clinical examination, b) laboratory data, namely increased plasma transferrin saturation and ferritin, followed by genetic testing which, in the case of *non-HFE* hemochromatoses, requires expert centers, and c) "Iron-MRI". MRI, whenever feasible, is mostly indicated if there are cofactors likely to increase serum ferritin, so that it no longer purely reflects body iron stores. MRI permits visualization and quantification of hepatic iron overload, and, by showing the absence of iron overload in the spleen, strongly supports the mechanism of hepcidin deficiency (or resistance). For liver complications, the key point is to establish whether or not there is cirrhosis (by transient elastography and/or liver biopsy), especially when serum ferritin has chronically been over 1,000 ng/ml and/or transaminases are raised. Detecting cirrhosis is essential since it will lead to screening for hepatocellular carcinoma by serial ultrasound examination.[1]

Main differential diagnoses

There are 2 in particular: a) non-genetic iron overload, mainly due to transfusions, excessive parenteral iron supplementation or ineffective erythropoiesis, and b) genetic non-hemochromatoses iron overload. This latter group includes in particular: i) *Ferroportin disease*[2] in which, due to an impaired iron export function of ferroportin, iron is trapped inside cells, especially splenic macrophages. Therefore, iron overload occurs through cellular iron retention, explaining why this type of iron overload is not accompanied by a raised plasma iron or transferrin saturation, and therefore why plasma NTBI is not present. Thus, there is rather mild disease; ii) *Hereditary aceruloplasminemia* in which the pathophysiological understanding of iron excess needs to be further clarified.[3] Most non-hemochromatoses iron overload entities are associated with anemia or a trend to anemia[4] in marked contrast with hemochromatoses where there is no anemia.

Therapeutic aspects (limited to iron overload therapy)

Phlebotomy remains the mainstay for removing established iron excess. The key target is to reach and maintain a serum ferritin of around 50 ng/ml.[5] Maintaining transferrin saturation around 50% may also be worthy of consideration.[6] Innovative approaches,[7] like parenteral exogenous hepcidin supplementation, parenteral endogenous stimulation of hepcidin synthesis, or inhibition of enterocyte iron absorption using an oral ferroportin antagonist, have achieved experimental proof of concept. Many advances, however, are still needed before these approaches, aimed at safely restoring normal systemic iron homeostasis, become clinically applicable as an adjunct to phlebotomy during the induction phase and/or to replace phlebotomy during maintenance therapy.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

PB and OL contributed equally.

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