**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 77490

**Manuscript Type:** MINIREVIEWS

**Haemochromatosis revisited**

Alvarenga AM *et al.* Haemochromatosis revisited

Aline Morgan Alvarenga, Pierre Brissot, Paulo Caleb Junior Lima Santos

**Aline Morgan Alvarenga, Paulo Caleb Junior Lima Santos,** Department of Pharmacology - Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo 04044-020, Brazil

**Pierre Brissot,** University of Rennes1, Rennes 35065, France

**Author contributions:** Alvarenga AM, Brissot P, and Santos PC have contributed equally to this work.

**Corresponding author: Paulo Caleb Junior Lima Santos, PhD, Adjunct Professor,** Department of Pharmacology - Escola Paulista de Medicina, Universidade Federal de São Paulo, 03 de Maio Street, 100. INFAR, 4° andar - Vila Clementino - São Paulo, SP, São Paulo 04044-020, Brazil. paulo.caleb@unifesp.br

**Received:** May 3, 2022

**Revised:** June 27, 2022

**Accepted:** November 2, 2022

**Published online:** November 27, 2022

**Abstract**

Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is associated with homozygosity for the *HFE* p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-*HFE* haemochromatosis) can also be caused by pathogenic variants in other genes (such as *HJV*, *HAMP,* *TFR2* and *SLC40A1*). A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) has concluded that the classification based in different molecular subtypes is difficult to be adopted in clinical practice and has proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, pathophysiology and therapeutic recommendations.

**Key Words:** Haemochromatosis; Iron overload; *HFE*; Molecular diagnosis; Hepcidin

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Alvarenga AM, Brissot P, Santos PCJ. Haemochromatosis revisited. *World J Hepatol* 2022; 14(11): 1931-1939

**URL:** <https://www.wjgnet.com/1948-5182/full/v14/i11/1931.htm>

**DOI:** https://dx.doi.org/10.4254/wjh.v14.i11.1931

**Core Tip:** Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is associated with homozygosity for the *HFE* p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-*HFE* haemochromatosis) can also be caused by pathogenic variants in other genes (such as *HJV, HAMP, TFR2* and *SLC40A1*). A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) has concluded that classification based on different molecular subtypes is difficult to be adopted in clinical practice and has proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, pathophysiology and therapeutic recommendations.

**INTRODUCTION**

Haemochromatosis is characterized as systemic iron overload of genetic origin caused by hepcidin deficiency, including decreased production of this hormone or decreased activity of hepcidin-ferroportin binding[1] (Figure 1). Iron overload leads to damage such as liver cirrhosis, cardiomyopathy, diabetes, arthritis, hypogonadism and skin pigmentation. Therapeutic phlebotomy is effective and safe[2]. Iron chelation, mostly confined to iron overload related to chronic anaemia needing repeated transfusions, is an alternative (or adjuvant) treatment in haemochromatosis, especially when phlebotomies are medically contraindicated[3] or iron overload is so great that iron depletion is urgently needed.

Mostly, the disease is related to homozygosity for the gene *HFE* p.Cys282Tyr genetic alteration (which is the classical type 1 haemochromatosis). p.Cys282Tyr/p.His63Asp compound heterozygosity has been reported to be linked to haemochromatosis. Rarely, the cases of haemochromatosis can be caused by pathogenic variants in the other genes (called non-*HFE* haemochromatosis). Juvenile haemochromatosis corresponds classically to type 2, which can be subdivided into type 2A, related to mutations in the hemojuvelin gene, and type 2B, related to mutations in the hepcidin gene. Furthermore, mutations in the *TFR2* and *SLC40A1* genes can be associated to haemochromatosis (more details below)[4].

The clinical diagnosis of iron overload is of course the starting point before treating and monitoring the patient. Early diagnosis and treatment are essential for improving survival and for a better quality of life[5]. The present review focuses on new information on classification, pathophysiology, and therapeutic recommendations.

**Epidemiology**

The HEIRS study evaluated, among other aspects, the prevalence of the *HFE* p.Cys282Tyr and p.His63Asp genetic alterations in a sample with 100 000 adults during a period of 5 years in the United States and Canada. Among the obtained results, 299 subjects were homozygous for p.Cys282Tyr, and the estimated prevalence of p.Cys282Tyr homozygous was of 0.44% in white non-Hispanic subjects, 0.11% in native and American indigenous, 0.027% in Hispanic, 0.014% in Black, 0.012% in Pacific Island descendants and 0.000039% in Asiatic[6] subjects.

A review that selected 27 studies, totalling 6302 samples of subjects of European countries, showed the average prevalence of 0.4% for p.Cys282Tyr homozygotes and 9.2% for p.Cys282Tyr heterozygotes[7]. A cohort study with 22 centres across England, Scotland, and Wales in UK Biobank, including 451243 participants of European descent, identified 2890 (0.6%) individuals with p.Cys282Tyr homozygous genotype. The authors diagnosed haemochromatosis in 21.7% (95% confidence interval 19.5%-24.1%, 281/1294) of men and 9.8% (8.4%-11.2%, 156/1596) of women. Since p.C282Y-associated iron overload is preventable and treatable provided intervention is early, their findings justify re-examination of options for expanded early case ascertainment and screening[8]. Another study in blood donors in Brazil found 2.1% for the *HFE* 282Tyr allelic frequencies[9].

**Systemic Iron Regulation**

Plasma iron finds its source in enterocytes and macrophages. It circulates, bound to transferrin, its iron transporter that can link up to two atoms of ferric iron (Fe3+). Transferrin-bound iron binds to transferrin receptor 1 on the plasma membrane of most cells, and forms a complex that is endocytosed. In the acidic environment of the endosome, ferric iron is reduced to ferrous iron (Fe2+) through the activity of a ferrireductase ( STEAP3). Ferrous iron is, then, released from the endosome to the cytosol *via* DMT1, and forms a labile iron pool. Iron leaves the cell through the activity of ferroportin, which is the only known protein to ensure cellular iron export into the plasma. Ferroportin export activity is regulated by the circulating hormone called hepcidin[10-13]. Hepcidin is a peptide essentially liberated by the hepatocytes[14-16]. The ferroportin-hepcidin binding at the level of the cell membrane induces the internalization, ubiquitination and degradation of intracellular ferroportin so that plasmatic levels of hepcidin strongly affect plasma iron concentration[17]. Low levels of hepcidin increase iron export from the enterocytes and macrophages, leading in turn to increased plasma iron concentration and transferrin saturation (TS) (Figure 2).

The adequate content of body iron requires the maintenance of plasma iron concentration within normal limits (12-25 μM) and the regulation of TS. Normal TS is between 20% and 45%, allowing adequate iron delivery to the cells[18]. In mammals, plasma iron binds to transferrin that is synthetized by the hepatocytes and, once released in the plasma, receives two atoms of ferric iron by an active process involving ferroxidase enzymes. When TS increases, non-transferrin bound iron may appear in the plasma and can lead to cell toxicity. The body is not capable of increasing iron excretion, even in case of iron excess. This holds true for genetic iron overload related to increased intestinal iron absorption, as well as for secondary iron overload that can be caused by repeated blood transfusions in the setting especially of chronic haemolytic anaemias, and various other haematological situations[19-24].

**Diagnosis**

The diagnostic approach to haemochromatosis has become a noninvasive one, meaning that liver biopsy is no more needed. Indeed, haemochromatosis can be diagnosed on the sole combination of clinical, laboratory and imaging data.

***Clinical features***

Haemochromatosis can be asymptomatic for many years, and the lack of symptoms usually persists until adulthood, > 30 years old (and often > 40 in men and > 50 in women) in *HFE*-related haemochromatosis. In non-*HFE* haemochromatosis, the symptoms can appear around 20-30 years old. In general, the symptoms are diverse, which explains the frequent and harmful diagnosis delay[25-27].

Among the most common symptoms are fatigue and joint pain[28]. The dermatological signs are mainly melanoderma (dark pigmentation of the skin), but can also include skin dryness and nails alterations (and paradoxically koilonychia, a classical symptom of iron deficiency anaemia). The main liver symptoms are hepatomegaly and slight transaminase increase, contrasting with well-preserved liver functioning. Haemochromatosis can cause diabetes, hypogonadism or hypopituitarism[29]. It is of utmost importance to have in mind that *HFE*-haemochromatosis is only present in Caucasian populations or descents, and that non-*HFE* haemochromatosis, although much rarer, can be observed in many ethnic groups.

***Laboratory tests***

The most common diagnostic biochemical tests consist of the following plasma parameters: iron, transferrin saturation (TS - determined from plasma transferrin concentration rather than from total iron binding capacity) and serum ferritin (SF). Increased TS is the earliest biochemical abnormality in haemochromatosis, reflecting increased iron absorption. It is > 45% (often > 60% in men and > 50% in women) and should be confirmed by a second assay. SF (> 300 μg/L in men and postmenopausal women, and > 200 μg/L in premenopausal women) can be raised in the inflammatory process, the metabolic syndrome (especially with diabetes), alcohol consumption and liver injury[30,31].

***Genetic testing***

Genetic testing is indicated whenever the patient has confirmed high levels of TS, provided other mechanisms than body iron excess have been ruled out (especially hypotransferrinemia due to hepatocellular failure, nephrotic syndrome or malnutrition). Haemochromatosis should not be seen as a simple monogenic disease, but as the complex result of the environment interaction, lifestyle and genetic factors that have not yet been fully identified. In case of *HFE* p.Cys282Tyr homozygosity, it is widely accepted that this genetic profile forms the necessary basis for the development of body iron excess[32]. Concerning the profile of compound heterozygosity p.Cys282Tyr and p.His63Asp, it can only predispose to mild iron overload and the physician should be careful when informing the patient, because alluding to haemochromatosis can cause unnecessary anxiety to the patient and its family[33,34].

When genetic testing for *HFE* provides a negative result, further genetic explorations, related to other genes involved in iron metabolism and hepcidin synthesis, can be conducted, requiring expert laboratories. Non-*HFE* haemochromatosis is less influenced by cofactors and characterized by a more severe and homogeneous clinical condition appearing at a younger age. Modern approaches, based on next generation sequencing (NGS), widely expand the possibilities of diagnosing these rare entities, but, at the same time, raise challenges for interpreting the results. NGS requires expert centres, either public or private, and its cost remains high but tend to decrease over time[35].

It should be kept in mind that, for most clinical practice worldwide, screening of *HJV*, *HAMP*, *TFR2* and *SLC40A1,* and even of *HFE,* through direct sequencing is not widely available. Treatment is usually not dependent on molecular diagnosis[36-39]. It is therefore important to remember that, in this setting of difficult access to genetic identification, patients with a clinical diagnosis of haemochromatosis should not wait for the result of a DNA test before starting treatment.

***Imaging tests***

Magnetic resonance imaging (MRI) can be useful to assess and quantify body iron overload, especially in the liver, without forgetting to evaluate also the iron status of the spleen (the contrast between major liver iron excess and absence of spleen iron overload being highly suggestive of hepcidin deficiency). Laboratory examinations together with MRI have now largely replaced liver biopsy[40,20-22].

**Therapeutic recommendations**

The standard treatment for haemochromatosis remains phlebotomy (or therapeutic bleeding). This treatment has been shown to be effective and safe and has contributed to the reduction of morbidity and mortality in patients with haemochromatosis[41]. With each phlebotomy of 500 mL blood, approximate 250 mg iron are extracted and subsequently mobilized in a compensatory process from the organs where it had accumulated (especially the liver). Repeated phlebotomies result in the total removal of excess iron from the body. The therapeutic schedule must be individually adapted to each patient, and should take into account the patient’s levels of ferritin (according to the local reference values), age, gender and comorbidities. Recent studies have observed a beneficial effect in early and sustained treatment of patients with excess iron, even when iron overload was mild and/or SF only mildly elevated[32,42].

Table 1 shows two treatment phases: initial or intensive (induction), and the maintenance phase. Haemochromatosis patients under venesection therapy should never stop watching their iron parameters since the natural trend of increased iron absorption persists opening the risk of progressive iron excess reconstitution. Oral iron chelation is the commonly recommended treatment for iron overload related to chronic anaemia requiring regular blood transfusions. However, iron chelators may also be used as an alternative, or adjuvant, form of treatment in rare cases of haemochromatosis in which phlebotomies are contraindicated, not feasible due to problems in venous access, or if efficacy may not be not sufficiently achieved with phlebotomies alone in case of massive iron excess[43].

In the future, hepcidin-based treatments could potentially become an adjunct treatment to phlebotomy in the intensive phase or a substitute in the maintenance phase. The interest of restoring hepicidin levels is, of course, based on the fact that hepcidin deficiency is the mechanism accounting for the development of iron overload in patients with haemochromatosis[44].

**Evolution of haemochromatosis nomenclature**

A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) proposed a new classification for haemochromatosis. The recent advances of pathophysiology and molecular basis of iron metabolism have highlighted that haemochromatosis is caused by mutations in at least five genes, resulting in insufficient hepcidin production or, rarely, resistance to hepcidin action. All these different data have led to a disease classification based on different molecular subtypes, mainly reflecting successive gene discoveries. When analysing the name of the disease, we can see the relation of something circulating in the blood haemo-) being responsible for skin and organ damage and pigmentation (-chromatosis). The work of recognizing excess iron as the aetiology of organ toxicity took several decades, and was attributable to Joseph Sheldon in 1935, who was also the first to suggest the genetic origin of the metabolic defect. Over time, it became evident that the genetic basis of haemochromatosis was more heterogeneous than initially thought, and several variants in other iron-controlling genes were progressively associated with the disorder. Unlike in the past, fully expressed and potentially lethal haemochromatosis with the full-blown picture associating liver cirrhosis, diabetes, endocrine dysfunction, and heart failure is rarely seen in current clinical practice. The novel classification aims to be practical whenever a detailed molecular characterization of haemochromatosis is not available[45].

***Previous classification of haemochromatosis***

Table 2 shows the previous classification of haemochromatosis. Most cases of haemochromatosis are caused by homozygous *HFE* p.Cys282Tyr genotype (type 1 haemochromatosis). The *HFE* gene is located on chromosome 6p21, encodes the haemochromatosis protein (HFE) which plays, through a not yet fully elucidated mechanism, a role in hepcidin regulation. As previously mentioned, the main symptoms are arthropathy, skin hyperpigmentation, liver damage, diabetes, endocrine dysfunctions, cardiomyopathy and hypogonadism. Haemochromatosis can also be caused, but much more rarely, by changes in other genes than *HFE*. These rare cases of haemochromatosis can be due to pathogenic variants in other genes, corresponding to non-*HFE* haemochromatosis. There were four entities: juvenile haemochromatosis (JH) or type 2 haemochromatosis, subdivided into two forms: type 2A JH, caused by mutations in the *HJV* gene on chromosome 1q21, and type 2B JH, caused by mutations in the *HAMP* gene on chromosome 19q13. Type 2A genetic changes are involved in hepcidin synthesis, and are related to the BMP co-receptor. It has an early onset, in subjects younger than 30 years, and corresponds to severe forms of haemochromatosis. Type 2B haemochromatosis is related to a genetic defect of the *HAMP* gene, which encodes hepcidin. The main signs and symptoms are hypogonadism and cardiomyopathy. Haemochromatosis types 3 and 4 are caused by mutations in the *TFR2* and *SLC40A1* genes on chromosomes 7q22 and 2q32. Type 4 haemochromatosis, due to *SLC40A1* mutations, is divided into 4A and 4B and has autosomal dominant inheritance. In type 4A, also named ferroportin disease, there is an alteration of ferroportin export activity leading to massive iron overload in the spleen, whereas TS is not elevated. Type 4B haemochromatosis is related to a gain of function process leading to ferroportin resistance to hepcidin and to clinical phenotype very close to that of type I haemochromatosis[46,47].

***New classification of haemochromatosis proposed by an international expert working group***

This working group proposed to de-emphasize the use of the molecular subtype criteria in favour of a classification better related to clinical issues. The group included both clinicians and basic scientists during a meeting in Heidelberg, Germany. The main ideas showing the need for changing the nomenclature were as follows: (1) Poor applicability in clinical practice; (2) Need for complex cooperation between geneticists, bioinformaticians and clinicians for resolving the most difficult cases, to determine the pathogenic nature or not of many variants; (3) Former type 4A haemochromatosis represents an iron overload syndrome strongly and clinically distinct from haemochromatosis (due to a different pathogenesis); (4) Former type 3 can correspond to JH; (5) Former type 3 haemochromatosis can be observed at an older age than JH[45]; and finally (6) Former type 4B, which corresponds to a hepcidin-refractory syndrome shares a similar phenotype to hepcidin-deficiency-related forms of haemochromatosis. Table 3 presents this new classification.

Rigorously speaking, the term haemochromatosis should now be reserved for a unique genetic clinicopathological condition characterized by increased TS, iron overload in the liver (but not in the spleen), prevalent involvement of periportal hepatocytes with iron spared Kupffer cells, and signs and/or symptoms associated with iron overload. Therefore, the term haemochromatosis should no longer be applied to all the previous subtypes. Finally, the panellists agreed that the definition of haemochromatosis should also include the absence of haematological signs of a primary/predominant red blood cell disorder, such as anaemia or reticulocytosis. In summary, as stated by the panellists, the novel classification proposed is based on a pathophysiological cornerstone (hepcidin deficiency) and a distinct clinical/biochemical phenotype. It recognizes the difficulties of a complete molecular characterization and has the potential of being easily shareable between practicing physicians and referral centres. Avoiding any ambiguity is essential for clear and effective communication that will facilitate proper diagnosis and treatment of haemochromatosis and was the main incentive for a real nomenclature review[48].

**CONCLUSION**

It is strongly proposed to adopt, from now on, this new and more relevant classification of haemochromatosis that can be easily shared between practicing doctors and reference canters and will contribute to facilitate the diagnosis and therefore to improve the therapeutic management of haemochromatosis patients.

**REFERENCES**

1 **Brissot P**, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. *Nat Rev Dis Primers* 2018; **4**: 18016 [PMID: 29620054 DOI: 10.1038/nrdp.2018.16]

2 **Santos PC**, Krieger JE, Pereira AC. Molecular diagnostic and pathogenesis of hereditary hemochromatosis. *Int J Mol Sci* 2012; **13**: 1497-1511 [PMID: 22408404 DOI: 10.3390/ijms13021497]

3 **Adams P**, Altes A, Brissot P, Butzeck B, Cabantchik I, Cançado R, Distante S, Evans P, Evans R, Ganz T, Girelli D, Hultcrantz R, McLaren G, Marris B, Milman N, Nemeth E, Nielsen P, Pineau B, Piperno A, Porto G, Prince D, Ryan J, Sanchez M, Santos P, Swinkels D, Teixeira E, Toska K, Vanclooster A, White D; Contributors and Hemochromatosis International Taskforce. Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype. *Hepatol Int* 2018; **12**: 83-86 [PMID: 29589198 DOI: 10.1007/s12072-018-9855-0]

4 **Alvarenga AM**, da Silva NK, Fonseca PFS, Oliveira TGM, da Silva Monteiro JB, Cançado RD, Naoum FA, Dinardo CL, Brissot P, Santos PCJL. Novel mutations in the bone morphogenetic protein 6 gene in patients with iron overload and non-homozygous genotype for the HFE p.Cys282Tyr mutation. *Blood Cells Mol Dis* 2020; **84**: 102444 [PMID: 32464486 DOI: 10.1016/j.bcmd.2020.102444]

5 **Fonseca PFS**, Cançado RD, Naoum FA, Dinardo CL, Fonseca GHH, Gualandro SFM, Krieger JE, Pereira AC, Brissot P, Santos PCJL. Quality of life scores differs between genotypic groups of patients with suspected hereditary hemochromatosis. *BMC Med Genet* 2018; **19**: 3 [PMID: 29301508 DOI: 10.1186/s12881-017-0513-5]

6 **McLaren CE**, Barton JC, Adams PC, Harris EL, Acton RT, Press N, Reboussin DM, McLaren GD, Sholinsky P, Walker AP, Gordeuk VR, Leiendecker-Foster C, Dawkins FW, Eckfeldt JH, Mellen BG, Speechley M, Thomson E; Hemochromatosis and Iron Overload Study Research Investigators. Hemochromatosis and Iron Overload Screening (HEIRS) study design for an evaluation of 100,000 primary care-based adults. *Am J Med Sci* 2003; **325**: 53-62 [PMID: 12589228 DOI: 10.1097/00000441-200302000-00001]

7 **Hanson EH**, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. *Am J Epidemiol* 2001; **154**: 193-206 [PMID: 11479183 DOI: 10.1093/aje/154.3.193]

8 **Pilling LC**, Tamosauskaite J, Jones G, Wood AR, Jones L, Kuo CL, Kuchel GA, Ferrucci L, Melzer D. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* 2019; **364**: k5222 [PMID: 30651232 DOI: 10.1136/bmj.k5222]

9 **Santos PC**, Cançado RD, Terada CT, Rostelato S, Gonzales I, Hirata RD, Hirata MH, Chiattone CS, Guerra-Shinohara EM. HFE gene mutations and iron status of Brazilian blood donors. *Braz J Med Biol Res* 2010; **43**: 107-114 [PMID: 20027482 DOI: 10.1590/s0100-879x2009007500031]

10 **Babitt JL**, Huang FW, Xia Y, Sidis Y, Andrews NC, Lin HY. Modulation of bone morphogenetic protein signaling in vivo regulates systemic iron balance. *J Clin Invest* 2007; **117**: 1933-1939 [PMID: 17607365 DOI: 10.1172/jci31342]

11 **Casanovas G**, Mleczko-Sanecka K, Altamura S, Hentze MW, Muckenthaler MU. Bone morphogenetic protein (BMP)-responsive elements located in the proximal and distal hepcidin promoter are critical for its response to HJV/BMP/SMAD. *J Mol Med (Berl)* 2009; **87**: 471-480 [PMID: 19229506 DOI: 10.1007/s00109-009-0447-2]

12 **Meynard D**, Kautz L, Darnaud V, Canonne-Hergaux F, Coppin H, Roth MP. Lack of the bone morphogenetic protein BMP6 induces massive iron overload. *Nat Genet* 2009; **41**: 478-481 [PMID: 19252488 DOI: 10.1038/ng.320]

13 **Corradini E**, Rozier M, Meynard D, Odhiambo A, Lin HY, Feng Q, Migas MC, Britton RS, Babitt JL, Fleming RE. Iron regulation of hepcidin despite attenuated Smad1,5,8 signaling in mice without transferrin receptor 2 or Hfe. *Gastroenterology* 2011; **141**: 1907-1914 [PMID: 21745449 DOI: 10.1053/j.gastro.2011.06.077]

14 **Huang FW**, Pinkus JL, Pinkus GS, Fleming MD, Andrews NC. A mouse model of juvenile hemochromatosis. *J Clin Invest* 2005; **115**: 2187-2191 [PMID: 16075059 DOI: 10.1172/JCI25049]

15 **Truksa J**, Lee P, Beutler E. Two BMP responsive elements, STAT, and bZIP/HNF4/COUP motifs of the hepcidin promoter are critical for BMP, SMAD1, and HJV responsiveness. *Blood* 2009; **113**: 688-695 [PMID: 18997172 DOI: 10.1182/blood-2008-05-160184]

16 **Xiao X**, Dev S, Canali S, Bayer A, Xu Y, Agarwal A, Wang CY, Babitt JL. Endothelial Bone Morphogenetic Protein 2 (Bmp2) Knockout Exacerbates Hemochromatosis in Homeostatic Iron Regulator (Hfe) Knockout Mice but not Bmp6 Knockout Mice. *Hepatology* 2020; **72**: 642-655 [PMID: 31778583 DOI: 10.1002/hep.31048]

17 **Fonseca PF**, Cançado RD, Uellendahl Lopes MM, Correia E, Lescano MA, Santos PC. HAMP Gene Mutation Associated with Juvenile Hemochromatosis in Brazilian Patients. *Acta Haematol* 2016; **135**: 228-231 [PMID: 27007796 DOI: 10.1159/000444119]

18 **Lescano MA**, Tavares LC, Santos PCJL. Juvenile hemochromatosis: *HAMP* mutation and severe iron overload treated with phlebotomies and deferasirox. *World J Clin Cases* 2017; **5**: 381-383 [PMID: 29085829 DOI: 10.12998/wjcc.v5.i10.381]

19 **Papanikolaou G**, Tzilianos M, Christakis JI, Bogdanos D, Tsimirika K, MacFarlane J, Goldberg YP, Sakellaropoulos N, Ganz T, Nemeth E. Hepcidin in iron overload disorders. *Blood* 2005; **105**: 4103-4105 [PMID: 15671438 DOI: 10.1182/blood-2004-12-4844]

20 **Piperno A**. “Classification and diagnosis of iron overload.” *Haematologica* 1998; **83**: 447-455 [DOI: 10.1017/cbo9780511666476.018]

21 **Andrews NC**. A genetic view of iron homeostasis. *Semin Hematol* 2002; **39**: 227-234 [PMID: 12382197 DOI: 10.1053/shem.2002.35632]

22 **Camaschella C**. Understanding iron homeostasis through genetic analysis of hemochromatosis and related disorders. *Blood* 2005; **106**: 3710-3717 [PMID: 16030190 DOI: 10.1182/blood-2005-05-1857]

23 **Fix OK,** Kowdley KV. “Hereditary hemochromatosis.” *Minerva medica* 2008; **99**: 605-617 [DOI: 10.1016/B978-1-4377-0121-0.50252-X]

24 **Barton JC**, McDonnell SM, Adams PC, Brissot P, Powell LW, Edwards CQ, Cook JD, Kowdley KV. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med* 1998; **129**: 932-939 [PMID: 9867745 DOI: 10.7326/0003-4819-129-11\_Part\_2-199812011-00003]

25 **Pietrangelo A**. Inherited metabolic disease of the liver. *Curr Opin Gastroenterol* 2009; **25**: 209-214 [PMID: 19342951 DOI: 10.1097/MOG.0b013e328329e13d]

26 **Brissot P**, Bardou-Jacquet E, Jouanolle AM, Loréal O. Iron disorders of genetic origin: a changing world. *Trends Mol Med* 2011; **17**: 707-713 [PMID: 21862411 DOI: 10.1016/j.molmed.2011.07.004]

27 **Pietrangelo A**. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology* 2010; **139**: 393-408, 408.e1-408.e2 [PMID: 20542038 DOI: 10.1053/j.gastro.2010.06.013]

28 **Powell,** Lawrie W., Rebecca C. Seckington, and Yves Deugnier. “Haemochromatosis.” *The Lancet* 2016; **388**: 706-716 [DOI: 10.1016/S0140-6736(15)01315-X]

29 **Doyard M**, Chappard D, Leroyer P, Roth MP, Loréal O, Guggenbuhl P. Decreased Bone Formation Explains Osteoporosis in a Genetic Mouse Model of Hemochromatosiss. *PloS One* 2016; **11**: e0148292 [PMID: 26829642 DOI: 10.1371/journal.pone.0148292]

30 **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**: 244-247 [PMID: 18097132 DOI: 10.1159/000112726]

31 **European Association For The Study Of The Liver**. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol* 2010; **53**: 3-22 [PMID: 20471131 DOI: 10.1016/j.jhep.2010.03.001]

32 **Bacon BR**, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 328-343 [PMID: 21452290 DOI: 10.1002/hep.24330]

33 **Santos PC**, Dinardo CL, Cançado RD, Schettert IT, Krieger JE, Pereira AC. Non-HFE hemochromatosis. *Rev Bras Hematol Hemoter* 2012; **34**: 311-316 [PMID: 23049448 DOI: 10.5581/1516-8484.20120079]

34 **Gurrin LC**, Bertalli NA, Dalton GW, Osborne NJ, Constantine CC, McLaren CE, English DR, Gertig DM, Delatycki MB, Nicoll AJ, Southey MC, Hopper JL, Giles GG, Anderson GJ, Olynyk JK, Powell LW, Allen KJ; HealthIron Study Investigators. HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis-related morbidity. *Hepatology* 2009; **50**: 94-101 [PMID: 19554541 DOI: 10.1002/hep.22972]

35 **Walsh A**, Dixon JL, Ramm GA, Hewett DG, Lincoln DJ, Anderson GJ, Subramaniam VN, Dodemaide J, Cavanaugh JA, Bassett ML, Powell LW. The clinical relevance of compound heterozygosity for the C282Y and H63D substitutions in hemochromatosis. *Clin Gastroenterol Hepatol* 2006; **4**: 1403-1410 [PMID: 16979952 DOI: 10.1016/j.cgh.2006.07.009]

36 **Sandhu K**, Flintoff K, Chatfield MD, Dixon JL, Ramm LE, Ramm GA, Powell LW, Subramaniam VN, Wallace DF. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. *Blood* 2018; **132**: 101-110 [PMID: 29743178 DOI: 10.1182/blood-2018-02-830562]

37 **Brissot P**, de Bels F. Current approaches to the management of hemochromatosis. *Hematology Am Soc Hematol Educ Program* 2006: 36-41 [PMID: 17124037 DOI: 10.1182/asheducation-2006.1.36]

38 **Cancado RD**, Alvarenga AM, Santos PCJ. HFE hemochromatosis: an overview about therapeutic recommendations. *Hematol Transfus Cell Ther* 2022; **44**: 95-99 [PMID: 34824033 DOI: 10.1016/j.htct.2021.06.020]

39 **Wood JC**. Estimating tissue iron burden: current status and future prospects. *Br J Haematol* 2015; **170**: 15-28 [PMID: 25765344 DOI: 10.1111/bjh.13374]

40 **St Pierre TG**, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005; **105**: 855-861 [PMID: 15256427 DOI: 10.1182/blood-2004-01-0177]

41 **Gandon Y.** “Non-invasive assessment of hepatic iron stores by MRI.” *The Lancet* 2004; **363**: 357-362 [DOI: 10.1016/S0140-6736(04)15436-6]

42 **Bardou-Jacquet E**, Morcet J, Manet G, Lainé F, Perrin M, Jouanolle AM, Guyader D, Moirand R, Viel JF, Deugnier Y. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. *J Hepatol* 2015; **62**: 682-689 [PMID: 25450707 DOI: 10.1016/j.jhep.2014.10.025]

43 **Cançado R**, Melo MR, de Moraes Bastos R, Santos PC, Guerra-Shinohara EM, Chiattone C, Ballas SK. Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: results of a 1-yr Phase 2 study. *Eur J Haematol* 2015; **95**: 545-550 [PMID: 25684349 DOI: 10.1111/ejh.12530]

44 **Ong Sim Y**. “Reduction of body iron in HFE-related haemochromatosis and moderate iron overload (Mi-Iron): a multicentre, participant-blinded, randomised controlled trial.” The Lancet Haematology 4.12 (2017): e607-e614 [DOI: 10.1016/S2352-3026(17)30214-4]

45 **Girelli D**, Busti F, Brissot P, Cabantchik I, Muckenthaler MU, Porto G. Hemochromatosis classification: update and recommendations by the BIOIRON Society. *Blood* 2022; **139**: 3018-3029 [PMID: 34601591 DOI: 10.1182/blood.2021011338]

46 **Liu J**, Sun B, Yin H, Liu S. Hepcidin: A Promising Therapeutic Target for Iron Disorders: A Systematic Review. *Medicine (Baltimore)* 2016; **95**: e3150 [PMID: 27057839 DOI: 10.1097/MD.0000000000003150]

47 **Santos PC**, Cançado RD, Pereira AC, Chiattone CS, Krieger JE, Guerra-Shinohara EM. HJV hemochromatosis, iron overload, and hypogonadism in a Brazilian man: treatment with phlebotomy and deferasirox. *Acta Haematol* 2010; **124**: 204-205 [PMID: 21071928 DOI: 10.1159/000321493]

48 **Brissot P**. “Hemochromatoses.” *Revue Francophone des Laboratoires* 2021; **533**: 33-43 [DOI: 10.1016/S1773-035X(21)00169-6]

**Footnotes**

**Conflict-of-interest statement:** All authors report no relevant conflict of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons>.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** May 3, 2022

**First decision:** June 8, 2022

**Article in press:** November 2, 2022

**Specialty type:** Genetics and heredity

**Country/Territory of origin:** Brazil

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

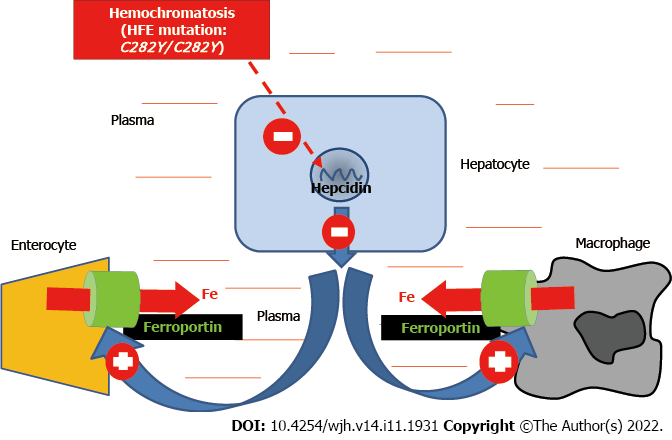
Grade C (Good): C

Grade D (Fair): 0

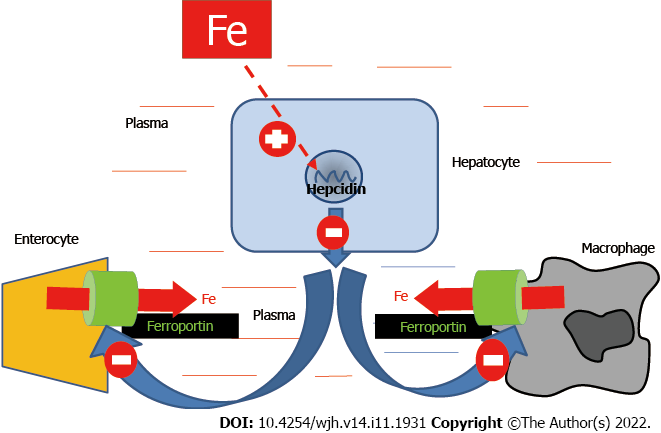
Grade E (Poor): 0

**P-Reviewer:** Barisani D, Italy; Liu Z, China **S-Editor:** Wu YXJ **L-Editor:** Kerr C **P-Editor:** Wu YXJ

**Figure Legends**



**Figure 1 Mechanism of iron overload in *HFE*-related hemochromatosis.** The *C282Y/C282Y* mutations (homozygosity for *C282Y*) lead to decreased synthesis of the iron hormone hepcidin, which in turn causes an increased activity of the iron export protein ferroportin both at the digestive and splenic levels. The result is increased plasma iron leading to organ iron overload.



**Figure 2 Schematic representation of systemic iron regulation.** Physiologically, increased plasma iron leads to an increased synthesis of the iron hormone hepcidin, causing in turn decreased activity of the iron export protein Ferroportin both at the digestive and splenic levels, which leads to compensatory decreased plasma iron. The reverse mechanism occurs in case of physiological iron deficiency. Please note that, in haemochromatosis, the body behaves as if it was chronically iron deficient.

**Table 1 Review about therapeutic recommendations**

|  |  |
| --- | --- |
| Who to start treatment | Patient with homozygous genotype *HFE p.Cys282Tyr (C282Y/C282Y)* and with biochemical indication of iron overload, namely, fasting transferrin saturation increase (≥ 45%) together with serum ferritin increase (> 300 μg/L for men and postmenopausal women, and > 200 μg/L in premenopausal women). |
| Initial phase or intensive (of induction) | Phlebotomies of 400-500 mL (according to body weight) weekly or every 2 wk (depending on the amount of initial iron excess). Objective: to reach a serum ferritin value of 50 μg/L, in the absence of anaemia. |
| Maintaining phase | One phlebotomy every 1-4 mo, depending on iron parameters. Objective: to maintain ferritin levels around 50 μg/L (without anaemia; haemoglobin levels should not be < 11 g/dL). Plasma ferritin should be verified prior to each phlebotomy, and transferrin saturation approximately twice a year. |
| When to stop | Patients presenting iron overload should never stop checking their iron parameters, and their treatment must be planned according to their iron parameters, general health condition, and age. |

**Table 2 Previous classification of haemochromatosis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Haemochromatosis types** | **Gene** | **Location** | **Inheritance** | **Gene product function** | **Main clinical manifestations** |
| 1 | *HFE* | 6p21.3 | AR | Involved in hepcidin synthesis via BMP6, interaction with TFR1. | Iron overload and known manifestation of classical haemochromatosis (*HFE* type). Arthropathy, skin hyperpigmentation, liver damage, diabetes, endocrine dysfunction, cardiomyopathy, hypogonadism. |
| 2A | *HJV* | 1p21 | AR | Involved in hepcidin synthesis, BMP co-receptor. | Type 2: earlier onset, < 30 yr. Severe iron overload and juvenile form of haemochromatosis. |
| 2B | *HAMP* | 19q13 | AR | Hepcidin, produced mainly in hepatocytes, downregulates iron efflux from enterocytes via ferroportin. | Hypogonadism and cardiomyopathy more prevalent. Severe iron overload and juvenile form of haemochromatosis. |
| 3 | *TFR2* | 7q22 | AR | Transferrin receptor 2, mediates cellular uptake of transferrin-bound iron and is involved in hepcidin synthesis. | Phenotypes can range from moderate to severe form of haemochromatosis. |
| 4A | *SLC40A1* | 2q32 | AD | Ferroportin is an iron exporter in duodenal. | Lower tolerance to phlebotomies with risk of anaemia. The phenotype strongly differs from newly defined haemochromatosis (mild clinical symptoms, major spleen iron overload, major hyperferritinemia without TS increase). |
| 4B | *SLC40A1* |  | AD | Ferroportin acting a hepcidin receptor. | Very rare; in general, clinically similar to *HFE*-haemochromatosis. |

*TFR2*: Transferrin receptor 2; *HFE*: Encodes *HFE* protein; *HJV*: Encodes hemojuvelin; *HAMP*: Encodes hepcidin; *TFR2*: Encodes transferrin receptor 2; *SLC40A1*: Encodes ferroportin; BMP6: Bone morphogenetic protein 6, AR: Autosomal recessive; AD: Autosomal dominant.

**Table 3 New classification of haemochromatosis proposed by the working group**

|  |  |  |
| --- | --- | --- |
| **New classification** | **Molecular pattern** | **Note** |
| *HFE*-related | *p.Cys282Tyr* homozygosity or compound heterozygosity of *p.Cys282Tyr* with other rare *HFE* pathogenic variants or *HFE* deletion. | Low penetrance; consider presence  of host-related or environmental  cofactors for iron overload. In subjects with other *HFE* genotypes (*p.Cys282Tyr/His63Asp* compound heterozygosity or p.His63Asp homozygosity) consider second-line genetic testing for rarer variants. |
| Non *HFE*-related | Rare pathogenic variants in non-*HFE* genes:  - *HJV*-related;  - *HAMP*-related;  - *TFR2*-related;  - *SLC40A1* (very rare gain-of-function variant)-related | Potentially, variants in any hepcidin-regulatory gene may be causative (the effects of novel mutations should be confirmed  through functional and  epidemiological studies).  Molecular subtypes characterization  only at specialized canters, but  diagnosis of non-*HFE* related haemochromatosis is  sufficient to start phlebotomies at nonspecialized centres1. |
| Digenic2 | Double heterozygosity and/or double homozygosity/heterozygosity for variants in two different genes involved in iron metabolism (*HFE* and/or non-*HFE*). | More commonly, *p.Cys282Tyr* variants in *HFE* gene might coexist with variants in other genes; rarely, both variants involve non-*HFE* genes. |
| Molecularly undefined | Molecular characterization (still) not available after sequencing of known genes (provisional diagnosis). | Patients should be referred (or DNA should be sent) to specialized centers. |

1Providing that iron overload is confirmed by magnetic resonance imaging (MRI). If MRI is not accessible, close monitoring of haemoglobin level is needed to avoid occurrence of anaemia.

2Caution is needed to interpret as digenic inheritance results from next generation sequencing outputs reporting several variants in gene panels. Whenever possible, strict criteria for defining pathogenic variants should be adopted, and corroborated by family segregation and/or functional studies.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**