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Genetic iron overload disorders

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ABSTRACT

Due to its pivotal role in orchestrating vital cellular functions and metabolic processes, iron is an essential component of the human body and a main micronutrient in the human diet. However, excess iron causes an increased production of reactive oxygen species leading to cell dysfunction or death, tissue damage and organ disease.

Iron overload disorders encompass a wide spectrum of pathological conditions of hereditary or acquired origin. A number of 'iron genes' have been identified as being associated with hereditary iron overload syndromes, the most common of which is hemochromatosis. Although linked to at least five different genes, hemochromatosis is recognized as a unique syndromic entity based on a common pathogenetic mechanism leading to excessive entry of unneeded iron into the bloodstream.

In this review, we focus on the pathophysiologic basis and clinical aspects of the most common genetic iron overload syndromes in humans.

1. Introduction

Iron is an essential microelement of pivotal importance for cells and organisms, involved in fundamental processes (Finch, 1965). By virtue of its unique electrochemical properties based on the redox switching between a ferric and ferrous form, iron is an ideal redox active cofactor for many biologic processes. However, this same property set the basis for its toxicity: in an aerobic environment, if not bound/chelated by specific serum carriers and storage proteins, such as serum transferrin (Tf) and cellular ferritin (Ft), iron can freely interact with vascular, cellular and subcellular structures and promote oxidative damage.

Iron overload disorders encompass a wide spectrum of pathologic conditions of hereditary, acquired or mixed origin. Most are characterized by systemic iron overload, while others result in iron accumulation in specific tissue, cell or sub-cellular compartments following disease processes or derangements of cell iron homeostasis, in the context of a normal/non-increased total body iron content (Table 1).

A number of 'iron genes' have been identified associated with hereditary iron overload syndromes (e.g. *HFE, TfR2, HAMP, HJV, FPN, CP, TF, DMT1*) (Table 2). Furthermore, some genetic diseases, such as hereditary iron-loading anemias, although not directly caused by a defect in genes primarily involved in iron homeostasis, are associated with iron overload states.

In this chapter, we will review basis, pathophysiology and clinical aspects of the most common genetic iron overload syndromes in humans.

2. Iron toxicity

In iron overload settings, the primary pathogenic event is the appearance in the blood or in the cell of labile fractions of iron with high propensity for redox activities, called labile plasma iron, LPI (a component of the non-transferrin bound iron, NTBI), in the blood, and labile cell iron, LCI, within the cell. A number of transporters potentially involved in LPI transfer through the cell membrane have been identified in cell culture studies and rodent models (e.g. calcium-channels, DMT1, ZIP 8 and ZIP 14) (Knutson, 2019). Normally, low amount of cytosolic and organelle LCI takes part into fundamental reactions, yielding, through reduction of the consumed oxygen, highly reactive chemical entities, called reactive oxygen species (ROS), which are engaged in important physiologic activities. When enzymatic and non-enzymatic antioxidants that dispose unwanted ROS are overcome by uncontrolled expansion of LCI, iron-induced oxidative damage of plasma membrane, organelles and DNA arises leading to cell death, and initiation or progression of fibrogenesis and carcinogenesis; iron overload-related immunologic aberrancies have also been described (Mehta et al., 2019; Torti et al., 2018).

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Nomenclature

List of abbreviations and acronyms

BMI	body mass index
CP	ceruloplasmin
DMT1	divalent metal transporter 1
GWAS	genome-wide association study
HC	hemochromatosis
J-HC	juvenile hemochromatosis
FD	ferroportin disease
Ft	ferritin
LCI	labile cell iron
LPI	labile plasma iron
NF	neuroferritinopathy
NBIA	neurodegeneration with brain iron accumulation
NTBI	non-transferrin bound iron
ROS	reactive oxygen species
SF	serum ferritin
Tf	transferrin
TS	transferrin saturation
ZIP	zinc transporter protein

Table 1
Main disorders associated with genetic and acquired iron overload or misdistribution.

	Systemic iron overload	Iron misdistribution/local iron deposition*
Genetic	• Hereditary hemochromatosis (HFE-, TfR2-, HJV-, HAMP-, or FPN-related) • Ferroportin disease • Aceruloplasminemia • Atransferrinemia • DMT-1 deficiency • Private/sporadic iron overload diseases (e.g. H-ferritin related iron overload) • Hereditary iron-loading anaemias due to inefficient erythropoiesis	• Congenital sideroblastic anemias# • Friederich ataxia • Neuroferritinopathy
Acquired	• Post-transfusion • Parenteral • Oral • Alloimmune neonatal hemochromatosis	• Chronic liver diseases • Neurodegenerative disorders (including NBIA unrelated to iron-genes) • Anemia of chronic diseases

* Iron deposition in specific subcellular compartments, cell types or tissues (mitochondrial iron overload in inherited sideroblastic anemias or Friederich ataxia; free-iron and ferritin in cytosol in neuroferritinopathy; parenchymal/mesenchymal iron deposits in chronic liver disorders; focal iron deposition in the brain in NBIA; iron retention in reticuloendothelial system in anemia of chronic diseases) in presence of normal/non-increased total body iron.
# Although altered iron utilization during heme production is the key and earliest manifestation of iron derangement (leading to deposition of non-heme iron in mitochondria of erythroid precursors), systemic iron overload due to ineffcient erythropoiesis may develop in some forms even in untransfused patients (e.g. ALAS2, GLRX5, and SLC25A38-associated sideroblastic anemia).

3. Genetic iron overload disorders

As reported in Table 1, a number of iron overload states are due to genetic defects. While being linked to mutations in different genes, a cluster of such disorders, share a common pathogenetic basis: the uncontrolled and unneeded expansion of the circulatory iron pool responsible for progressive accumulation of toxic iron in parenchymatous organs. Today, we embrace those disorders in the same syndromic entity, historically known as (genetic or hereditary) hemochromatosis (HC). The common cause is, in fact, the genetic loss of different proteins involved in the synthesis or activity of a single peptide, hepcidin, the iron hormone that normally restrains iron entry into the bloodstream and orchestrate body iron homeostasis.

It is anticipated that disruption of any regulatory mechanisms that, beyond the central hepcidin homeostatic axis, prevents an unregulated flux of iron toward the blood, in the presence of normal erythropoietic activity, will lead to a syndrome similar to HC. In this context, it has been reported that intestinal ferritin H gene deletion in mice leads to body iron overload indicating that intestinal ferritin H is also required to limit iron efflux from intestinal cells toward circulation (Vanoaica et al., 2010). Interestingly, iron overload resembling HC has been described in a Japanese pedigree carrying a mutation of H-ferritin (Kato et al., 2001). Yet, that H ferritin is an iron-loading gene also in humans awaits further confirmatory data.

Other genetic diseases are linked to defects affecting iron release (ferroportin disease, aceruloplasminemia) or handling (e.g. DMT1-deficiency, hypo/atransferrinemia), or to local (cellular or subcellular) deregulation of iron homeostasis (neuroferritinopathy and Friedreich ataxia) (Table 2).

Finally, a number of hereditary anemias may present variable iron overload states due to increased iron absorption secondary to hepcidin down-regulation by ineffective erythropoiesis (e.g. iron-loading anemias).

Moreover, although unrelated to iron-genes, some genetic diseases can associate over time with the development of tissue iron excess (e.g. neurodegeneration with brain iron accumulation (NBIA) except aceruloplasminemia and neuroferritinopathy). These disorders are out of the scope of this review.).

3.1. Hemochromatosis (genetic or hereditary)

Human hemochromatosis (HC) is caused by pathogenic mutations in genes encoding key proteins engaged in the hepcidin-ferroportin axis, in particular, in the iron-sensing machinery controlling hepcidin synthesis in the liver, such as *HFE* (Feder et al., 1996), TfR2 (Camaschella et al., 2000) and *HJV* (Papanikolaou et al., 2004). Rarer cases are associated with mutations of the *HAMP* gene itself (Roetto et al., 2003) or gain-of-function mutations of ferroportin (FPN) (Njajou et al., 2001).

All the different genetic forms of HC share the same pathophysiologic basis (i.e. lack of hepcidin synthesis or activity) responsible for progressive expansion of the circulatory iron pool, tissue iron accumulation and organ damage and disease (Fig. 1). The specific HC phenotype is determined largely by the rate and magnitude of the circulatory and tissue iron overload, which depends on the specific role that the defective HC protein plays in hepcidin biology. Rapid and massive influx of iron into the plasma causes severe and early-onset organ disease characteristic of the *juvenile* forms due to mutations of hemojuvelin, a key regulator of hepcidin expression, or hepcidin itself (e.g. HJV- and HAMP-associated HC). Slow and progressive iron loading leads to a milder phenotype with later onset (e.g. classic HFE-associated HC), while an "intermediate phenotype" is typical of TfR2-associated HC. The pattern of inheritance of all forms is autosomal recessive, with the exception of FPN-associated HC (autosomal dominant trait).

3.1.1. HFE-hemochromatosis

3.1.1.1. Genetics. HFE-HC is associated with homozygosity for the c.845G≥A polymorphism in *HFE* resulting in the Cys282Tyr (C282Y) change in the protein. The C282Y polymorphism probably arose in north-western European ancestors but whether of Celtic or Viking origin, or originated in mainland Europe before 4000 BCE, is still debated. Its high prevalence in Caucasians (allelic frequency around

Table 2
Iron-overload disorders due to mutations in genes primarily involved in iron homeostasis.

Disorder (inheritance)	Gene/s and protein function		Mechanism/s of iron overload	Phenotype	Treatment options (standard of care and other strategies)	Innovation and future directions
'Classic' Hemochromatosis (AR)	*HFE*	Regulation of hepcidin expression	Inappropriately low levels of hepcidin. Uncontrolled expansion of circulatory iron pool and progressive tissue iron accumulation.	Unimpaired erythropoiesis TS ↑ Ferritin ↑ Iron load in parenchymal organs: liver, pancreas, endocrine glands, heart.	Phlebotomy Erythrocytapheresis Iron chelators	Hepcidin replacement strategies. Hepcidin-ferroportin axis modulation. Gene therapy
Non-HFE hereditary hemochromatosis (HJV/HAMP/TFR2: AR; SLC40A1: AD)	*HJV*	Regulation of hepcidin expression	Inappropriately low levels of hepcidin. Uncontrolled expansion of circulatory iron pool and progressive tissue iron accumulation.	Unimpaired erythropoiesis TS ↑ Ferritin ↑ Iron load in parenchymal organs: heart, endocrine glands, pancreas, liver Juvenile onset Usually severe manifestations.		
	HAMP	Restrains iron entry into the bloodstream by degrading ferroportin (FPN)	Lack of hepcidin. Uncontrolled expansion of circulatory iron pool and progressive tissue iron accumulation.			
	TFR2	Regulation of hepcidin expression	Inappropriately low levels of hepcidin. Uncontrolled expansion of circulatory iron pool and progressive tissue iron accumulation.	Unimpaired erythropoiesis TS ↑ Ferritin ↑ Iron load in parenchymal organs: liver, pancreas, endocrine glands, heart		
	SLC40A1	Iron export	Resistance of FPN to hepcidin activity. Uncontrolled expansion of circulatory iron pool and progressive tissue iron accumulation.			
Ferroportin disease (AD)	*SLC40A1*	Iron export	Iron retention (mainly in cells with high-iron flux) due to decreased export.	Anemia possible in conditions of increased iron demand for erythropoiesis TS normal/↓ Ferritin ↑ Iron entrapment mainly in macrophages. Iron load in spleen, liver and bone marrow.	Non-aggressive phlebotomy (Iron chelators)	Iron-transfer small molecules by-passing FPN defect
Aceruloplasminemia (AR)	*CP*	Ferroxidase activity, involved in iron export and binding to transferrin.	Iron retention due to decreased export	Anemia and/or microcytosis TS ↓ Ferritin ↑ Very low/undetectable serum ceruloplasmin Iron load in several organs: brain, liver, pancreas (heart, thyroid, other?)	Iron chelators (Combined infusion of fresh frozen plasma (to enhance CP pool) and iron chelation)	CP replacement therapy Gene therapy Iron-transfer small molecules by-passing CP defect
Hypo/Atransferrinemia (AR)	*TF*	Iron transport in the bloodstream and delivery to erythroid precursors.	Increased iron adsorption secondary to anemia/iron-deficient erythropoiesis.	Anemia (microcytic/hypochromic, severe) Very low/undetectable serum transferrin TS ↑ Ferritin variably ↑ Iron load in parenchymal organs: liver, heart, endocrine glands	Infusion of fresh frozen plasma (to enhance the Tf pool). Blood transfusion may be required. Iron chelators	TF replacement therapy Gene therapy
DMT-1 deficiency (AR)	*DMT1*	Apical membrane iron transporter in intestinal epithelial cells and endosomal iron transporter in transferrin-cycle endosomes of other cells	Impaired iron acquisition/utilization in red cell precursors (Altered inorganic iron import from the intestine).	Anemia (microcytic/hypochromic, severe) TS ↑ Ferritin ↑/normal (ferritin levels can be disproportionately low compared to liver iron overload) Iron load in the liver (not in all patients at a young age)	Erythropoietin Blood transfusion often required.	Gene therapy

Abbreviations: AR, autosomal recessive; AD, autosomal dominant; *CP*, ceruloplasmin gene; *DMT-1*, divalent metal transporter 1 gene; *HJV*, hemojuvelin; *HAMP*, hepcidin antimicrobial peptide gene; *HFE*, High Fe or homeostatic iron regulator or hemochromatosis gene; *TFR2*, transferrin receptor 2 gene; TS, transferrin saturation; *SLC40A1*, solute carrier family 40 member 1 or ferroportin1 gene.

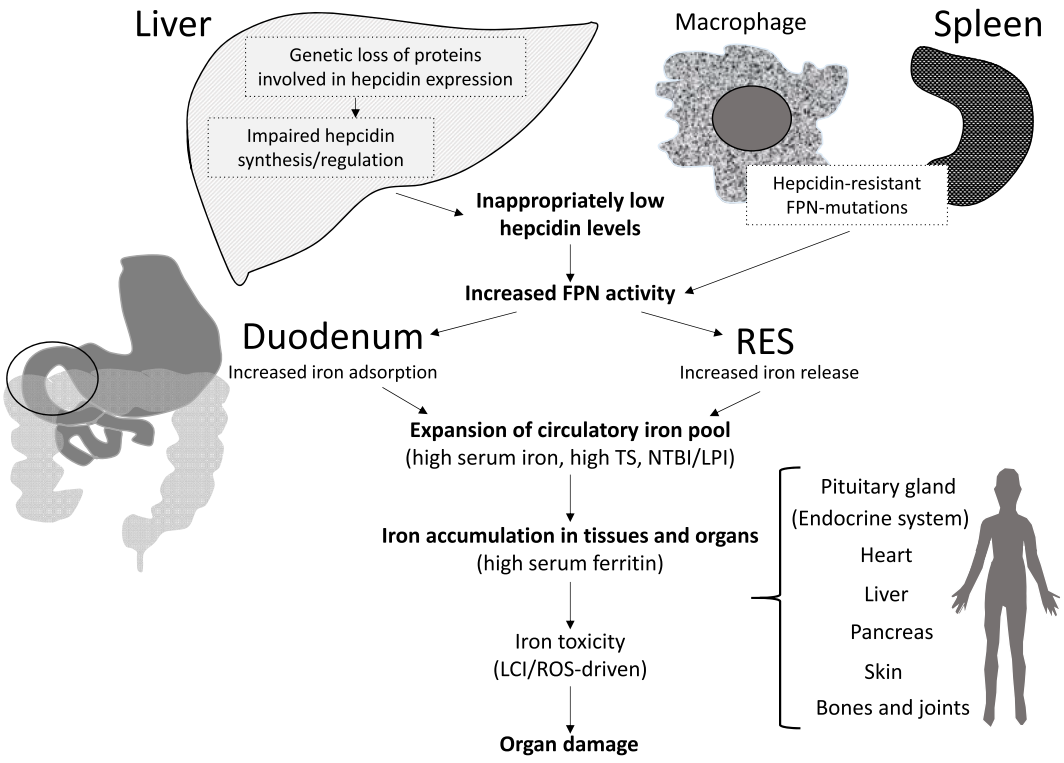

Fig. 1. Disease mechanisms of HFE, TFR2, HJV, HAMP and FPN-related hemochromatosis *Abbreviations*: FPN, ferroportin; LCI, labile cell iron; LPI, labile plasma iron; RES, reticuloendothelial system; ROS, reactive oxygen species; TS, transferrin saturation; NTBI, non transferrin-bound iron.

6%) (European Association For The Study Of The, 2010) suggests that it may have constituted or constitutes an environmental or genetic advantage for asymptomatic carriers (Hollerer et al., 2017).

The prevalence of C282Y homozygosity among Caucasians is 1:200–300, with a gradient from Northern to Southern Europe (from 12.5% in Ireland to 0% in southern regions). The H63D polymorphism is highly prevalent in the general population (average allelic frequency ~ 14%), but its clinical impact is very limited. Even lower if any is the expressivity of the isolated S65C polymorphism. Compound heterozygosity (H63D/C282Y) or H63D homozygosity may present with abnormal iron biochemistry or increased hepatic iron when associated to co-morbidities (European Association For The Study Of The, 2010). Also some private mutations have been reported on the HFE gene in trans to C282Y (Aguilar-Martinez et al., 2011).

3.1.1.2. Clinical expressivity. Clinical penetrance in C282Y homozygotes is low; half of them will not develop iron overload and two-third will not present HC-associated morbidity (European Association For The Study Of The, 2010).

Generally, clinical expressivity is higher in male as compared to premenopausal female homozygotes, because of menstruation, lactation and pregnancy, and possibly hormonal factors (e.g. suppressive effect of testosterone on hepatic hepcidin (Latour et al., 2014)).

In rare cases, combined mutations of HFE and other iron-genes, such as *HAMP, HJV and TfR2* or polymorphic variants of BMP-2, are also reportedly associated with higher penetrance of HFE-HC (reviewed in Brissot et al., 2018; Pietrangelo, 2015; Piperno et al., 2020). In recent years, next generation gene sequencing studies have provided new information on the role of genetic modifiers in HFE-HC. Novel loci affecting iron homeostasis in individuals at risk for HC have been recently reported: SNP rs884409 is in the CYBRD1 promoter, the rs3811647 polymorphism in the transferrin gene or the p.D519G variant in the glyceronephosphate O-acyltransferase (GNPAT) gene (reviewed in (Piperno et al., 2020)).

3.1.1.3. Clinical presentation. Today, the historical presentation of HC as a multiorgan disease is rare, mainly because HFE testing has allowed detection of C282Y homozygosity in asymptomatic individuals or at early disease stages. Isolated high serum iron (and transferrin saturation (TS)), more commonly accompanied with increased serum ferritin (SF), is invariably detected in asymptomatic individuals. Non-specific symptoms include fatigue, malaise and arthralgia. Hepatomegaly is an early sign and usually indicates clinically relevant iron excess, and often associates with sinusoidal and portal fibrosis at liver biopsy.

3.1.1.4. Disease manifestations. The clinical spectrum of a fully expressed HFE-HC includes liver disease, diabetes, endocrine failure, joint inflammation, heart disease and bronze skin.

Cirrhosis is part of the classic clinical manifestations and relates to the degree of iron loading. A critical threshold of hepatic iron concentration greater than 236/283 μmol/g dry weight (normal, 0–35 μmol/g) has been proposed for cirrhosis in HFE-HC, but higher liver iron concentrations may be also found in the absence of cirrhosis (Deugnier and Turlin, 2011). Additional acquired and genetic host-related factors are important for disease development and/or progression. Such factors include alcohol abuse, diabetes, fatty liver or high BMI, and, according to recent GWAS studies, polymorphic variants in the patatin-like phospholipase domain containing-3 gene (PNPLA3) (Valenti et al., 2012) or the proprotein convertase subtilisin/kexin type 7 (PCSK7) gene (Stickel et al., 2014) (reviewed in Piperno et al., 2020).

Hepatocellular carcinoma is a complication in homozygotes, with a relative risk of about 200 fold (European Association For The Study Of The, 2010). A cholangiocellular differentiation is also possible (Morcos et al., 2001). Cases of liver cancer in the absence of cirrhosis or even fibrosis have been also reported (Morcos et al., 2001).

Liver-related mortality, due to cirrhosis complications or cancer, has been shown to be the leading cause of death of HFE-HC patients, directly related to the amount and duration of iron excess (Niederau et al., 1996).

Glucose intolerance or diabetes is common in HC patients. The

pathogenesis of diabetes in human was originally related to a toxic effect of iron on pancreatic beta-cells (McClain et al., 2006), but additional factors seem to contribute, including insulin-resistance associated to the progression of the liver disease and disfunctions in liver and muscle glucose and fatty acid metabolism (Huang et al., 2007).

Endocrine manifestations include hypogonadotropic hypogonadism, leading to impotence in men, particularly frequent in cirrhotics, amenorrhea and infertility in women; other manifestations are hypothyroidism, osteoporosis and osteopenia, often related to low testosterone in men (Guggenbuhl et al., 2005).

Iron toxicity-driven cardiomyopathy and arrhythmias are well known in HFE-HC (Gulati et al., 2014), while, surprisingly, a lower prevalence of cardiovascular disease has been also reported. The reduced cardiovascular risk may be linked to reduced low-density lipoprotein (LDL) cholesterol plasma levels in C282Y homozygous (Adams et al., 2009), possibly due to increased LDL receptor expression and LDL clearance in hemochromatotic liver (Demetz et al., 2020).

Joint disease is common and typically involves the proximal interphalangeal joints of the hands, but also wrists, shoulders, knees and ankles. Synovial inflammation is common, as calcium pyrophosphate dihydrate deposition disease. Most typical associated radiologic features are chondrocalcinosis, subchondral cyst formation, osteopenia and squaring of the metacarpophalangeal joint (Guggenbuhl et al., 2011). An increased risk of hip and knee replacement has also been reported (Elmberg et al., 2013). Joint symptoms do not strictly correlate with body iron overload.

3.1.1.5. Diagnosis. Abnormal TS has high sensitivity for an expressing HC and is usually elevated before iron-overload develops (and SF increases) in young HC patients. In a Caucasian symptomatic patient presenting with one or more classic components of HC, TS and SF will be invariably high, and the HFE test will confirm the C282Y homozygosity. Liver biopsy, once the gold standard to diagnose HC, is today a prognostic tool in patients with SF > 1000 μg/L to identify a cirrhotic stage, or in those older than 40 years, with increased transaminase levels and hepatomegaly. Instead, in presence of SF < 1000 μg/L, non-increased alanine transaminase and normal liver volume or platelet count >200.000/mm3, severe fibrosis can be excluded with a negative predictive value close to 100% (Guyader et al., 1998) (Beaton et al., 2002). In C282Y/H63D or H63D/H63D patients, liver biopsy can be indicated to assess concomitant or different liver diseases. Transient elastography may help restrict the need for liver biopsy but validation is still required (Legros et al., 2015).

In symptomatic patients, with or without organ disease, with increased SF but normal TS, HFE-HC is normally ruled out. The workup should instead focus on other causes of hyperferritinemia, such as metabolic disorders, inflammation, cancer, alcohol abuse etc. If not found, the next step will address the presence of tissue (liver) iron by

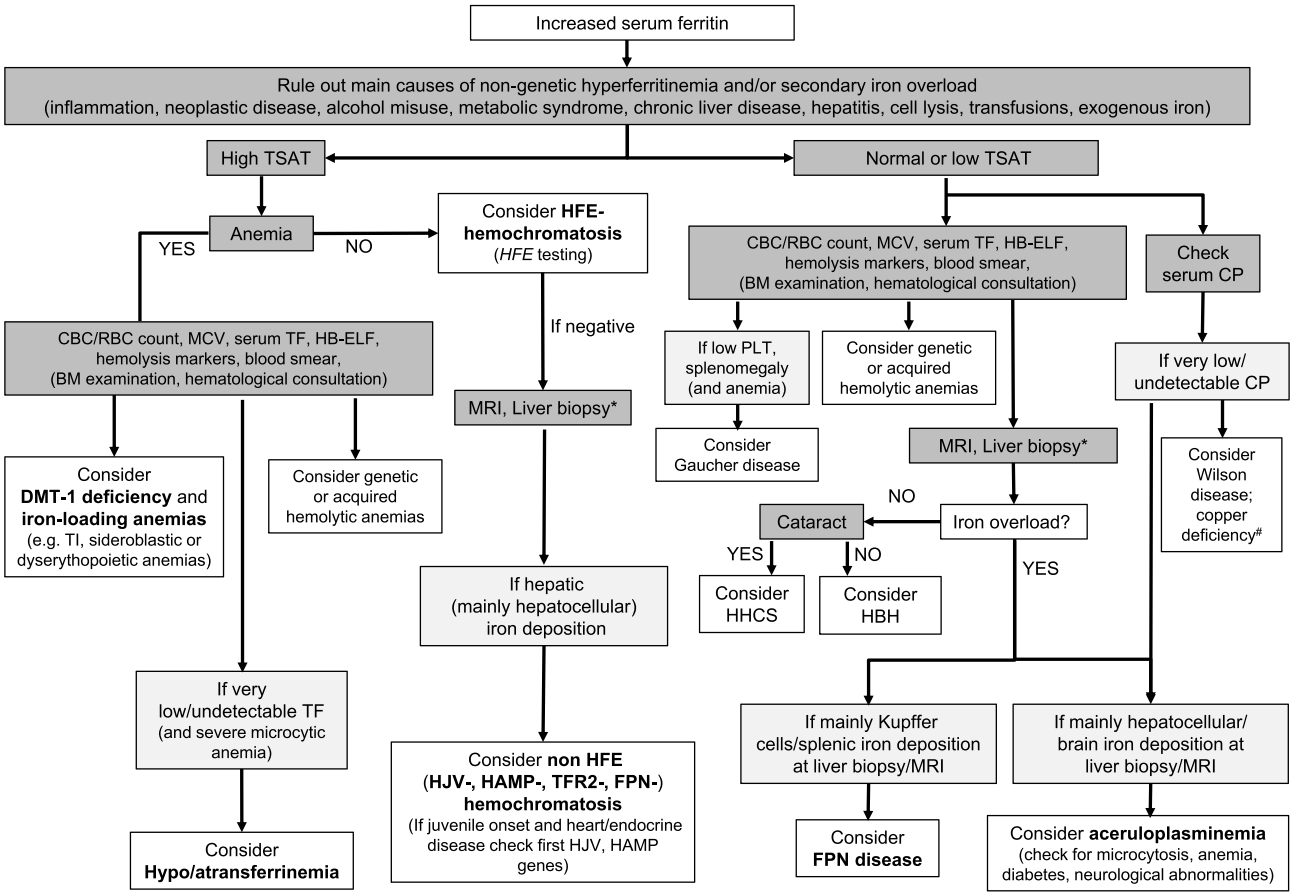

Fig. 2. Diagnostic flow-chart for the main genetic iron overload disorders starting from hyperferritinemia.The diagram provides a guide for the differential diagnosis of genetic iron-overload disorders and is not exhaustive of all the conditions associated with hyperferritinemia. *In all cases of suspected iron overload, MRI is generally recommended to evaluate body iron deposition (and liver iron quantification) and determine the need of iron-depletion; liver biopsy is required to determine liver damage and/or concomitant causes of liver disease (and for iron quantification). #In presence of low CP levels with concomitant hyperferritinemia, Wilson disease and copper deficiency should be considered (N.B: the diagram does not include all causes of low serum CP levels). *Abbreviations*: CBC, complete blood count; CP, ceruloplasmin; HB-ELF, hemoglobin electrophoresis; HBH, hereditary benign hyperferritinemia; HHCS, hereditary hyperferritin-cataract syndrome; MCV, mean cell volume; MRI, magnetic resonance imaging; HHF, hereditary hyperferritinemia; RBC, red blood cell; TF, serum transferrin; TI, thalassemia intermedia; TSAT, transferrin saturation.

magnetic resonance imaging or liver biopsy. If iron overload is documented, hereditary non–HFE-related iron overload can be considered. Elevated SF and normal TS in the absence of body iron accumulation have been reported in familial cases of autosomal dominant hyperferritinemia cataract syndrome or benign hyperferritinemia (Beaumont et al., 1995; Girelli et al., 1995; Kannengiesser et al., 2009) (Fig. 2).

3.1.1.6. Management. Phlebotomy is the standard treatment for all forms of HC. It is safe and effective for removing iron from tissues and preventing complications. Treatment is conventionally initiated when SF exceed the normal range. Also, young subjects with pre-clinical diagnosis and normal SF can be invited to consider blood donation when allowed.

The goal of bloodletting is SF level of 20–50 μg/L, through weekly removal of one unit (400–500 ml) of blood (which contains approximately 200–250 mg of iron) provided that there is no anemia (haemoglobin $\geq$ 11–12 g/dL). Maintenance therapy, which typically involves the removal of 2–4 unit/year, is then started to keep SF between 50 and 100 ng/ml. Despite its non-specificity, SF should always be monitored during phlebotomy. Observational data suggest that general and joint symptoms may be related to long-term exposure to TS >50% regardless of SF being <50 ng/ml (Bardou-Jacquet et al., 2017), indicating that TS should be monitored in conjunction with SF. When possible, blood taken from patients with HC should be made available for transfusion. If phlebotomy is contraindicated due to severe anemia or cardiac failure or poorly tolerated, other strategies can be considered, such as the use of iron chelators (Phatak et al., 2010).

Survival benefits of phlebotomy have never been evaluated in HC patients with confirmed C282Y homozygosity, but historical series of patients with clinically diagnosed HC treated with phlebotomy revealed increased survival compared with patients inadequately or never phlebotomized (Niederau et al., 1985; Williams et al., 1969). In the absence of cirrhosis or diabetes, the life expectancy of treated HC patients is similar to that of the general population. Bloodletting seems to improve transaminase levels, skin pigmentation, and hepatic fibrosis. Significant improvement of fibrosis stage in non-cirrhotic HC patients and even the regression of bridging fibrosis and initial cirrhosis, in 69% and 35% of patients respectively (Falize et al., 2006) have been reported after venesection therapy. A recent retrospective multicentre study in patients with biopsy-proven fibrosis, while confirming these data, showed fibrosis regression and long-term risk for liver cancer reduction in a median follow-up of 19,1 years (Bardou-Jacquet et al., 2020). Hypogonadism, cirrhosis, destructive arthritis, and insulin-dependent diabetes are usually irreversible, but daily insulin requirements, elevated aminotransferase levels, weakness, lethargy, abdominal pain may be improved by phlebotomy. Joint symptoms do not always respond to iron depletion. Erythrocytapheresis has been used but is less available, requires more expertise and equipment and is more expensive in the maintenance phase than phlebotomy.

Despite scarce evidence and limited data on clinical relevance and quality of life, dietary modification may affect iron accumulation in hemochromatosis patients (Moretti et al., 2013). It is advisable to avoid high intake of alcohol, regular meet consumption and oral iron supplementation.

Systemic complications of HC should be assessed, monitored and treated. End-stage liver disease and hepatocellular carcinoma are frequently treated by liver transplantation, but post-transplant survival rates in these cases are reduced compared to those of non-HFE-HC patients likely due to cardiac and infectious complications (Kowdley et al., 2005).

3.1.2. Non-HFE HC

This group includes so far HC associated with mutations of TfR2, HJV, HAMP genes and gain-of-function mutations of FPN gene. Unlikely HFE, such forms are not restricted to Northern Europeans.

3.1.2.1. Juvenile HC (J-HC). Most cases are due to a number of damaging HJV mutations, including the commonest p.Gly320Val variant (Papanikolaou et al., 2004), while a minority has been linked to private homozygous mutations of the HAMP gene itself (Roetto et al., 2003). In J-HC iron loading occurs at a greatly accelerated rate leading to earlier age of onset (first to third decade) and more severe course of disease than HFE-HC. A recent review of published cases (Sandhu et al., 2018) shows that affected individuals are more likely to present with cardiomyopathy and endocrine failure (mainly pituitary hypogonadism, possibly presenting as secondary amenorrhea). Importantly, if not treated, affected patients can develop and die of severe heart failure before age 30. Hepatic fibrosis/cirrhosis is often present at diagnosis. Diabetes/reduced glucose tolerance, arthropathy and skin pigmentation can also be part of the syndrome. The typical presenting picture could be the result of different factors: the severity of genetic defects, a possibly higher susceptibility of heart and endocrine glands to a rapid iron overload early in life (with respect to the liver which has a physiologic role or iron deposit), the clinically silent hepatic fibrosis until (decompensated) cirrhotic phase, and the young age at diagnosis. HJV-HC patients with milder disease and late onset were recently described in Asia and Europe, suggesting the presence of phenotype modifiers or lower pathogenicity variants. Also, patients presenting with combined mutations of HFE and TfR2 have been reported to have the same phenotype as J-HC (Pietrangelo et al., 2005).

Although there is no standardized treatment due to the rarity of disease and its quite variable expressivity, venesection represents a therapeutic pillar also for J-HC. In severe or more advanced cases, iron-chelation can be considered as combined or sequential therapy. In complicated cases, a combination of two iron-chelating drugs (similarly to thalassemia patients) has been effectively used (Fabio et al., 2007).

3.1.2.2. TfR2-associated HC. TfR2-HC has been reported mostly in pedigrees of Italian extraction with high consanguinity, in single families in France, Portugal, Spain, and in individuals of mixed European descent. Few cases have been reported in Taiwan and Japan. Currently, less than 30 pathogenic mutations have been described (Sandhu et al., 2018). Generally, this type of HC differs from the classic HFE-HC because an earlier onset (secondo to third decade) and more severe presentation, as a sort of ‘intermediate’ form between adult and juvenile-HC.

3.1.2.3. FPN-associated HC. Another rare form of HH, similar to the classic HFE-HH, is caused by heterozygous unusual gain-of-function FPN-1 gene mutations (Njajou et al., 2001; Sham et al., 2005; Wallace et al., 2004): affected patients present hyperferritinemia, high TS, iron-spared macrophages, and progressive parenchymal cell iron load. It must therefore be distinguished from the so-called ‘ferroportin disease’ (see section 3.2) associated with loss-of-function variants (Fig. 3).

Ethnic background and age of presentation of reported cases of FPN-HC are variable. Clinical presentation and management is identical to HFE-HC.

3.2. Ferroportin disease

The Ferroportin Disease (FD), one of the commonest forms of hereditary iron overload and the most frequent cause of hereditary hyperferritinemia, is due to pathogenic (usually missense) mutations of the ferroportin1 (*FPN1; SLC40A1)* gene. The FD was first reported in 1999 in a large Italian pedigree with a phenotype characterized by predominant reticuloendothelial cell overload, hyperferritinemia coexisting with normal-low TS and tendency to hypochromic anemia (Pietrangelo et al., 1999). The disorder is due to lack-of-function mutations of FPN1 that impair its iron-export capability particularly in cells with high iron turnover (such as tissue macrophages) (Fig. 3). Differently from HFE, TFR2, HJV and HAMP-HC, the pattern of inheritance of the

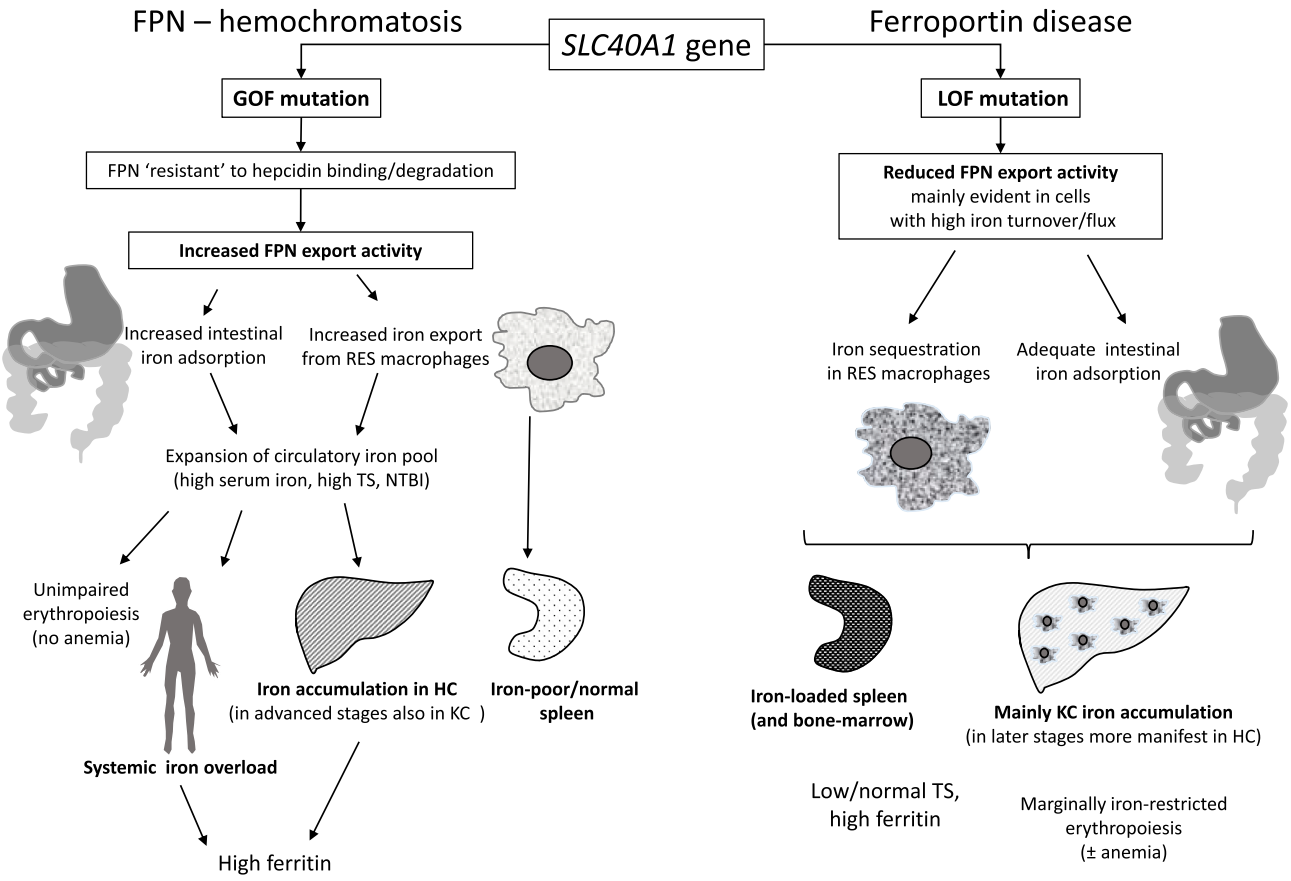

Fig. 3. Disease mechanisms of FPN-associated hemochromatosis and Ferroportin disease. *Abbreviations*: FPN, ferroportin; GOF, gain of function; HC, hepatocytes; KC, Kupffer cells; LOF, loss of function; NTBI, non transferrin-bound iron; RES, reticuloendothelial system; TS, transferrin saturation.

FD is autosomal dominant.

Numerous mutations of the FPN1 gene have been identified worldwide, regardless of ethnicity (Pietrangelo, 2017). A few common FPN1 mutations have been reported in independent pedigrees, which have likely occurred multiple times in isolated populations in different countries (e.g. Val192del, A77D, G80S) (Pietrangelo, 2017). FPN1 variants are highly prevalent in African populations. In fact, global analysis of variants in the SLC40A1 gene gave a predicted pathogenic genotype carrier rate that approaches the frequency of HFE-HC (Wallace and Subramaniam, 2016) largely due to the relatively high allele frequencies of African variants, in particular the Q248H (Pietrangelo, 2017).

The pathogenesis of the FD has been long elusive and controversial. Recently, FPN1 topology and membrane organization has been largely uncovered, thereby helping depiction of pathogenic models for the FD (Pietrangelo, 2017). Uncertainties remain on the functional effect of different FPN variants and FD pathogenesis, as most studies have been performed in transfected cell lines, which present obvious limitations (Vlasveld et al., 2019). In macrophages from FD patients (Sabelli et al., 2017), FPN1 monomers can still reach the cell surface and sufficiently export iron in cells that are exposed in vivo to a relatively low flux of iron, such as enterocytes. But in cells undergoing in vivo high iron turnover, such as tissue macrophages where higher amount of protein is needed at the cell surface, sufficient FPN1 is prevented from reaching the plasma membrane, possibly due to traffic jam in the degradation and/or endocytic cycling pathways. This model is consistent with the clinical manifestation of the FD characterized by early iron accumulation in hepatic Kupffer cells and normal TS (indicating that mutant FPN1 activity is not limiting for intestinal iron transfer) which instead become critically low in young female at menarche or after aggressive phlebotomy, when high iron demands for erythropoiesis likely impose increased FPN1 traffic/cycling within tissue macrophages (Pietrangelo, 2004).

Of note, a recent study performed in a cell line has suggested that a partial hepcidin resistance could contribute to the iron overload phenotype associated with some loss-of-function FPN-1 gene variants (Viveiros et al., 2020).

Clinical presentation appears heterogeneous, but overall, expressivity is mild (Le Lan et al., 2011; Pietrangelo, 2004; Pietrangelo et al., 1999). In the original FD pedigree, after discontinuation of phlebotomy, the proband, carrier of an occult HBV infection, developed a liver cancer and two siblings showed a liver fibrosis progression, suggesting a co-factorial pathogenic role of iron in the FD (Corradini et al., 2007).

The disease must be suspected in any individual with unexplained hyperferritinemia and low-normal TS, or prevalent non-parenchymal cells siderosis at liver biopsy or liver and spleen iron accumulation at MRI. Hyperferritinemia in FD appears very early in life, and even in children/young adults MRI, a useful non-invasive tool to categorize and diagnose the disorder (Pietrangelo et al., 2006), can show iron accumulation in the spleen, spine and liver, the classic "SSL triad".

Although data on natural history and evidence-based therapeutic strategies are lacking, patients are commonly offered an iron-depletive treatment. Venesection is the mainstay of therapy, but it may not be tolerated equally in all patients and low TS with anemia may appear despite SF being still high (Pietrangelo, 2004). Therefore, TS levels should be monitored during treatment, whose ideal target is reaching the lowest acceptable ferritin level (usually 100–200 μg/L) before anemia appears. Iron-chelation may be an option in selected cases (Unal et al., 2015).

3.3. Aceruloplasminemia

Aceruloplasminemia (AC) is a very rare autosomal recessive disorder

caused by mutations of ceruloplasmin (CP), that plays a key role in iron efflux from the cell by promoting iron release to plasma Tf and stabilizing membrane ferroportin (Miyajima, 2015). The absence/deficiency of CP activity causes iron overload in several organs (liver, pancreas, heart, thyroid) including the central nervous system, and iron-restricted erythropoiesis (Kono, 2013).

Although firstly reported in Japan (Miyajima, 2015), AC has a worldwide geographical distribution and variable clinical expressivity (Vila Cuenca et al., 2020; Vroegindeweij et al., 2015). Laboratory data encompass absent/reduced serum CP, hyperferritinemia, low/normal TS, micro/normocytic anemia, isolated microcytosis (Vila Cuenca et al., 2020). Main clinical manifestations are diabetes mellitus, retinal degeneration, and a wide spectrum of neurological signs and symptoms (Kono, 2013).

Iron excess mainly involves the liver, largely the hepatocytes, and the brain (and possibly other sites). Interestingly, in spite of the key role of macrophage ferroportin in iron recycling, the spleen is spared, while massive hepatocellular iron overload does not elicit evident fibrosis.

Neurodegeneration may be also contributed by neuronal iron starvation because of reduced release of iron from astrocytes (Kono, 2013; Miyajima, 2015). A cell-type specific damage due to reduced iron supply from surrounding cells may occur in other organs as well (Piperno and Alessio, 2018).

AC has a progressive and potentially fatal course, therefore treatment must be pursued, although the therapeutic strategy is not standardized and iron chelators' efficacy can be poor on neuro/psychiatric symptoms (Piperno and Alessio, 2018).

3.4. Hypo/atransferrinemia

Congenital hypo/atransferrinemia is a very rare autosomal recessive disorder due to mutations of transferrin (TF) gene. A total of 18 (not all genetically confirmed) patients have been reported worldwide (Dabboubi et al., 2020).

Inefficient Tf-mediated delivery of iron to the bone marrow results in severe microcytic hypochromic anemia from birth, while intestinal iron absorption is unaffected or further stimulated by anemia. NTBI-like transfer mechanisms cause iron overload in the liver, myocardium, pancreas and thyroid. Laboratory features include undetectable/low levels of fully saturated Tf and high SF (Dabboubi et al., 2020). Patients may require blood transfusion, and benefit from combined infusion of fresh frozen plasma (to enhance the Tf pool) and chelation therapy (Piperno et al., 2020). Nevertheless, variability in clinical expression is reported and, since total absence of Tf seems incompatible with life, the disease phenotype could be related to the severity of the reported mutations and other genetic or acquired modifiers.

3.5. DMT-1 deficiency

This rare autosomal recessive disease is due to mutations of DMT-1, involved in inorganic iron absorption from enterocytes and Tf-iron processing within acidified endosomes (Iolascon and De Falco, 2009). Patients present with hypochromic microcytic anemia of variable severity, similarly to the rodent disease model (Iolascon and De Falco, 2009), but also with raised serum iron and TS, slightly increased SF and hepatic iron overload which usually manifests at a young age (Iolascon and De Falco, 2009; Mims et al., 2005). Iron overload may be largely contributed by increased iron absorption through the heme-iron pathway, unaffected by the underlying genetic defect (Mims et al., 2005). Patients may require blood transfusion. Iron chelation is not indicated/effective, while treatment with erythropoietin could be of benefit (Pospisilova et al., 2006).

4. Miscellaneous genetic disorders with systemic or local iron deposition

4.1. Genetic anemias with iron overload

Other genetic anemias may exhibit some degree of excess iron accumulation due to different, often concomitant, processes.

Paradigmatic "iron-loading anemias" consist of not-transfused thalassemia intermedia and congenital sideroblastic or dyserythropoietic anemias whose main mechanism for iron-accumulation is increased iron absorption due to the hepcidin suppression by anemia/inefficient erythropoiesis, tissue hypoxia and erythropoietin (Camaschella and Nai, 2016; Coates, 2014).

In other forms, (e.g. transfusion-dependent thalassemias, sickle cell disease) iron-loading secondary to transfusion or chronic hemolysis can be also present or prevail.

Other pathogenic mechanisms of iron dis-regulation in hereditary anemias may take place, as suggested by recent studies pointing to altered hepcidin control (Andolfo et al., 2020).

4.2. Neuroferritinopathy

Neuroferritinopathy (NF) is a very rare, autosomal dominant, adult-onset disease caused by mutations in L-ferritin gene (FTL) (Curtis et al., 2001). NF, like AC, belongs to the NBIA disorders (characterized by focal iron accumulation in the brain, usually in the basal ganglia), of which only AC and NF are linked to genes directly involved in iron homeostasis (Levi and Rovida, 2015).

NF pathology is characterized by aggregates of (mutant and wild type) ferritin and iron in the brain, but also in other tissue (skin, liver, kidney, muscle). Patients present low/normal SF levels and neurological symptoms, including movement disorders. The key element in the complex FN pathogenesis is free iron-mediated oxidative damage, due to impaired ferritin storage capacity, to which the brain tissue is particularly sensitive (Levi and Rovida, 2015). The apparent invulnerability of non-neural tissues deserves further study.

4.3. Friedreich ataxia

Friedreich ataxia, the most common inherited ataxia, is characterized by progressive degeneration of the central and peripheral nervous systems and non-neural tissues including the heart and endocrine pancreas (Delatycki and Bidichandani, 2019). Loss of the mitochondrial protein frataxin, involved in iron–sulfur cluster biogenesis, causes disruption of mitochondrial iron homeostasis and mitochondrial iron accumulation evident in cardiomyocytes and other organs. However, the complex disease pathogenesis is not fully understood, and the role of iron has not yet been completely clarified (Llorens et al., 2019).

4.4. Hmox1-deficiency

Heme oxygenases isoform 1 (HMOX1) deficiency, has been described in two children showing growth retardation, severe anemia and hyperferritinemia, hepatic and renal iron overload, intravascular hemolysis, endothelial and vascular injury and early death (Kawashima et al., 2002; Radhakrishnan et al., 2011). Tissue iron deposition seems secondary to altered iron recycling, intravascular hemolysis and heme accumulation.

5. Conclusions

Although all characterized by iron excess, genetic iron overload disorders include pathological conditions with different phenotypes, clinical expressivity and severity. The most frequent forms, such as HFE-HC at earliest stage and FD, appear to be less severe, while others, less frequent, such as the non-HFE HC juvenile forms, are potentially life-threatening.

There are still gaps in the knowledge of the pathogenic basis of most of these disorders. Furthermore, new genes responsible for disease or disease modifiers are likely to be discovered by exploiting new approaches, including wider and comprehensive next-generation sequencing and biotechnology strategies as well as large international patient disease registries efforts. In addition, innovative and promising therapies using small molecules and other molecular tools are under investigation.

On this basis, disease awareness, clinical suspicion and continuing medical education are crucial for patient diagnosis and management.

Author contribution

All authors contributed to literature review and writing and approved the final version.

Declaration of competing interest

The authors declare that they have no competing interests.

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