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Hereditary Hemochromatosis: Pathogenesis, Diagnosis, and Treatment

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In the late 1800s, hemochromatosis was considered an odd autoptic finding. More than a century later, it was finally recognized as a hereditary, multi-organ disorder associated with a polymorphism that is common among white people: a 845G→A change in *HFE* that results in C282Y in the gene product. Hemochromatosis is now a well-defined syndrome characterized by normal iron-driven erythropoiesis and the toxic accumulation of iron in parenchymal cells of liver, heart, and endocrine glands. It can be caused by mutations that affect any of the proteins that limit the entry of iron into the blood. In mice, deletion of the iron hormone hepcidin and any of 8 genes that regulate its biology, including *Hfe*, *transferrin receptor* 2 (*Tfr2*), and *hemojuvelin* (*Hjv*) (which all sense the accumulation of iron that hepcidin corrects) or *ferroportin* (*Fpn*) (the cellular iron exporter down-regulated by hepcidin), cause iron overload but not organ disease. In humans, loss of TfR2, HJV, and hepcidin itself or FPN mutations result in full-blown hemochromatosis. Unlike these rare instances, in white people, homozygotes for C282Y polymorphism in HFE are numerous, but they are only predisposed to hemochromatosis; complete organ disease develops in a minority, when these individuals abuse alcohol or from other unidentified modifying factors. *HFE* gene testing can be used to diagnose hemochromatosis, but analyses of liver histology and clinical features are still required to identify patients with rare, non-HFE forms of the disease. The role of hepcidin in the pathogenesis of hemochromatosis reveals its similarities to endocrine diseases such as diabetes and indicates new approaches to diagnosis and management of this common disorder in iron metabolism.

Keywords: Iron Metabolism; Hereditary Disorders; Micronutrients; Hepcidin; HFE.

Hemochromatosis is a well-defined syndrome characterized by normal iron-driven erythropoiesis and toxic accumulation of iron in parenchymal cells of vital organs that can be caused by mutations in any gene that limits iron entry into the blood. A milestone in hemochromatosis research occurred in 1996 when Feder et al discovered that mutation in *HFE* caused hereditary hemochromatosis.[1] Research in the fields of hemochromatosis and iron metabolism have progressed, side by side, for 150 years (Table 1). The presence of iron in the blood was first shown in 1713,[2] but more than 2 centuries passed before the first iron protein, ferritin, was characterized[3] and the basic principles of iron homeostasis were discovered.[4] In the mid-1800s, hemochromatosis was described from an autopsy of a patient with diabetes by the French physician Armand Trousseau,[5] who was struck by the "bronze-like appearance of [the patient's] countenance." The liver, he noted, was "granular, of a uniform grayish-yellow color, and very dense." At the time, the only known iron disease was the condition known today as iron-deficient hypochromic anemia, referred to as chlorosis or, given its frequency in adolescent girls and young women, morbus virgineous.[6] Trousseau advocated treating chlorosis with iron but classified it as a "nervous disease." Soon other French physicians described a syndrome known as "bronze diabetes and pigmented cirrhosis,"[7,8] and until the mid-20th century this condition was attributed to diabetes, hemolysis, toxins, or metabolic disturbances. In 1935, Joseph Sheldon described the multi-visceral nature of the syndrome and the probable role of iron among its causes.[9] He was also the first to suggest that the disease resulted from an inherited metabolic defect. Over the next few decades, studies of ferrokinetics provided more information about iron regulation,[10] and by the 1950s bloodletting was introduced to treat hemochromatosis.[11]

Abbreviations used in this paper: BMP, bone morphogenic protein; FPN, ferroportin; HAMP, hepcidin gene; HJV, hemojuvelin; RGM, repulsive guidance molecule; TfR, transferrin receptor; TS, transferrin saturation.

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Table 1. Timeline of Iron Metabolism and Hemochromatosis Research

Year	Discovery	Researchers	References
1554	First description of "chlorosis"	Lange	6
1713	Human blood shown to contain iron	Lemery & Geoffroy	2
1865	A case of "bronze diabetes and cirrhosis" is described	Trousseau	5
1871/1882	Hypertrophic pigmentary cirrhosis and diabetes	Troisier–Hanot & Chauffard	7,8
1889	The term "hemochromatosis" is coined to describe bronze-colored organs and tissues at autopsy	Von Recklinghausen	27
1935	Hemochromatosis is hypothesized to be hereditary and related to iron metabolism	Sheldon	9
1937	The first iron protein (ferritin) is identified and crystallized	Laufberger	3
1937	First study on the role of intestinal absorption in iron metabolism	Widdowson & McCance	4
1946	An iron-binding protein (transferrin) is identified in human plasma	Schade & Caroline	121
1950	Blood letting reported as a treatment for hemochromatosis	Davis & Arrowsmith	11
1950	Liver biopsy reported as a tool for diagnosing hemochromatosis	Davis & Laurens	122
1951	First report of juvenile hemochromatosis	Plattner, Nussbaumer, & Rywlin	21
1951	Radioiron studies of intestinal absorption in hemochromatosis	Alper & Bothwell	10
1955	First comprehensive review on hemochromatosis	Finch & Finch	123
1961	Hemochromatosis as a variant of alcoholic cirrhosis and nutritional siderosis	MacDonald	12
1963	Intestinal iron absorption shown to be regulated at the enterocyte/blood interface	Crosby	124
1969	Phlebotomy reported to improve survival in hemochromatosis	Williams & Sherlock	125
1975	Hemochromatosis is shown to be a hereditary autosomal recessive HLA-linked disease	Simon	13
1976	First description of the translational control of ferritin	Zahringer & Munro	126
1983	First description and characterization of iron-mediated oxidative damage in hemochromatosis	Bacon & Recknagel	127
1985	Survival and causes of death reported in a large series of hemochromatosis patients	Niederau & Strohmeyer	116
1987	"Iron responsive elements" are found in the mRNA of ferritin	Aziz & Munro–Hentze & Klausner	128,129
1988	First large population screening study using blood iron measures in HLA-linked hemochromatosis	Edwards & Kushner	130
1989	Defective iron retention by reticuloendothelial macrophages is described in hemochromatosis	Fillet	37
1991	Increased iron absorption in hemochromatosis linked to increased mucosal iron transfer to the plasma	McLaren	38
1994	Molecular and cellular basis of hepatic fibrogenesis in hemochromatosis are described	Pietrangelo	131
1996	Identification of the gene mutated in HLA-linked hemochromatosis: *HFE*	Feder & Wolf	1
1997	Divalent metal transporter 1 (DMT1)–the first mammalian transmembrane iron transporter–is identified	Fleming & Andrews–Gunshin & Hediger	132,133
1999	Description of non-HFE-related hemochromatosis in adults (later identified as ferroportin disease)	Pietrangelo	14
1999	Identification of transferrin-receptor 2 (TfR2) gene	Kawabata	19
2000	Description of TfR2-associated hemochromatosis	Camaschella & Gasparini	20
2000	Description of liver-expressed antimicrobial protein (hepcidin) in human	Krause & Adermann	22
2000	Identification of ferroportin1 (MTP-1; IREG-1) gene	Abboud & Hailie–Donovan & Zon	16,17,18
2001	Description of ferroportin-associated iron overload ("ferroportin disease")	Montosi & Pietrangelo–Njajou & Heutink	15,115
2001	Hepcidin expression in the liver is linked to iron	Pigeon & Loreal	23
2002	Decreased hepcidin levels documented in HFE null mice	Ahmad & Fleming	66
2000–06	Documentation of the penetrance of HFE-associated hemochromatosis	Kushner–Beutler–Olynyk–Powell	98,134,135,136
2003	Description of hepcidin-associated hemochromatosis	Roetto & Camaschella	25
2003	Decreased hepcidin expression documented in human HFE-related hemochromatosis	Bridle & Anderson–Gehrke & Stremmel	67,68
2004	HJV gene isolated and HJV-related hemochromatosis reported	Papanikolaou	26
2005	Hepcidin is shown to cause FPN degradation in vitro: a model for regulation of iron homeostasis in vivo	Nemeth & Kaplan	44
2004–08	Low progression rate of HFE-related hemochromatosis is documented	Olynyk–Andersen & Nordestgaard–Allen	100,101,102
2006	HJV/BMP signaling shown to regulate hepcidin and iron metabolism	Babitt & Lin	74
2006	A model for iron sensing based on HFE/TfR2 interaction is proposed	Goswami & Andrews	137
2009	ER stress controls hepcidin expression and iron metabolism in vivo	Vecchi & Pietrangelo	56
2009	BMP6 shown to be the key endogenous regulator of iron metabolism	Andriopoulos, Corradini, Xia & Babitt–Meynard & Roth	32,33
2009	BMP6 signalling shown to be impaired in HFE null mice	Corradini & Babitt–Kautz & Roth	78,79

NOTE. Green lines show the milestones in hereditary hemochromatosis.

Eventually, research on hemochromatosis was no longer limited to postmortem observations. Researchers like MacDonald questioned the hereditary nature of hemochromatosis and advocated the pathogenic role of alcohol and dietary iron[12] until 1975, when Simon et al linked the syndrome to the major histocompatibility complex on chromosome 6.[13] Twenty years later, Feder et al cloned *HFE*, leading to genetic studies in humans and mice that provided important new information about iron metabolism and hemochromatosis. As genetic tests were developed for *HFE* polymorphisms and larger genetic studies were performed, it became clear that the disorder was more complicated than previously believed. Sporadic and familial cases of hemochromatosis were identified that were not associated with *HFE*, particularly in southern Europe. In 1999, a large pedigree of patients with hereditary iron overload was described, but the trait was autosomal dominant and iron accumulated in the reticuloendothelial, rather than parenchymal, cells.[14] Two years later this phenotype was associated with a