HFE Genotype and Dietary Iron Exposure (Literature Review)

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ABSTRACT

Background:
Iron is indispensable for erythropoiesis and haemoglobin-mediated oxygen transport, yet excess body iron promotes tissue injury because iron balance is regulated predominantly through absorption rather than physiologic excretion. (Hurrell and Egli, 2010; Vujić, 2014) Common variants in *HFE* — particularly p.Cys282Tyr (C282Y; rs1800562), p.His63Asp (H63D; rs1799945) and p.Ser65Cys (S65C; rs1800730) — modify the hepcidin-mediated regulation of intestinal iron uptake and thereby contribute to inter-individual differences in iron absorption efficiency and long-term iron loading risk across individuals and populations (Jouanolle et al., 1997; Vujić, 2014; European Association for the Study of the Liver, 2022)

Methods:
A narrative synthesis was performed integrating molecular mechanisms of *HFE*–hepcidin regulation with population-genetic data on *HFE* variant frequencies and clinical evidence on penetrance, diagnostic pathways, and therapeutic iron depletion. (Moirand et al., 1999; Crownover and Covey, 2013; Vujić, 2014) Practice guidance on diagnosis and management of haemochromatosis and screening recommendations were incorporated to contextualize genotype-informed dietary counselling within contemporary clinical decision-making. (U.S. Preventive Services Task Force, 2006; European Association for the Study of the Liver, 2022)

Results:
In many European-ancestry cohorts, *HFE* p.C282Y homozygosity accounts for a substantial proportion of clinically recognized *HFE*-related haemochromatosis, whereas compound heterozygosity and rarer combinations (including S65C-containing genotypes) are generally associated with milder and more variable phenotypes. (Jouanolle et al., 1997; Moirand et al., 1999; Wallace et al., 2002; European Association for the Study of the Liver, 2022) Population prevalence shows strong geographic gradients within Europe, supporting a founder-driven distribution with highest frequencies in north-western regions. (Jouanolle et al., 1997; Carella et al., 1997; European Association for the Study of the Liver, 2022) Clinical penetrance is incomplete and strongly sex-dependent, with biochemical iron loading substantially more common than overt end-organ disease, which has direct implications for dietary advice and screening intensity.

(Crownover and Covey, 2013; Vujić, 2014; European Association for the Study of the Liver, 2022)

Discussion:
A genotype-aware approach to dietary iron should reconcile two competing risks: iron deficiency in settings of low bioavailable iron intake and iron overload in genetically predisposed individuals, particularly when iron-rich diets, fortification, or supplementation are combined with absorption-enhancing co-factors such as ascorbic acid. (Hallberg et al., 1986; Hurrell and Egli, 2010; Vujić, 2014) Because ferritin elevation is common and non-specific, risk stratification should rely on transferrin saturation, ferritin dynamics, and appropriately targeted *HFE* genotyping rather than routine, untargeted screening in unselected populations. (Moirand et al., 1999; U.S. Preventive Services Task Force, 2006; European Association for the Study of the Liver, 2022) Early therapeutic phlebotomy can prevent cirrhosis, hepatocellular carcinoma and metabolic complications when instituted before advanced organ damage, underscoring the preventive value of timely recognition in genetically susceptible groups. (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Subjects: Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Iron

INTRODUCTION

Iron occupies a central position in human physiology because it enables oxygen transport and cellular respiration while simultaneously posing a toxicological hazard when present in excess as redox-active iron. (Hurrell and Egli, 2010; Vujić, 2014) The distinctive regulatory feature of iron metabolism is the absence of a controlled excretory pathway, which renders intestinal absorption the dominant lever of systemic iron balance across the life course. (Hurrell and Egli, 2010; European Association for the Study of the Liver, 2022) Consequently, inter-individual variability in absorption — whether driven by genetic determinants, inflammation, or diet composition — can translate into clinically meaningful differences in long-term iron stores and disease susceptibility. (Hurrell and Egli, 2010; Vujić, 2014; European Association for the Study of the Liver, 2022)

Among inherited determinants, variation in *HFE* has relevance because *HFE*-related haemochromatosis is among the most prevalent genetic iron-overload disorders in populations of European ancestry and is mechanistically linked to inadequate hepcidin signaling. (Jouanolle et al., 1997; Vujić, 2014; European Association for the Study of the Liver, 2022) The clinical salience of *HFE* genetics is not limited to rare severe phenotypes, because common alleles such as C282Y and H63D occur at appreciable frequencies and contribute to a spectrum of iron phenotypes ranging from normal regulation to progressive iron loading. (Jouanolle et al., 1997; Moirand et al., 1999; Crownover and Covey, 2013) This spectrum intersects directly with nutritional practice, as dietary patterns differ markedly in iron density and bioavailability, and absorption is modulated by enhancers such as vitamin C and inhibitors such as phytates and polyphenols. (Hallberg et al., 1986; Hurrell and Egli, 2010; Hallberg et al., 1989)

A scientifically defensible framework for “optimal” iron intake therefore requires integration of (i) the molecular basis of *HFE*–hepcidin regulation, (ii) the population distribution of key *HFE* alleles, (iii) genotype–phenotype associations including penetrance and sex effects, and (iv) dietary modifiers of bioavailability that can amplify or attenuate genetic predisposition. (Vujić, 2014; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) The present synthesis focuses on these components to derive academically grounded implications for genotype-informed dietary counselling and for rational approaches to testing and monitoring. (Moirand et al., 1999; U.S. Preventive Services Task Force, 2006; European Association for the Study of the Liver, 2022)

Evolutionary and Population-Genetic Context of *HFE* Variation

The high prevalence of *HFE* variants in north-western Europe has motivated both founder-effect explanations and hypotheses of historical selective pressures in iron-limited environments, although the latter remain difficult to prove directly and should be treated as interpretive rather than definitive. (Jouanolle et al., 1997; Vujić, 2014; European Association for the Study of the Liver, 2022) Empirically, strong geographic gradients are consistently observed, with higher frequencies of p.C282Y homozygosity in north-western Europe and lower frequencies in southern Europe, supporting a founder-driven distribution compatible with regional demographic history. (European Association for the Study of the Liver, 2022; Carella et al., 1997; de Juan et al., 2001) Studies in defined European subpopulations, including Brittany and Italy, further demonstrate

substantial between-region heterogeneity in *HFE* genotypes among clinically characterized haemochromatosis patients, underscoring that “European ancestry” is not genetically uniform with respect to *HFE*. (Jouanolle et al., 1997; Carella et al., 1997; Moirand et al., 1999)

The colloquial label “Celtic” burden has been used to describe this north-western enrichment, yet clinical risk remains a function of genotype class, penetrance modifiers and environment rather than ancestry alone. (Crownover and Covey, 2013; Vujić, 2014; European Association for the Study of the Liver, 2022) Importantly, a high carrier frequency does not imply that most carriers will develop clinically significant iron overload, because heterozygosity and several compound genotypes typically confer only modest shifts in iron indices. (Moirand et al., 1999; Crownover and Covey, 2013; Wallace et al., 2002) This distinction between population prevalence and individual clinical expression is central to responsible dietary guidance and to the ethics of broad genetic screening initiatives. (U.S. Preventive Services Task Force, 2006; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Molecular Mechanisms: The *HFE*–Hepcidin Axis and Intestinal Iron Uptake

At the mechanistic level, *HFE*-related haemochromatosis is best conceptualized as a disorder of hepcidin insufficiency, in which impaired signaling yields inappropriately high iron absorption and progressive tissue iron deposition. (Vujić, 2014; European Association for the Study of the Liver, 2022) *HFE* encodes an MHC class I–like protein that interacts with components of iron sensing and hepcidin regulation, thereby influencing ferroportin-mediated iron export from enterocytes and macrophages. (Beutler et al., 1997; Vujić, 2014; European Association for the Study of the Liver, 2022) When hepcidin signaling is inadequate, intestinal absorption remains elevated even as body iron stores rise, creating a long latency trajectory in which iron accumulates over decades before organ injury becomes clinically apparent. (Vujić, 2014; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Dietary iron enters the absorptive pathway as heme iron (primarily from animal tissue) and non-heme iron (primarily from plant and fortified sources), with non-heme iron absorption particularly sensitive to luminal chemistry and co-ingested enhancers or inhibitors. (Hurrell and Egli, 2010; Hallberg et al., 1986; Hallberg et al., 1989) Because absorption is the main regulatory point and because physiological excretion is minimal, even moderate genetically driven increases in fractional absorption can translate into substantial cumulative differences in total body iron over time. (Hurrell and Egli, 2010; Vujić, 2014; European Association for the Study of the Liver, 2022) This principle provides the biological rationale for framing dietary advice as an exposure problem — balancing intake, bioavailability, and absorption propensity — rather than as a simple comparison against a single universal intake target. (Hurrell and Egli, 2010; Vujić, 2014; European Association for the Study of the Liver, 2022)

Clinically Relevant *HFE* Variants and Genotype Stratification

Three *HFE* variants are repeatedly emphasized in clinical and population studies: C282Y (rs1800562), H63D (rs1799945) and S65C (rs1800730), each contributing differently to iron

phenotypes. (Jouanolle et al., 1997; Mura et al., 1999; Wallace et al., 2002) In patients meeting phenotypic criteria for haemochromatosis in north-western European settings, C282Y homozygosity can account for the large majority of cases, supporting its role as the dominant pathogenic genotype in classic *HFE*-haemochromatosis. (Jouanolle et al., 1997; Moirand et al., 1999; European Association for the Study of the Liver, 2022) By contrast, H63D is common in the general population and is typically associated with milder or absent clinical disease unless present in compound states, while S65C is rarer and has been mainly linked to mild iron loading in selected contexts. (Mura et al., 1999; Wallace et al., 2002; Asberg et al., 2002)

Population-based genotype stratification is useful for dietary and clinical counselling because it maps onto expected absorption phenotypes in probabilistic terms. (Hurrell and Egli, 2010; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Wild-type *HFE* genotypes generally support "normal" iron regulation in the presence of balanced diets, whereas heterozygosity for common variants is often associated with small upward shifts in iron indices without a high probability of end-organ injury. (Moirand et al., 1999; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Homozygosity for C282Y confers the highest risk state for progressive iron loading, though even here clinical outcomes vary substantially due to sex and environmental modifiers. (Crownover and Covey, 2013; Vujić, 2014; European Association for the Study of the Liver, 2022)

Table 1: Key Studies on *HFE* Variants and Iron Overload

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s)/Focus Investigated	Main Outcome(s)
Feder et al., 1996	Gene discovery / mutation identification	Hereditary haemochromatosis (HH) cases and controls	*HFE*; key HH mutation C282Y (rs1800562)	Identified *HFE* (MHC class I–like) as the gene mutated in HH; described the major causal variant C282Y (Feder, 1996).
Carella et al., 1997	Case series / mutation analysis	75 Italian HH patients	C282Y (rs1800562), H63D (rs1799945)	C282Y accounted for most HH alleles; C282Y homozygosity common in clinically defined HH (Carella, 1997)
Beutler et al., 1997	Molecular genetic study	HH patients **not** homozygous for C282Y	*HFE*/*HLA-H* sequencing; related proteins	Sequenced *HFE* and related proteins in non–C282Y-homozygous HH to assess additional genetic contributors (Beutler, 1997).
Jouanolle et al., 1997	Case series / genotype frequency study	132 HH patients (Brittany, France)	C282Y (rs1800562), H63D (rs1799945)	>92% of patients were C282Y homozygotes, supporting HFE as the principal HH locus in this population (Jouanolle, 1997).
Mura et al., 1999	Large case series	711 HH probands (plus controls)	S65C (rs1800730); interaction with C282Y/H63D	S65C was implicated in milder HH phenotypes, particularly in compound genotypes (Mura, 1999).

Moirand et al., 1999	Narrative review (clinical genetics)	Human clinical/lab evidence	*HFE* mutation spectrum	Summarized clinical expression and genotype–phenotype patterns for *HFE*-related HH (Moirand, 1999).
de Juan et al., 2001	Case–control	35 HH cases; 116 controls (Basque)	*HFE* mutations (population distribution)	Characterized population-specific frequencies of *HFE* mutations in Basque HH vs controls (de Juan, 2001).
Wallace et al., 2002	Case–control within genotype-defined group	309 C282Y heterozygotes; 315 controls	S65C (rs1800730) among C282Y heterozygotes	S65C was more frequent in C282Y heterozygotes with biochemical iron overload vs controls, suggesting a modest modifier effect (Wallace, 2002).
Åsberg et al., 2002	Population screening + clinical follow-up	65,238 screened; S65C carriers clinically assessed	S65C (rs1800730)	S65C heterozygosity was associated with mild–moderate iron overload, particularly with other HFE mutations (Åsberg, 2002).
Crownover & Covey, 2013	Clinical review	Primary care–oriented synthesis (human)	*HFE*-related HH (clinical diagnosis/management)	Consolidated evidence for risk stratification and clinical management of *HFE*-HH (Crownover, 2013).
Vujić, 2014	Mechanistic review	Human genetics + molecular basis	*HFE* → hepcidin axis; iron homeostasis	Detailed the molecular basis of *HFE*-hemochromatosis, linking variants to dysregulated iron homeostasis (Vujić, 2014).

Clinical Expression and Penetrance: From Biochemical Loading to Organ Injury

The natural history of *HFE*-haemochromatosis is characterized by slow iron accumulation and a prolonged asymptomatic phase, followed by non-specific manifestations such as fatigue and arthralgia and, in advanced cases, hepatic fibrosis/cirrhosis, diabetes and other endocrine complications, cardiac involvement, and skin hyperpigmentation. (Crownover and Covey, 2013; Vujić, 2014; European Association for the Study of the Liver, 2022) A major clinical challenge is that these symptoms overlap with common conditions, which contributes to diagnostic delay and under-recognition unless iron studies are considered early in evaluation pathways. (Moirand et al., 1999; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) The frequent reference to “bronze diabetes” captures the historical association of iron overload with pigmentation and glucose dysregulation, but contemporary management emphasizes earlier identification before such late-stage features emerge. (Vujić, 2014; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

It is useful to distinguish biochemical penetrance (elevated transferrin saturation and/or ferritin) from clinical penetrance (end-organ damage), as these are not equivalent in HFE disease (end-organ damage), which are not equivalent in *HFE* disease. (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022; Moirand et al., 1999) Recent guideline-synthesized evidence indicates substantially higher biochemical

penetrance than clinical disease, with marked sex differences that likely reflect iron loss through menstruation and pregnancy in premenopausal women. (European Association for the Study of the Liver, 2022; Crownover and Covey, 2013) The clinical implication is that genotype alone should not be treated as destiny, yet it remains a strong risk stratifier that justifies tailored monitoring and avoidance of unnecessary high-iron exposures in high-risk genotypes. (U.S. Preventive Services Task Force, 2006; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

The diagnostic evaluation typically integrates transferrin saturation and serum ferritin interpreted in clinical context; *HFE* genotyping may support etiologic clarification and family counselling, and hepatic iron assessment (e.g., MRI or biopsy) can be considered for staging and differential diagnosis when indicated (Crownover and Covey, 2013; Moirand et al., 1999; European Association for the Study of the Liver, 2022) Serum ferritin is prognostically informative but non-specific, as elevations can occur in inflammatory states, metabolic dysfunction, alcohol-related liver disease and other conditions that may coexist with or mimic haemochromatosis. (Moirand et al., 1999; Hurrell and Egli, 2010; European Association for the Study of the Liver, 2022) Accordingly, genotype-informed dietary recommendations should be anchored in measured iron phenotypes rather than inferred solely from ancestry or isolated ferritin values. (Crownover and Covey, 2013; U.S. Preventive Services Task Force, 2006; European Association for the Study of the Liver, 2022)

Therapeutic venesection (phlebotomy) is the foundational treatment for *HFE*-haemochromatosis and is effective at reducing iron stores, improving biochemical indices, and preventing progression when initiated before advanced cirrhosis. (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Treatment is commonly guided by serial ferritin (and, where appropriate, transferrin saturation) measurements during an induction phase followed by individualized maintenance, with the aim of preventing re-accumulation while avoiding iatrogenic iron deficiency (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) However, established organ damage — particularly advanced fibrosis, arthropathy, or endocrine sequelae — may not fully reverse despite successful iron depletion, underscoring the preventive importance of early detection and sustained maintenance. (Vujić, 2014; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Dietary Modifiers of Iron Bioavailability and Their Interaction with *HFE* Genotype

Dietary iron exposure is shaped not only by total iron content but also by bioavailability, which differs substantially between mixed omnivorous diets and plant-based diets and is influenced by meal composition and host iron status. (Hurrell and Egli, 2010; Hallberg et al., 1986; Hallberg et al., 1989) Heme iron from animal tissue is typically more efficiently absorbed than non-heme iron, and mixed diets therefore tend to have higher effective iron bioavailability than vegetarian patterns, particularly in individuals with low iron stores. (Hurrell and Egli, 2010; Hallberg et al., 1989) In practical terms, plant-derived iron sources such as cereal products and pseudocereals can contribute materially to intake, yet absorption may be constrained by phytates unless enhancers are co-consumed. (Hurrell and Egli, 2010; Hallberg et al., 1986)

Ascorbic acid is a robust enhancer of non-heme iron absorption, acting through reduction of ferric to ferrous iron and by maintaining iron in soluble forms that resist inhibitory ligands in the intestinal lumen. (Hallberg et al., 1986; Hallberg et al., 1989) Controlled meal studies demonstrate that ascorbic acid can meaningfully increase absorption from meals rich in inhibitors, indicating that the same total iron intake can yield different absorbed iron doses depending on co-ingested vitamin C or acidic fruit components. (Hallberg et al., 1986; Hurrell and Egli, 2010) This interaction is nutritionally advantageous for individuals at risk of deficiency — particularly those consuming diets with lower bioavailable iron — yet it can be undesirable for individuals with high-absorption genotypes or established iron loading, where the goal is to limit net absorbed iron. (Hurrell and Egli, 2010; Vujić, 2014; European Association for the Study of the Liver, 2022)

A genotype-aware dietary approach therefore has two distinct counselling logics depending on risk state. (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) For individuals with genotypes associated with normal regulation, maintaining adequate iron intake remains important because iron-poor patterns can precipitate deficiency, particularly when physiologic demands are increased, and bioavailability strategies such as pairing plant iron sources with vitamin C can be appropriate. (Hurrell and Egli, 2010; Hallberg et al., 1986; Hallberg et al., 1989) For individuals with high-risk genotypes or biochemical evidence of loading, routine iron supplementation and highly absorbable iron exposures should generally be avoided unless a competing indication exists, and dietary counselling may focus on moderating iron-dense animal foods and limiting absorption enhancers in high-iron meals. (Crownover and Covey, 2013; Vujić, 2014; European Association for the Study of the Liver, 2022)

Because iron regulation is responsive to body stores, host status remains a key modifier even within genotype classes, and the same diet may produce different iron trajectories in different physiologic contexts. (Hurrell and Egli, 2010; European Association for the Study of the Liver, 2022) This dynamic underscores why dietary guidance should be coupled to periodic assessment of transferrin saturation and ferritin where genetic predisposition is known or suspected, rather than relying solely on static genotype-based assumptions. (Crownover and Covey, 2013; Moirand et al., 1999; European Association for the Study of the Liver, 2022)

Implications for Screening, Diagnostics, and Preventive Management

Genotype-informed prevention can be conceptualized as a tiered strategy: targeted identification of high-risk genotypes, phenotypic monitoring of iron indices, and timely initiation of iron-depleting therapy when biochemical loading is established. (Moirand et al., 1999; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Family-based testing is commonly considered because HFE-haemochromatosis is inherited in an autosomal recessive pattern and first-degree relatives of affected individuals have increased pre-test probability of clinically relevant genotypes; however, approaches to broader screening vary by guideline and health-system context (Moirand et al., 1999; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Contemporary clinical practice guidelines emphasize that elevated transferrin saturation and ferritin should prompt *HFE* genotyping, and that non–C282Y homozygous presentations require further confirmation of hepatic iron overload to avoid misclassification. (European Association for the Study of the Liver, 2022; Moirand et al., 1999) This diagnostic architecture is particularly important because elevated ferritin is common and non-specific, and because metabolic and alcohol-related liver disease can coexist with genetic predisposition, shaping both iron indices and outcomes. (Moirand et al., 1999; Hurrell and Egli, 2010; European Association for the Study of the Liver, 2022)

From a preventive-management perspective, the treatability of iron overload through venesection is a defining feature of *HFE*-haemochromatosis and supports proactive monitoring in genetically susceptible individuals, especially men and postmenopausal women. (Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Nevertheless, preventive strategies should not be reduced to simplistic assurances of near-perfect protection, because effectiveness depends on adherence, timing relative to organ injury, and co-morbid factors that influence liver and metabolic risk. (Vujić, 2014; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Dietary counselling should thus be framed as one component of a broader prevention package that includes laboratory surveillance and, where indicated, structured phlebotomy programmes with defined ferritin targets. (European Association for the Study of the Liver, 2022; Crownover and Covey, 2013)

CONCLUSION

A scientifically rigorous account of “the right amount” of dietary iron must be grounded in the biology of absorption-driven homeostasis, the molecular role of the *HFE*–hepcidin axis, and the population distribution and penetrance of key *HFE* variants. (Hurrell and Egli, 2010; Vujić, 2014; European Association for the Study of the Liver, 2022) *HFE* genetics meaningfully shifts absorption propensity, but clinical risk is probabilistic and strongly modified by sex, age, co-morbid liver or metabolic disease, and diet composition. (Crownover and Covey, 2013; Moirand et al., 1999; European Association for the Study of the Liver, 2022) This complexity argues against simplistic genotype-to-diet rules and instead supports an integrated model in which genotype informs the intensity of phenotypic monitoring and the caution applied to high-iron exposures, including supplementation and absorption-enhancing meal patterns. (Hallberg et al., 1986; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

Dietary modifiers have a dual role: they can mitigate deficiency risk in low-bioavailability diets by leveraging enhancers such as vitamin C, and they can exacerbate loading risk when combined with high-absorption genotypes or pre-existing iron accumulation. (Hallberg et al., 1989; Hurrell and Egli, 2010; Vujić, 2014) Clinically, transferrin saturation and ferritin remain the indispensable phenotypic anchors for interpreting genetic risk, given the non-specificity of ferritin elevations and the heterogeneity of iron overload etiologies. (Moirand et al., 1999; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022) Finally, the availability of effective iron depletion therapy supports targeted testing in appropriate clinical contexts and early intervention pathways, while the incomplete penetrance of disease justifies ongoing caution toward

indiscriminate population genetic screening in asymptomatic individuals. (U.S. Preventive Services Task Force, 2006; Crownover and Covey, 2013; European Association for the Study of the Liver, 2022)

REFERENCES

- Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet. 1996;13(4):399-408.
- Carella M, D'Ambrosio L, Totaro A, Grifa A, Valentino MA, Piperno A, et al. Mutation analysis of the HLA-H gene in Italian hemochromatosis patients. Am J Hum Genet. 1997;60(4):828-32.
- Beutler E, West C, Gelbart T. HLA-H and associated proteins in patients with hemochromatosis. Mol Med. 1997;3(6):397-402.
- Jouanolle AM, Fergelot P, Gandon G, Yaouanq J, Le Gall JY, David V. A candidate gene for hemochromatosis: frequency of the C282Y and H63D mutations. Hum Genet. 1997;100(5-6):544-7. doi:10.1007/s004390050549.
- Mura C, Raguenes O, Férec C. HFE mutations analysis in 711 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis. Blood. 1999;93(8):2502-5.
- Moirand R, Deugnier Y, Brissot P. Haemochromatosis and HFE gene. Acta Gastroenterol Belg. 1999;62(4):403-9.
- de Juan D, Reta A, Castiella A, Pozueta J, Prada A, Cuadrado E. HFE gene mutations analysis in Basque hereditary haemochromatosis patients and controls. Eur J Hum Genet. 2001;9(12):961-4. doi:10.1038/sj.ejhg.5200731.
- Wallace DF, Walker AP, Pietrangelo A, Clare M, Bomford AB, Dixon JL, et al. Frequency of the S65C mutation of HFE and iron overload in 309 subjects heterozygous for C282Y. J Hepatol. 2002;36(4):474-9. doi:10.1016/S0168-8278(01)00304-X.
- Åsberg A, Thorstensen K, Hveem K, Bjerve KS. Hereditary hemochromatosis: the clinical significance of the S65C mutation. Genet Test. 2002;6(1):59-62. doi:10.1089/109065702760093933.
- U.S. Preventive Services Task Force. Screening for hemochromatosis: recommendation statement. Ann Intern Med. 2006;145(3):204-8. doi:10.7326/0003-4819-145-3-200608010-00008.
- Hallberg L, Brune M, Rossander L. Effect of ascorbic acid on iron absorption from different types of meals. Studies with ascorbic-acid-rich foods and synthetic ascorbic acid given in different amounts with different meals. Hum Nutr Appl Nutr. 1986;40(2):97-113.
- Hallberg L, Brune M, Rossander L. The role of vitamin C in iron absorption. Int J Vitam Nutr Res Suppl. 1989;30:103-8.
- Hurrell R, Egli I. Iron bioavailability and dietary reference values. Am J Clin Nutr. 2010;91(5):1461S-1467S. doi:10.3945/ajcn.2010.28674F.
- Crownover BK, Covey CJ. Hereditary hemochromatosis. Am Fam Physician. 2013;87(3):183-90.
- Vujić M. Molecular basis of HFE-hemochromatosis. Front Pharmacol. 2014;5:42. doi:10.3389/fphar.2014.00042.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022;77(2):479-502. doi:10.1016/j.jhep.2022.03.033.