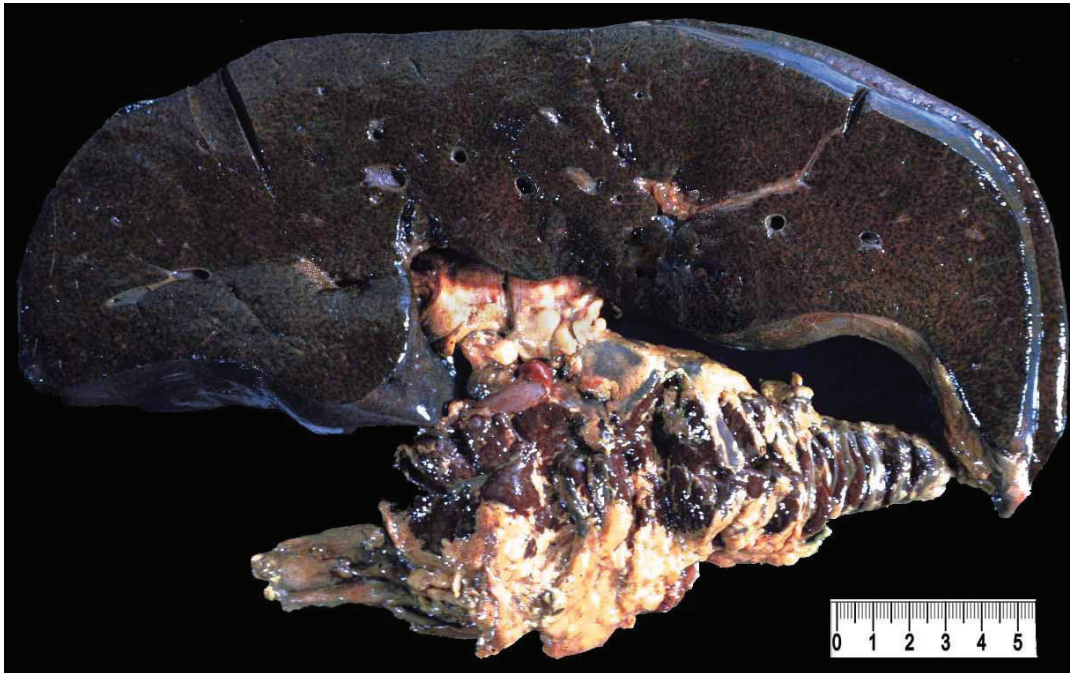


## Hereditary hemochromatosis

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Hereditary hemochromatosis (HH) is the most commonly identified autosomal recessive genetic disorder in the white population, characterized by increased intestinal iron absorption and secondary abnormal accumulation in parenchymal organs, not infrequently accompanied by functional impairment.<sup>1</sup> This entity is associated with mutations of the HFE gene (located on the short arm of chromosome 6 at location 6p22.2; closely linked to the HLA-A3 locus), which encodes the HFE protein, a membrane protein thought to regulate iron absorption by affecting the interaction between transferrin receptor and transferrin. One of

these mutations results in a substitution of tyrosine for cysteine at the amino acid 282 position (C282Y).<sup>2,3</sup> Subsequently two additional mutations have been noted, aspartate for histidine (H63D), and cysteine for serine (S65C), however the most common form of HFE-related HH is associated with the C282Y homozygous mutation.<sup>4</sup> The presence of this mutation varies between 69% to 100% in series from USA, France, Italy, Australia, Germany.<sup>5-9</sup> Other HFE defects in addition to homozygosity for C282Y, are found: homozygosity for the H63D mutation, heterozygosity for the C282Y or H63D mutation, or compound

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heterozygosity.<sup>10</sup> Less commonly, the hemojuvelin, hepcidin, ferroportin, or ceruloplasmin encoding genes may also be associated with HH.

There is a substantial controversy on the likelihood of homozygous patients for C282Y developing clinically apparent disease. In a USA screening study involving 41,000 adults, 152 individuals were positive for C282Y homozygosity, but only one fit the criteria for the diagnosis of HH (penetrance < 1%).<sup>11</sup> In contrast, the Australian series of 31,192 subjects of northern European ancestry found 203 C282Y homozygous. These individuals were followed for 12 years, with 28% of men and 1.2% of women presenting with clinical HH.<sup>12</sup>

Once thought to be a rare disease, HH was initially considered when the patient presented an unusual manifestation such as “bronze diabetes”. Indeed the first case description by Armand Trousseau, in 1865, was of a diabetic patient with hepatic cirrhosis and bronzed skin. The name hemochromatosis was applied in subsequent 1890 report by Daniel von Recklinghausen. Recklinghausen suggested the association between tissue iron storage and the resultant condition. The image above shows well the brown discoloration of the liver and also the pancreas, the body of which is almost mahogany. The inherited nature of the disease was first explained by J.H. Sheldon in his textbook *Haemochromatosis*. He also suggested an abnormality of iron metabolism as the basis for the disease.

With genetic studies, families have been accurately studied showing that transferrin saturation values greater than 60% in men and greater than 50% in women (in the absence of hepatopathy of any etiology) indicates the presence of abnormality in iron metabolism with 95% accuracy. In the USA and Europe the frequency of HFE mutations among Caucasian is 10% for heterozygous and 5 per 1000 (0.5%) for homozygous.<sup>13</sup>

Body iron stores inversely correlate with the normal intestinal absorption of heme and non-heme iron. In HH this regulation is lost and iron overload ensues since there is no mechanism for excess excretion. Clinical symptoms appear when greater than 20g of iron is accumulated in the body, typically occurring after the age of 40 in men and, when menstruation occurs, 50 in women. Differing from acquired (secondary)

hemochromatosis, HH iron is initially stored in parenchymal cells and later in the reticuloendothelial system cells.

The clinical picture reflects the involvement of liver, skin, pancreas, joints, and heart, with impotence in males.<sup>14</sup> Liver function abnormalities, weakness and fatigue, and skin hyperpigmentation were present in more than 70% of cases in the series by Niederau et al<sup>14</sup>.

Liver involvement manifests as hepatomegaly, increasing fibrosis and eventual cirrhosis, potentially reversible in early stages. Although infection with hepatitis-C virus may potentiate fibrosis, the major risk co-factor for the development of liver disease is excess alcohol intake. The deposition of iron alone in hepatocytes is not inflammatory and hepatic fibrosis may ensue with low or normal serum aminotransferase determinations.<sup>15,16</sup> However in almost 50% of patients with HH, another cause of liver disease is present that is more likely responsible for hepatic liver enzyme elevations. Hepatocellular carcinoma is the most serious complication of the hepatic iron overload. The magnitude of the risk varies between 20- to 200-fold.<sup>17,18</sup>

Pancreatic deposition of iron occurs in beta cells and diabetes is clinically demonstrable in 50% of symptomatic patients. Although insulin and C-peptide secretion are reduced, the alpha cell function remains intact, and glucagon values are similar to those in type-1 diabetes.<sup>19</sup>

HH can lead to dilated cardiomyopathy, heart failure and conduction disturbances, such as sick sinus syndrome.<sup>20,21</sup>

Arthritis associated with HH clinically resembles rheumatoid arthritis with predominant involvement of metacarpophalangeal joints. The iron deposition within the joints triggers an inflammatory process that is often complicated by calcium pyrophosphate deposition (“pseudogout”) and subsequent chondrocalcinosis and chronic arthropathy.<sup>22-24</sup>

Secondary hypogonadism, responsible for impotence and decreased libido in men, is the result of iron deposition in the anterior pituitary, which results in low levels of trophic hormones (e.g., follicle stimulating hormone) and therefore testosterone. Amenorrhea rarely occurs in women and is much less common than hypogonadism in men.<sup>25,26</sup>

The diagnostic workup of HH includes determination of iron overload (increased body

iron burden), family history of this disorder and genetic studies. In addition to serum iron assay, liver biopsy and magnetic resonance imaging studies are usually employed. However liver biopsy is often not performed for patients with HH when the diagnosis is clearly established based upon genetic testing, including findings of C282Y/C282Y, heterozygous C282Y, and C282Y/H63D genotypes. The findings of H63D homozygosity or heterozygosity is of uncertain significance since most will not present iron overload.<sup>27,28</sup>

**Keywords:** hemochromatosis, Iron Overload, Liver Diseases, Pancreatic Disease.

## REFERENCES

- Fleming RE, Sly WS. Mechanisms of iron accumulation in hereditary hemochromatosis. *Annu Rev Physiol.* 2002;64(1):663-80. <http://dx.doi.org/10.1146/annurev.physiol.64.081501.155838>. PMID:11826284
- NCBI. Entrez Gene. HFE hemochromatosis. Available from: <http://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=3077>
- Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet.* 1996;13(4):399-408. <http://dx.doi.org/10.1038/ng0896-399>. PMID:8696333
- European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol.* 2010;53(1):3-22. <http://dx.doi.org/10.1016/j.jhep.2010.03.001>. PMID:20471131
- Jouanolle AM, Gandon G, Jézéquel P, et al. Haemochromatosis and HLA-H. *Nat Genet.* 1996;14(3):251-2. <http://dx.doi.org/10.1038/ng1196-251>. PMID:8896550
- Jazwinska EC, Cullen LM, Busfield F, et al. Haemochromatosis and HLA-H. *Nat Genet.* 1996;14(3):249-51. <http://dx.doi.org/10.1038/ng1196-249>. PMID:8896549
- Beutler E, Gelbart T, West C, et al. Mutation analysis in hereditary hemochromatosis. *Blood Cells Mol Dis.* 1996;22(2):187-94. <http://dx.doi.org/10.1006/bcmd.1996.0027>. PMID:8931958
- Carella M, D'Ambrosio L, Totaro A, et al. Mutation analysis of the HLA-H gene in Italian hemochromatosis patients. *Am J Hum Genet.* 1997;60(4):828-32. PMID:9106528.
- Nielsen P, Carpinteiro S, Fischer R, Cabeda JM, Porto G, Gabbe EE. Prevalence of the C282Y and H63D mutations in the HFE gene in patients with hereditary haemochromatosis and in control subjects from Northern Germany. *Br J Haematol.* 1998;103(3):842-5. <http://dx.doi.org/10.1046/j.1365-2141.1998.01037.x>. PMID:9858243
- Sham RL, Raubertas RF, Braggins C, Cappuccio J, Gallagher M, Phatak PD. Asymptomatic hemochromatosis subjects: genotypic and phenotypic profiles. *Blood.* 2000;96(12):3707-11. PMID:11090050.
- Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet.* 2002;359(9302):211-8. [http://dx.doi.org/10.1016/S0140-6736\(02\)07447-0](http://dx.doi.org/10.1016/S0140-6736(02)07447-0). PMID:11812557
- Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med.* 2008;358(3):221-30. <http://dx.doi.org/10.1056/NEJMoa073286>. PMID:18199861
- Edwards CQ, Kushner JP. Screening for hemochromatosis. *N Engl J Med.* 1993;328(22):1616-20. <http://dx.doi.org/10.1056/NEJM199306033282208>. PMID:8110209
- Niederau C, Strohmeyer G, Stremmel W. Epidemiology, clinical spectrum and prognosis of hemochromatosis. *Adv Exp Med Biol.* 1994;356:293-302. [http://dx.doi.org/10.1007/978-1-4615-2554-7\\_31](http://dx.doi.org/10.1007/978-1-4615-2554-7_31). PMID:7887234
- Adams PC, Barton JC. A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation. *J Hepatol.* 2011;55(2):453-8. <http://dx.doi.org/10.1016/j.jhep.2011.02.010>. PMID:21354228
- Adams PC, Speechley M, Barton JC, McLaren CE, McLaren GD, Eckfeldt JH. Probability of C282Y homozygosity decreases as liver transaminase activities increase in participants with hyperferritinemia in the hemochromatosis and iron overload screening study. *Hepatology.* 2012;55(6):1722-6. <http://dx.doi.org/10.1002/hep.25538>. PMID:22183642
- Yang Q, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of Multiple-Cause Mortality Data. *Ann Intern Med.* 1998;129(11):946-53. [http://dx.doi.org/10.7326/0003-4819-129-11\\_Part\\_2-199812011-00005](http://dx.doi.org/10.7326/0003-4819-129-11_Part_2-199812011-00005). PMID:9867747
- Bradbear RA, Bain C, Siskind V, et al. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. *J Natl Cancer Inst.* 1985;75(1):81-4. PMID:2989605.
- Nelson RL, Baldus WP, Rubenstein AH, Go VL, Service FJ. Pancreatic alpha-cell function in diabetic hemochromatotic subjects. *J Clin Endocrinol Metab.* 1979;49(3):412-6. <http://dx.doi.org/10.1210/jcem-49-3-412>. PMID:381322
- Olson LJ, Edwards WD, McCall JT, Ilstrup DM, Gersh BJ. Cardiac iron deposition in idiopathic hemochromatosis: histologic and analytic assessment of 14 hearts from autopsy. *J Am Coll Cardiol.* 1987;10(6):1239-43. [http://dx.doi.org/10.1016/S0735-1097\(87\)80124-9](http://dx.doi.org/10.1016/S0735-1097(87)80124-9). PMID:3680791

21. Cabot RC, Scully RE, Mark EJ, et al. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-1994. A 25-year-old man with the recent onset of diabetes mellitus and congestive heart failure. *N Engl J Med*. 1994;331(7):460-6. <http://dx.doi.org/10.1056/NEJM199408183310708>. PMID:8035843
22. Schumacher HR. Articular cartilage in the degenerative arthropathy of hemochromatosis. *Arthritis Rheum*. 1982;25(12):1460-8. <http://dx.doi.org/10.1002/art.1780251212>. PMID:7150378
23. Dymock IW, Hamilton EB, Laws JW, Williams R. Arthropathy of haemochromatosis. Clinical and radiological analysis of 63 patients with iron overload. *Ann Rheum Dis*. 1970;29(5):469-76. <http://dx.doi.org/10.1136/ard.29.5.469>. PMID:5476674
24. Hamilton EB, Bomford AB, Laws JW, Williams R. The natural history of arthritis in idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. *Q J Med*. 1981;50(199):321-9. PMID:7330169
25. Walton C, Kelly WF, Laing I, Bu'lock DE. Endocrine abnormalities in idiopathic haemochromatosis. *Q J Med*. 1983;52(205):99-110. PMID:6683854.
26. Kelly TM, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. *Ann Intern Med*. 1984;101(5):629-32. <http://dx.doi.org/10.7326/0003-4819-101-5-629>. PMID:6435491
27. Moirand R, Jouanolle AM, Brissot P, Le Gall JY, David V, Deugnier Y. Phenotypic expression of HFE mutations: a French study of 1110 unrelated iron-overloaded patients and relatives. *Gastroenterology*. 1999;116(2):372-7. [http://dx.doi.org/10.1016/S0016-5085\(99\)70134-4](http://dx.doi.org/10.1016/S0016-5085(99)70134-4). PMID:9922318
28. Leão GD, Freire JM, Cunha Fernandes AL, et al. Analysis of HFE genes C282Y, H63D, and S65D in patients with hyperferritinemia from northeastern Brazil. *J Clin Lab Anal*. 2014;28(3):178-85. <http://dx.doi.org/10.1002/jcla.21663>. PMID:24395214

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