



☆ Topic: *HFE*-related Hereditary Hemochromatosis

☆ **Summary:** *HFE* Hereditary Hemochromatosis (*HFE*-HH) is the most common and best-described form of iron overload disorder worldwide. The major *HFE* gene mutation identified in Caucasians is C282Y. Not all individuals with a genetic predisposition to HH will go on to develop high serum ferritin or iron overload. Therapeutic phlebotomy (when necessary) can prevent life-threatening complications such as cirrhosis. Iron overload can be completely prevented in asymptomatic individuals with a genetic predisposition.

☆ **Bottom line:** Patients should be offered genetic counselling/testing if they have elevated serum ferritin and transferrin saturation, signs or symptoms suggestive of iron-overload disorder, or a first-degree relative with *HFE* hemochromatosis.

✓ The Disease

- *HFE* Hereditary Hemochromatosis (*HFE*-HH) is one of the most common autosomal recessive disorders in Caucasians. Iron overload from *HFE*-HH can sometimes lead to permanent liver, pancreatic and cardiac damage.
- There are less common forms of HH due to other genes such as *HJV*, *HAMP*, and *TFR2*.
- About 4-5 per 1000 individuals of northern European ancestry are genetically susceptible to *HFE*-HH, but fewer individuals actually develop the disease.^{1,2}
- Cause: very high absorption of iron in the duodenum results in excessive storage of iron in the liver, skin, pancreas, heart, joints, and pituitary.
- Symptoms: Abdominal pain, weakness, lethargy, and weight loss are early symptoms. Without therapy, males most commonly develop symptoms between 40 and 60 years of age (range 20s to 70s) and females after menopause.
- Liver Disease: Early signs and symptoms of liver involvement include right upper quadrant pain and hepatomegaly. Hepatic fibrosis or cirrhosis may occur after the age of 40, and may eventually lead to hepatocellular carcinoma.
- Other findings in untreated individuals may include progressive skin pigmentation (“bronzing”), type 2 diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism.
- Suspect HH in individuals with elevated transferrin saturation and elevated serum ferritin.
- Surveillance: Routine iron studies (transferrin saturation and ferritin).
- Treatment: removal of excess iron by phlebotomy— cheap and very effective. Note that initiation of phlebotomy is indicated when serum ferritin is >1000µg/L; more moderate elevations may require clinical judgment.³
- Dietary management of individuals with HH includes avoidance of iron supplements, iron-containing cooking pots/pans, excess vitamin C, and uncooked shellfish (due to potential infection with *Vibrio vulnificus*). Those with hepatic involvement are advised to avoid alcohol consumption.

✓ The Gene

- The *HFE* gene, on chromosome 6, makes a cell-surface protein that binds transferrin and plays a role in iron absorption.
- The two common mutations are called C282Y and H63D.
- The frequency of C282Y in a population of European descent is 6.2% but ranges from 12.5% in Ireland to 0% in Southern Europe.²
- H63D may modify iron levels but is unlikely to cause iron overload in the absence of C282Y.⁴

✓ Consequences of having one or two faulty *HFE* genes

One faulty gene → unaffected carrier

- Carriers are NOT expected to develop clinical findings of iron overload because their “normal” copy of the *HFE* gene (located on their other chromosome 6) compensates.

Double dose of the faulty gene → tendency to iron overload

- Most individuals with iron overload caused by hereditary hemochromatosis have two copies of the C282Y mutation.
- Individuals with one copy of C282Y and one of H63D may have high iron indices in middle age but iron-overload related disease is uncommon in this group.⁵
- Men who have two copies of the C282Y mutation are much more likely to develop disease related to iron overload than women with the same genotype. A woman’s risk is moderated by iron loss during menstruation, with overload only occurring later in life.
- Many individuals with two *HFE* mutations will not express the disease (the penetrance is low, especially in females).
- There are emerging reports of *HFE* genotypes in association with increased risks for diseases such as breast and colorectal cancer,⁶ heart disease in women⁷ and other disease endpoints.⁸ Further validation of these associations is required.

✓ Who should consider genetic counselling/testing?

- Adult patients with a first degree relative with hemochromatosis
 - Family studies should be performed stepwise to minimize unnecessary testing.
 - There is a 25% risk for the sibs of an affected individual to be affected.
 - Note: All offspring of an affected individual will have at least one faulty *HFE* gene. Spouses should generally be offered testing before offspring. DNA testing of young children is generally not indicated.
- Individuals with biochemical evidence of iron overload i.e. elevated transferrin saturation and ferritin
- Individuals with clinical features suggestive of HH such as unexplained hepatomegaly or elevated liver enzymes; or early-onset type 2 diabetes, heart disease, sexual dysfunction or arthralgia. Look out for other causes of iron overload (e.g. excess alcohol use, unrelated liver disease).

✓ Testing - for the faulty gene

- If you suspect HH, check fasting serum transferrin saturation (most sensitive test) and serum ferritin. Adults with serum transferrin saturation >45% warrant genetic testing. Ferritin >200 mcg/L in premenopausal women and >300 mcg/L in postmenopausal women or men indicates possible iron overload. Note: ferritin is an acute phase reactant and can be elevated for other reasons such as inflammation and malignancy. Thus, an elevated serum ferritin should be followed by other tests before the diagnosis of hemochromatosis is made.
- Population-based screening is not recommended.
- Once the gene change is found in a person, his/her parents, siblings and adult children should be offered testing. The spouse could also be tested if the couple has younger children.
- For information about ordering genetic testing for *HFE*, contact your local genetics clinic.

✓ Benefits of genetic testing

- Clarification of diagnosis
- Identification of asymptomatic individuals at risk of *HFE*-HH early enough to prevent end organ damage for this readily treatable condition.

✓ Harms/limitations of genetic testing

- Labeling a healthy person with a “disease” (just because they have altered genes, ascertained through an affected relative) when they may never manifest the symptoms of this “disease.”
- Insurance concerns.

- Potential to reveal non-paternity (e.g., if a child of an affected parent tests negative as a carrier).
- Genetic testing for *HFE*-HH has not been reported to be associated with negative psychosocial consequences.⁹

☆ **Web Resources:**

www.geneclinics.org

Canadian Hemochromatosis Society: <http://www.cdnhemochromatosis.ca/>

Centre for Disease Control

<http://www.cdc.gov/ncbddd/hemochromatosis/index.htm>

☆ **References:**

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Dr Carroll is Principal Investigator of the GenetiKit Project and is the Sydney G Frankfort Chair in Family Medicine at Mount Sinai Hospital and an Associate Professor in the Department of Family Medicine at the University of Toronto.

In alphabetical order, other members of the GenetiKit Team are as follows: **Dr Allanson** is Chief of the Department of Genetics at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario and Full Professor in the Department of Pediatrics at the University of Ottawa. **Dr Blaine** is an Assistant Professor in the Department of Family and Community Medicine at the University of Toronto in Ontario and Lead Physician of the STAR Family Health Team in Stratford, Ontario. **Ms Cremin** is a Clinical Assistant Professor in the Department of Medical Genetics, University of British Columbia. **Ms Dorman** is a Genetic Counselor at the Sudbury Regional Hospital in Ontario. **Ms Gibbons** is a Genetic Counselor at the North York General Hospital in Ontario. **Dr Graham** is Vice-President of Knowledge Translation, Canadian Institutes of Health Research. **Dr Grimshaw** is a Professor in the Department of Medicine and Director of the Clinical Epidemiology Program at the Ottawa Health Research Institute. **Ms Honeywell** is an Assistant Professor in the Department of Pediatrics at the University of Ottawa and in the CHEO Departments of Genetics and Cardiology. **Dr Meschino** is a Clinical Geneticist at North York General Hospital and Assistant Professor in the Department of Paediatrics at the University of Toronto. **Ms Permaul** is a Research Associate in the Granovsky Gluskin Family Medicine Centre at Mount Sinai Hospital. **Dr Wilson** is an Associate Professor in the Department of Epidemiology and Community Medicine at the University of Ottawa.