HEREDITARY HEMOCHROMATOSIS

Bottom line: HH is a common inherited predisposition to absorb excess iron from the diet caused by mutations in the *HFE* gene. Most individuals with the predisposition do not develop clinical disease. HH has the potential to cause morbidity and mortality. **With early identification of at-risk individuals, appropriate surveillance of iron indices, and treatment when indicated, complications can be avoided.**

Genetic testing should be considered for:

- ✓ Adults with biochemical evidence of iron overload (>45% fasting transferrin saturation and >300μg/L serum ferritin in men and post-menopausal women or >200μg/L SF in pre-menopausal women)
- ✓ Any adult whose first-degree relative has the C282Y *HFE* gene mutation

WHAT IS HEREDITARY HEMOCHROMATOSIS?

Hereditary Hemochromatosis (HH) is an autosomal recessive predisposition to absorb excess iron from the diet. The most common cause of HH is mutations in the *HFE* gene disrupting the iron absorption pathway. In some predisposed individuals, excessive iron absorption and subsequent storage in various organs (i.e. liver, pancreas, heart, joints) eventually lead to cellular injury. If untreated, over time this can cause irreversible tissue/organ damage and shorten life expectancy. Typically, symptoms of *HFE*-HH present in men aged 40 to 60 and in post-menopausal women; however, age of onset is variable. Symptoms are non-specific and include weakness, lethargy, skin discoloration (bronze or grey), abdominal pain with or without hepatomegaly, joint pain and/or stiffness, arthritis, diabetes, cardiomyopathy, hepatocellular dysfunction, cirrhosis, hepatocellular carcinoma, testicular atrophy, impotence, and menstrual irregularity. While any of these health concerns can be caused by *HFE*-HH, the presence of two or more should greatly increase suspicion that the condition is present. Iron overload due to *HFE* mutations does not occur in childhood**,** and as HH is an adult onset predisposition, genetic testing in children is not recommended.

With early identification of at-risk individuals, appropriate surveillance of iron indices, and treatment when necessary, all complications can be avoided.

Standard testing by North American molecular genetics laboratories is targeted mutation analysis to look specifically for the two most common *HFE* mutations, C282Y and H63D. These mutations account for over 90% of all mutations found.

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

A patient with:

- Biochemical evidence of iron overload (>45% fasting transferrin saturation (TS) and >300μg/L serum ferritin (SF) in men and post-menopausal women or >200μg/L SF in pre-menopausal women.) Biochemical evidence of iron overload will be present before the onset of symptoms.
- Unexplained chronic liver disease and increased transferrin saturation

Elevation of ferritin alone is not necessarily due to iron overload. Ferritin is an acute phase reactant and can be elevated due to infection, inflammation and malignancy.

Individuals with HFE-HH occasionally demonstrate a normal TS and an elevated ferritin. If clinical suspicion is high and/or the patient has a family history of HFE-HH, genetic testing is still warranted.

FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC TESTING

- Adult patient with a first-degree relative (sibling, parent or child) with one of the following genetic test results:
    a. C282Y/C282Y (homozygote - 2 mutated copies of the gene)
    b. C282Y/H63D (compound heterozygote - 2 different mutated copies of the gene)
    c. C282Y/S65C (compound heterozygote)
    d. C282Y heterozygote (carrier - 1 mutated copy of the gene)
- Family history of iron overload, liver disease, type II diabetes, arthritis, heart disease (relatives with symptoms of *HFE*-HH)

PREVALENCE

About 1 in 3 individuals of northern European ancestry are carriers (heterozygotes) of the C282Y or H63D *HFE* gene mutation. About 1 in 260 individuals have two copies of (are homozygous for) the C282Y *HFE* gene mutation (genotype C282Y/C282Y). The prevalence of *HFE*-HH in other ethnicities is lower.

WHAT DOES THE GENETIC TEST RESULT MEAN?

The actual risk to develop iron overload is dependent on how many and which gene mutations have been inherited, in addition to other genetic and non-genetic factors (gender, alcohol intake, the use of iron and vitamin C supplements and menstrual/pregnancy-associated iron losses).

- Two mutations identified confirm the *HFE*-HH diagnosis in an individual with biochemical evidence of iron overload.
- Two mutations identified in an asymptomatic individual with normal iron indices suggest future potential risk of developing iron overload. Yearly monitoring of iron indices is recommended.

***HFE* mutations identified**	**Risk of iron overload**	**Recommendation**
C282Y/C282Y	Highest risk of developing iron overload (38-50%); nonetheless, many of these individuals never accumulate enough iron to cause disease. About 10-33% may develop HH-related symptoms. That risk is likely higher for those identified through family screening versus those identified through population based screening.	• Annual monitoring of TS and SF • Elevated: >45% TS and >300µg/L SF in men and post-menopausal women, or >200µg/L SF in pre-menopausal women • If elevated, consider referral to specialist (gastroenterologist/ hematologist) to be assessed for complications and consideration of treatment
C282Y/H63D	About a 2% lifetime risk of developing iron overload	
C282Y/S65C	Low lifetime risk of developing iron overload - similar to C282Y/H63D	
H63D/H63D	About a 1% lifetime risk of developing iron overload	

See www.geneticseducation.ca for the full-length GEC-KO Messenger on *HFE*-HH and how to connect to your local genetics centre or molecular genetics laboratory.

For guidelines on the management of patients with HH, see Bacon *et al.,* Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 54:328–43

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