GEC•KO Messenger
Genetics Education Canada - Knowledge Organization
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HEREDITARY HEMOCHROMATOSIS

Bottom line: Hereditary Hemochromatosis (HH) is a common inherited predisposition to absorption of excess iron from one's diet; most individuals with the predisposition do not develop clinical disease. However, HH has the potential to cause morbidity and mortality.

Genetic testing should be considered for:

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

WHAT IS HEREDITARY HEMOCHROMATOSIS?

Hereditary Hemochromatosis (HH) can be caused by mutations in different genes. Mutations in the *HFE* gene are the most common cause of adult onset iron overload.[1,2,3] This GECKO Messenger deals EXCLUSIVELY with *HFE*-associated HH.

Mutations in the *HFE* gene alter the regulation of iron absorption through the mucosal lining of the gastrointestinal tract. In some predisposed individuals, excessive iron absorption and subsequent storage in various organs (Table 1) eventually lead to cellular injury. If untreated, over time this can cause irreversible damage and shorten life expectancy. With early identification of at-risk individuals, proper surveillance of iron indices, and treatment when necessary, many complications can be avoided.[3]

Table 1. Organs at risk of damage due to excessive iron storage[4].

Organ	Damage
Liver	Hepatomegaly, cirrhosis, hepatocellular carcinoma
Pancreas	Diabetes mellitus
Heart	Dilated cardiomyopathy, congestive heart failure +/- arrhythmia
Joints	Arthritis
Skin	Hyperpigmentation
Testes	Hypogonadism

While any of these health concerns can be caused by HH, the presence of two or more should greatly increase suspicion that the condition is present.

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF HH?

Inherited HH is most commonly caused by mutations in the *HFE* gene on chromosome 6. Standard testing by 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 HH.[4] Some laboratories may also test for a rare *HFE* gene mutation, S65C.[5]

PATTERN OF INHERITANCE

Autosomal recessive

- An individual who has inherited two mutations in the *HFE* gene, one from each parent, has the predisposition to develop iron overload.
- A person with a single mutation is called a 'carrier' and is not at risk of iron overload.

HOW COMMON IS *HFE*-HH?

About 1 in 3 individuals of northern European ancestry are carriers (heterozygotes) of the C282Y or H63D *HFE* gene mutations.[4] About 1 in 150 individuals have two copies of (are homozygous for) the C282Y *HFE* gene mutation (genotype C282Y/C282Y).[3] The prevalence of *HFE*-HH in other ethnicities is lower.

WHO SHOULD BE OFFERED GENETIC TESTING?

GENETIC TESTING should be offered to[1,2,4]:

- ✓ Adults with biochemical evidence of iron overload (transferrin saturation >45% and serum ferritin >300μg/L in men and post-menopausal women or >200μg/L in pre-menopausal women)
- ✓ Adults with a first-degree relative (sibling, parent or child) who is a C282Y/C282Y homozygote.
- ✓ Individuals who are symptomatic and have a first-degree relative with one of the following genetic test results:
    a. C282Y/H63D (compound heterozygote)
    b. C282Y/S65C (compound heterozygote)
    c. C282Y heterozygote (carrier)
- ✓ Adults with unexplained chronic liver disease and increased transferrin saturation

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.

WHO SHOULD NOT BE OFFERED GENETIC TESTING?

Population screening for *HFE*-HH is not recommended as the disease penetrance is low.[1,2,6]

Children do not require genetic testing for *HFE*-HH. Please refer to the Canadian Paediatric Society and the Canadian College of Medical Geneticists published guidelines relating to the question of genetic testing of healthy children. For conditions that will not present until adulthood (susceptibility or predictive testing) and where there is no benefit to the child, testing should be deferred until the child is competent to understand the purpose of the test and make an autonomous decision.[7]

WHO SHOULD BE OFFERED BIOCHEMICAL TESTING FOR IRON OVERLOAD?

If your patient has suggestive symptoms, physical findings or a family history of HH, transferrin saturation and serum ferritin are ideally ordered together to determine the likelihood of iron overload.

Transferrin saturation (TS)
TS is a reliable screen for iron overload and does not vary with age or the presence of clinical findings. A fasting TS of greater than 45% is considered a sensitive but not specific threshold for identifying individuals who may have iron overload. TS should be performed on a fasting sample as the result can be falsely elevated if a patient has not been fasting.

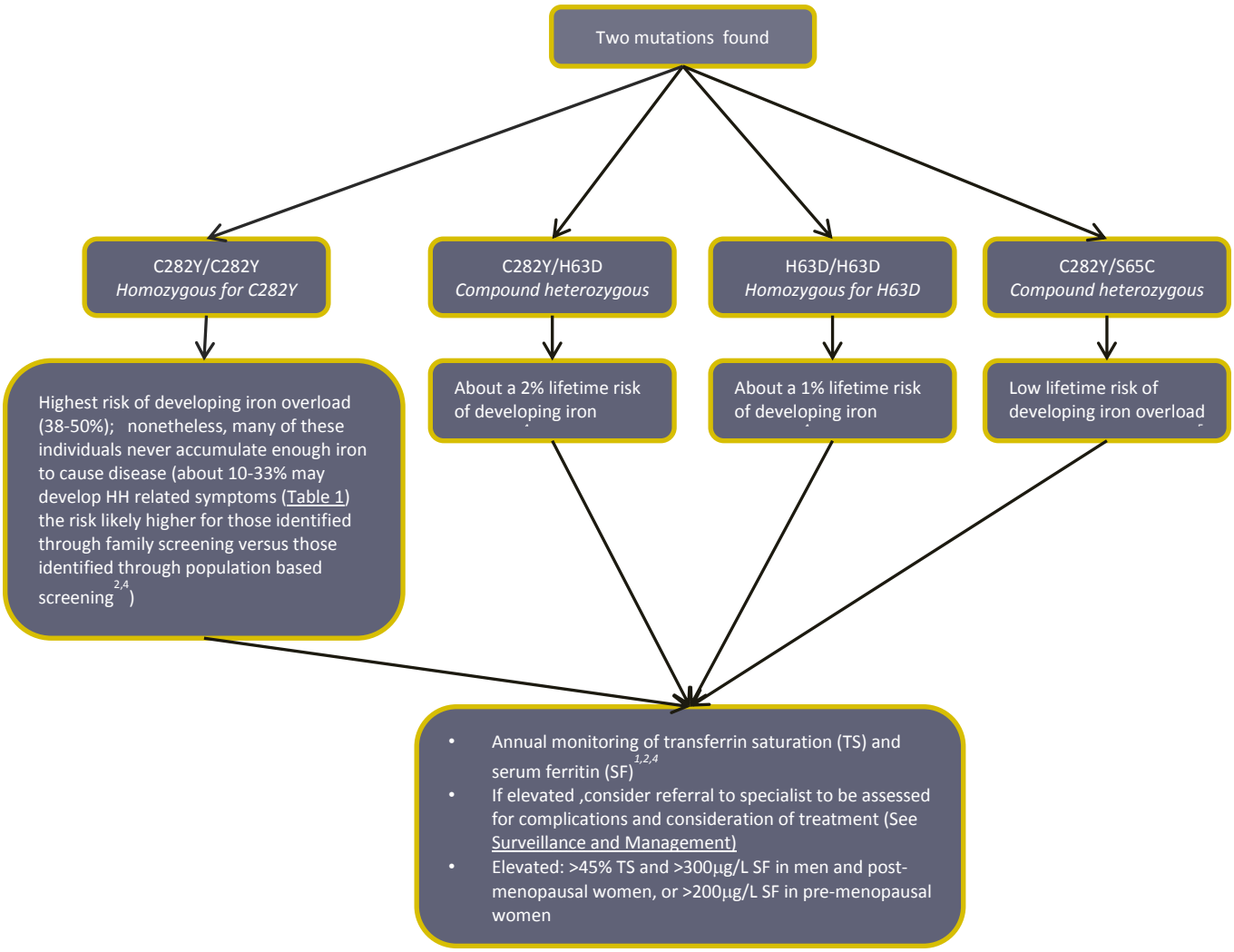
Serum ferritin (SF)
Normal ranges for SF vary with gender and age and vary slightly from lab to lab. In combination with persistent elevation of fasting TS, ferritin levels of greater than 300µg/ml in men or post-menopausal women and greater than 200µg/mL in pre-menopausal women are suspicious for iron overload.

Remember that SF is an acute phase reactant that can be elevated by other inflammatory processes. Therefore an elevated SF does not necessarily imply iron overload and is not a reliable first or only screen.

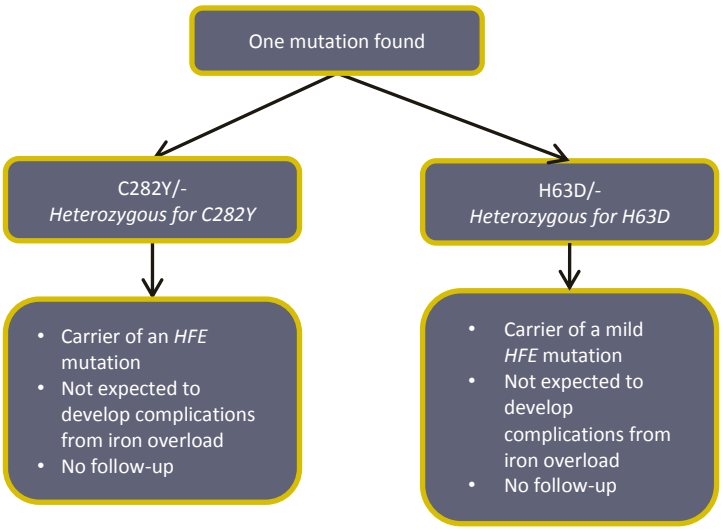
WHAT DOES THE GENETIC TEST RESULT MEAN?

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.

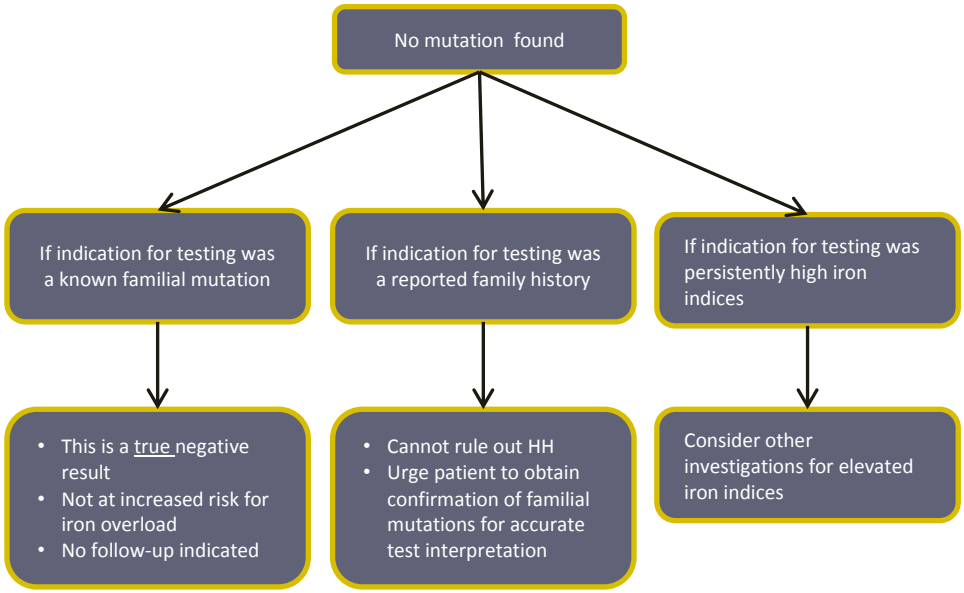
- ✓ Patient has two *HFE* gene mutations



✓ Patient has one *HFE* gene mutation



✓ Patient has no *HFE* gene mutation



HOW DO I ORDER THE GENETIC TEST?

Genetic testing for HH is performed in a specialized hospital laboratory on a blood sample. Click here to find your closest molecular genetics laboratory and the requisition to order testing. Many laboratories prefer that you attach their requisition to the Provincial Ministry of Health requisition. This process will expedite and simplify genetic testing when blood is drawn at a community laboratory.

It is important to include the following information on any requisition for the best test interpretation:

- ✓ Indication for testing e.g. 'symptoms of indicated disease' or 'abnormal iron indices' or 'positive family history'
- ✓ Ethnicity e.g. Northern European
- ✓ Relevant family history e.g. parent/sibling with HH (include genetic test results of affected individual if known)
- ✓ Relevant medical history/investigations; e.g. biochemical iron overload

WHERE DO I REFER MY PATIENT?

Click here to find your local genetics clinic.

You might refer to genetics if your patient has had a positive genetic test result and would like genetic counselling to discuss the implications for self and family.

Note that genetics clinics vary with regard to the referrals they choose to accept. You may want to contact your local centre for more information.

Include all relevant information on your referral (e.g. family history, genetic test results, and investigations like iron indices) to prevent unnecessary delays due to further clarification needed before an appointment can be booked.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

If mutations are identified

- Appropriate surveillance and management of the risk of iron overload can be initiated

If no mutations are identified

- If your patient was tested because of a known family mutation, they no longer need frequent monitoring of iron indices and are not at increased risk to develop iron overload. The test has ruled out HH.
- If your patient was tested because of a reported positive family history, more information is needed before ruling out HH in this individual. Your patient should be encouraged to obtain confirmation of the familial mutations and/or diagnosis.
- If your patient was tested because of persistently high iron indices, additional investigations should be considered.

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

Limitation: Targeted mutation analysis

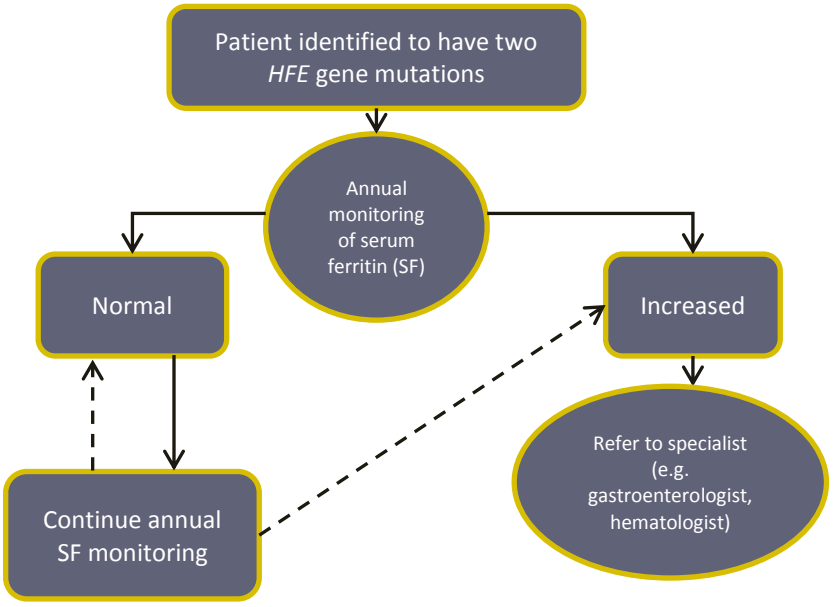
- Not every *HFE* gene mutation is looked for, however, the most common mutations account for more than 90% of all mutations, thus fewer than 10% will be missed using current testing strategies.

Insurance discrimination

- Historically, genetic testing in an asymptomatic individual may have affected their ability to obtain life, disability, critical illness, long-term care and/or extended health insurance. However, in 2017 Canada passed the Genetic Information Non-Discrimination Act (GNA) that protects individuals from having their genetic test results used to prevent them from obtaining insurance.

Surveillance and Management

Care map for surveillance and management of your patient identified to have two *HFE* gene mutations. (Adapted from [2])



Treatment is usually initiated and monitored by a specialist (e.g. haematologist or gastroenterologist). Therapeutic phlebotomy, which is both safe and effective, is the mainstay of treatment for iron overload. With treatment many complications can be avoided.[3] Treatment is usually indicated in the presence of biochemical evidence of iron overload, symptoms (Table 1 in What is HH?), end-organ damage, and/or a SF of 1000 µg/L or greater.[1,2,4]

Iron, cast-iron cooking utensils and vitamin C supplements should not be used by those at risk for, and those with, iron overload. Raw and undercooked shellfish should be avoided because they may carry bacteria that thrive on iron. Dietary iron modification does not significantly alter SF levels and is not a substitute treatment for individuals with iron overload.[1,2,4]

Individuals with two *HFE* gene mutations should consider the hepatitis A&B vaccines.[4]

Clinical Tips

- ✓ Women are less likely to develop iron overload as a result of menstruation and pregnancy[1,2,4]
- ✓ Iron overload due to *HFE* mutations does not occur in childhood[1,2,4]
- ✓ Typically, symptoms of HH present in men aged 40 to 60 and in post-menopausal women; however, onset is variable and can occur much earlier or much later[4]
- ✓ Early symptoms are nonspecific and include weakness, lethargy, joint pain and/or stiffness, and abdominal pain with or without hepatomegaly[4]
- ✓ Before the onset of symptoms, biochemical evidence of iron overload will be present: >45% transferrin saturation (TS) and >300µg/L serum ferritin (SF) in men and post-menopausal women, or >200µg/L SF in pre-menopausal women[1,2,4]
- ✓ Alcohol consumption can exacerbate iron overload and HH- related liver disease[4]

RESOURCES FOR HEALTH PROFESSIONALS

[1] Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011. 54:328–343.

[2] European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol. 2010. 53:3–22.

[3] Pilling LC, Tamosauskaite J, Jones G, Wood AR, Jones L, Kuo C, et al. Common conditions associated with hereditary haemochromatosis genetics variants: cohort study in UK Biobank. BMJ. 2019. 364:k5222.

[4] GeneReviews. *HFE*-Associated Hemochromatosis. http://www.ncbi.nlm.nih.gov/books/NBK1440/ Updated September 17th, 2015 [Accessed January 2019].
Expert-authored, peer-reviewed, current disease descriptions that apply genetic testing to the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.

[5] 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):474-479.

[6] Porto G, Brissot P, Swinkels DW, Zoller H, Kamarainen O, Patton S, et al. EQMN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). Eur J Med Genet. 2016. 24:479-495.

[7] Arbour L, Canadian Paediatric Society and Bioethics Committee. Guidelines for genetic testing of healthy children. http://www.cps.ca/en/documents/position/guidelines-for-genetic-testing-of-healthy-children Posted January 1, 2003, Updated April 1, 2008, Reaffirmed January 30, 2017 [Accessed January 2019].

RESOURCES FOR PATIENTS AND THE PUBLIC

Canadian Hemochromatosis Society. Established to create awareness about the disorder. Additionally provides information and support. www.toomuchiron.ca [Accessed January 2019].

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