LifeLabs GENETICS™

Genetic Testing for Hemachromatosis

What is Hemochromatosis?

Hemochromatosis is a condition in which iron builds up over time in various organs, such as the liver and heart. Hemochromatosis can be acquired or inherited. Acquired hemochromatosis can be a result of other conditions, such as liver disease, cancer, inflammatory disorders (i.e. rheumatoid arthritis), repeated blood transfusions, and excessive iron intake from foods, etc. **Hereditary hemochromatosis** occurs as a result of genetic changes in the HFE genes, which are inherited from mom and dad.

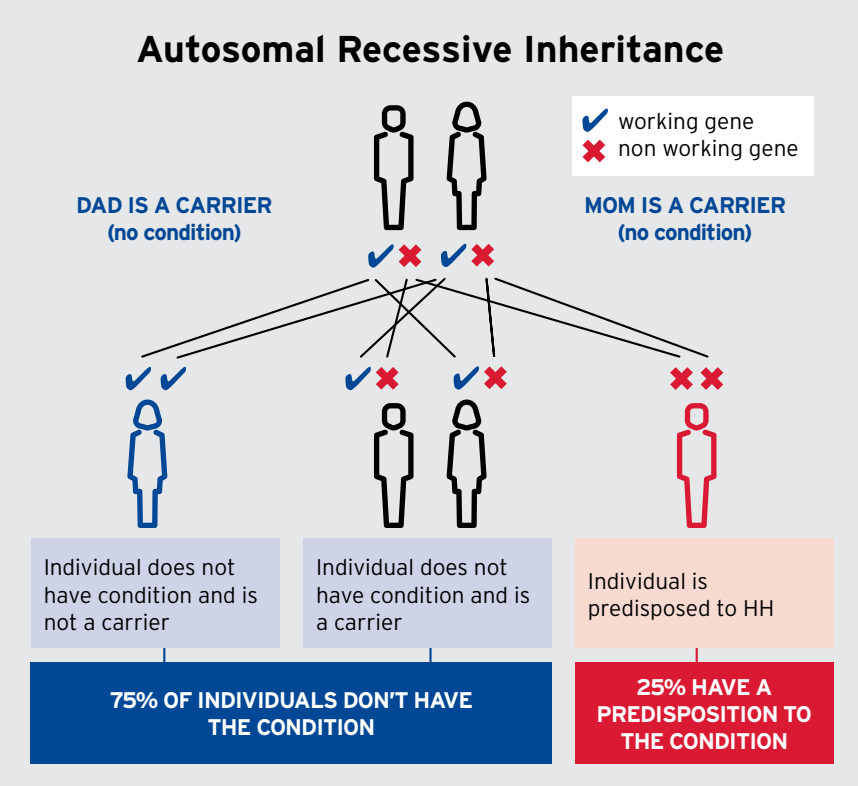
Hereditary Hemochromatosis (HH)

HH is one of the most common inherited conditions, affecting approximately 1/300 individuals of Northern European ancestry. Individuals with HH are born with changes (mutations) in both copies of their hemochromatosis (*HFE*) gene, which means they have two non-working *HFE* genes. The *HFE* gene can be thought of as a brake light, or stop sign, for controlling how much iron from our diet is absorbed into the cells of our body. When the *HFE* gene doesn't work, an excessive amount of iron is absorbed, which can create a buildup of iron in our organs (i.e. iron overload). If left untreated, iron overload can cause damage to organs in the body. Symptoms in early stages of iron overload include skin bronzing, fatigue, weakness, abdominal pain, joint pain, loss of sexual drive, and weight loss. More serious complications, such as diabetes, liver disease, and heart disease, can follow if the iron overload is untreated.

While HH-related health problems generally occur between 40-60 years of age, the timing, onset and severity are variable. It is likely that other less well-understood genetic factors also influence iron absorption. Fortunately, if detected early, HH is treatable and individuals can lead a normal, healthy life. With monitoring of iron levels and blood removal (phlebotomy) as the need arises, serious complications of HH can be prevented.

Inheritance of Hereditary Hemochromatosis

HH is an autosomal recessive condition. The cells in our bodies contain thousands of genes, which provide instructions that tell our bodies how to grow and function. We have two copies of each gene; one copy is inherited from our mother and the other from our father. Sometimes, a change or mistake in a gene can occur, like a spelling error in a word of a book. This is called a variant. Specifically, there exist harmful variants, referred to as mutations, that may cause the gene to not work properly. An individual who has two non-working copies of the *HFE* gene has a predisposition for HH. Autosomal recessive conditions, like HH, are usually passed on by two carrier parents. Carriers have one working copy of *HFE* (no mutation) and one non-working copy of *HFE* (has a mutation). The carrier's health is rarely affected. With each pregnancy, two carriers of HH have a 25% chance of having an unaffected child with two working genes; a 50% chance of having an unaffected child who is also a carrier; and a 25% chance of having an affected child with two non-working genes who would be predisposed to iron overload in adulthood. Current research estimates that 1 in 9 Canadians are carriers of an *HFE* gene mutation.[1]



NOTE: the above image does not have any impact on predisposition to HH. Males and females have an equal chance of acquiring an autosomal recessive condition.

Risks of developing HH

The two most common mutations in the *HFE* gene are C282Y and H63D, which account for the majority of all cases of hemochromatosis. The S65C variant has been found to be associated with milder forms of hemochromatosis, especially in C282Y/S65C individuals. A small percentage of individuals with HH may have unidentified mutations in the *HFE* gene or another gene. The chance of developing the disease depends on which gene mutations are inherited (as well as other possible co-existing factors):

Genotype (results of HFE genetic testing)	**% of people with HH**[2,3,4]	**% of people who will develop signs or symptoms**[2,3,4] (e.g. Increased ferritin/transferrin saturation and/or clinical symptoms)
C282Y / C282Y	60-90%	~70%
C282Y / H63D	3-8%	~0.5-2%
H63D / H63D	~1%	rare
S65C / C282Y or S65C / H63D or S65C / S65C	Rare	S65C/C282Y – possibly mild/moderate liver iron overload but negligible risk for clinical symptoms or liver complications

It is important to note that not everyone who has a predisposition to HH (two non-working copies of *HFE*) will develop iron overload, but guidelines recommend they are monitored accordingly.

Canadian guidelines recommend genetic testing to individuals with suspected HH, based on elevated fasting transferrin saturation and ferritin, and is typically covered by the Provincial Ministry of Health. Predictive genetic testing is also recommended for first degree relatives (parents, siblings, adult children) of an individual who has a genetically confirmed diagnosis of HH. Guidelines vary from province to province in terms of what mutations are tested for under government funding.

Monitoring and Treatment

Management of individuals with HH involves periodic phlebotomy (i.e. regular blood draws) to remove the excess iron. Once the iron levels are adequately reduced, routine blood tests are performed to monitor the amount of iron in the body.

Screening for liver cirrhosis and/or liver biopsy is dependent on the ferritin levels. If liver cirrhosis is present, individuals should be followed and regularly screened for liver cancer.

Individuals with HH should avoid iron and vitamin C supplements, as well as raw seafood. For individuals with advanced stage disease, alcohol should also be avoided, as it has been shown to worsen symptoms.

At risk relatives

Once an individual is diagnosed with HH, it is important that their siblings, in particular, have their iron profiles tested and monitored regularly. They should be referred to their local genetics clinic for genetic counselling to discuss the option of genetic testing to determine if they are at risk. The parents, spouses, and adult children of individuals with 2 gene changes, as well as those of C282Y carriers, are also advised to seek genetic counselling.

If you have two *HFE* gene changes, your children will inherit one *HFE* gene change from you. Your children will only be at risk for HH if your partner is also either affected with or a carrier of HH.

Children should not be tested for HH, as this is an adult onset condition. Young children are not at risk for health problems related to *HFE* gene mutations. Therefore, genetic testing would be available when they are adults, if they wish to pursue testing.

Insurance issues

Any adult who does not have a diagnosis of iron overload and is considering genetic testing should be aware that a positive genetic test result might place them in a higher risk category from an insurance point of view. The Genetic Non-Discrimination Act (GNA) prohibits insurance companies from requesting the disclosure of genetic tests; however it doesn't protect insurers basing their decisions on current symptoms and diagnoses.

How to order

Provincial funding may be available through local provincial labs and healthcare providers and patients should check with their local genetics labs before pursuing private pay testing.

STEP 1

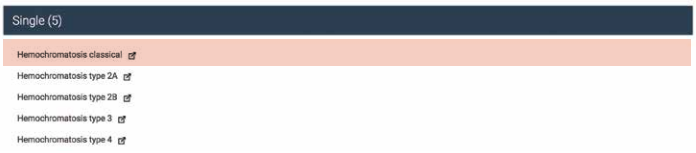
HFE hotspot testing needs to be ordered by a healthcare provider (HCP).

STEP 2

Search for "hemochromatosis" using the search tool on the **www.lifelabsgenetics.com** website:

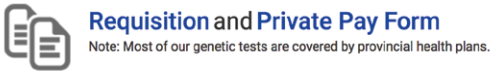
STEP 3

Choose "hemochromatosis classical"



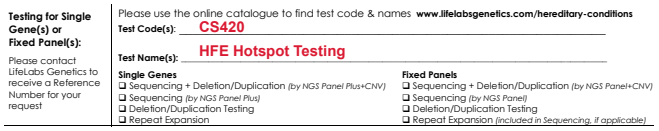
STEP 4

Print off and complete requisition and payment form from webpage **https://www.lifelabsgenetics.com/search-details/?id=4595**



STEP 5

Fill in the requisition with the following information:
Test code: **CS420**
Test name: **HFE Hotspot Testing**



STEP 6

The patient brings the requisition and payment form into any LifeLabs patient service centre (ON, BC, and SK): **http://locations.lifelabs.com/**. For other provinces, contact 1-84-GENEHELP or **Ask.Genetics@LifeLabs.com** to find a collection facility near you. Saliva kits can also be sent out to patients directly when residing outside of a collection network.

STEP 7

Results available to HCPs in 2 weeks, from the day the sample is received in the lab, via CentoPortal or fax.

STEP 8

Once the HCP reviews the results with the patient, the patient may contact 1-84-GENEHELP or **Ask.Genetics@LifeLabs.com** to book an appointment with a Canadian board-certified Genetic Counsellor to review the information and results. Sessions are available in English and French.

Visit www.lifelabsgenetics.com to learn more about our diagnostic panels.
Contact us Ask.Genetics@LifeLabs.com | 1-84-GENEHELP (1-844-363-4357)

References

1. Canadian Hemochromatosis Society. https://www.toomuchiron.ca/
2. Bacon et al. Diagnosis and Management of Hemochromatosis: 2011 Practice Guideline by the American Association for the Study of Liver Diseases. Hematology. 2011
3. Kowdley KV, Bennett RL, Motulsky A. Current. HFE-Associated Hereditary Hemochromatosis Gene Reviews http://www.ncbi.nlm.nih.gov/books/NBK1440#hemochromatosis
4. Holstrom et al. Mild iron overload in patients carrying the HFE S65C gene mutation: A retrospective study in patients with suspected iron overload and healthy controls. Gut. 2002

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