HEREDITARY HEMOCROMATOSIS
GENETIC TESTING
A Guide for Families

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Over one-half million people in the United States have the potential to develop hereditary hemochromatosis. New developments in genetic testing have made it possible to test for the risk of hereditary hemochromatosis through a painless and inexpensive cheekbrush sample. The testing can also be done using a small sample of blood. This information is designed to help you understand hereditary hemochromatosis and how you and your family can be tested for it.

What is hereditary hemochromatosis?
Hemochromatosis is a disease that results from storage of excess iron in the body. It will occur anytime there is more iron in the body than required. Many affected individuals have a genetic predisposition to store iron; therefore, they are at increased risk to develop hereditary hemochromatosis.

Hereditary hemochromatosis (referred to as “HH”) is an inherited genetic disorder affecting many parts of the body, including the skin, heart, liver, pancreas, and skeleton. It is caused by changes (mutations) in the HFE gene. In a person with HH, the cells in the intestine absorb too much iron from food and beverages. The extra iron is stored in the blood and the organs of the body. Frequently, early symptoms of HH are ignored and the diagnosis is not made until serious damage has occurred. If the disease goes undiagnosed, individuals can have life-threatening complications and a shortened life span.

How hemochromatosis affects the body:

- Skin: bronze or gray discoloration
- Liver: cirrhosis, cancer, failure
- Pancreas: diabetes mellitus
- Heart: arrhythmia, failure
- Skeletal: arthritis, joint pain

Other symptoms include:
- fatigue
- anemia
- impotence
- early menopause
- weight loss
- abdominal pain
- menstrual irregularity

The potential to develop HH is present from birth, but symptoms usually occur much later in life. The disease affects both males and females. Men are generally symptomatic at an earlier age than women.

Who is at risk for developing HH?
One in 250 people in the Caucasian population are diagnosed with HH. It is possible for people with no known family history to develop HH.

Not everyone who has a genetic predisposition will develop symptoms of HH. Mutations in the HFE gene in combination with environmental factors determine whether you will have symptoms of the disease and at what age those symptoms will develop. Environmental factors include dietary iron intake and alcohol consumption, among other things. Menstruation and childbearing also play a role in the onset of symptoms.

What causes HH?
HH is a genetic disorder caused by a pair of genes that is not working correctly. Genes are responsible for our physical traits and body functions. Most of our genes come in pairs, with one copy from each parent. A gene can sometimes be changed to a non-working form. This change is called a mutation.

- A person with HH has a mutation in both copies of their HFE gene.
- A person who only has a mutation in one copy of the gene is called a carrier.

If only one parent is a carrier, then the risk of HH in a child is very small. When both parents are carriers, each child has a 1 in 4 (25%) chance to inherit a mutation from both parents and therefore has the potential to develop HH. There is also a 1 in 2 (50%) chance that the child would only inherit a mutation from one parent and be a carrier, and a 25% chance that the child would not inherit a mutation from either parent (see picture below).

The chance for you to inherit two HFE mutations is increased if you are related to someone who has HH or who is a carrier. The likelihood to inherit an HFE mutation is dependent on who in your family has HH and how closely they are related to you.
The table below shows the risks of having an HFE mutation based on your relationship to the person who has HH. In the first column, find the relative who is affected in your family and look across to the next column to determine the chance that you have inherited an HFE mutation. For example, if you have a brother with HH, your chance of having at least one HFE mutation is 3 in 4 (75%). (There is a 2 in 4 chance to be a carrier and a 1 in 4 chance to inherit 2 mutations.)

<table>
<thead>
<tr>
<th>If your relative with HH is your...</th>
<th>Then your carrier risk is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>1 in 1 (100%)</td>
</tr>
<tr>
<td>Child</td>
<td>1 in 1 (100%)</td>
</tr>
<tr>
<td>Brother/Sister</td>
<td>3 in 4 (75%)</td>
</tr>
<tr>
<td>Aunt/Uncle</td>
<td>1 in 2 (50%)</td>
</tr>
<tr>
<td>First cousin</td>
<td>1 in 4 (25%)</td>
</tr>
</tbody>
</table>

How is HH diagnosed?
Until a short while ago, HH could only be diagnosed by measuring iron stores in the blood and by liver biopsy. In many cases, people had already suffered irreversible liver, heart, and pancreatic damage by the time they were diagnosed.

Three mutations - C282Y, H63D, and S65C - in the HFE gene account for approximately 90% of HH families. Genetic testing is now available for these three mutations. Genetic testing can determine if a person has the potential to develop HH before symptoms occur and may prevent the need for a liver biopsy. A liver biopsy may still be necessary in symptomatic patients to determine the progression of liver disease.

Genetic testing can currently identify mutations in 90% of Caucasians who have the diagnosis or are at risk to develop HH. The detection rate is lower in other ethnic groups such as African or Asian. Also, not everyone with HH will have two mutations in the HFE gene. It is likely there is another unidentified gene in the population that contributes to the risk for HH.

To date, there is no way to fix the gene mutations causing HH; however, if the disease is recognized early it can be easily treated. Management of HH consists of the removal of blood (phlebotomy) until iron levels have decreased. It may take several months to a year before results are seen. Once the excess iron is controlled, only a few phlebotomies a year may be necessary. Your physician should follow your ferritin and iron levels as well as blood cell count to determine when you need phlebotomy. Your physician may also modify your dietary iron intake.

Phlebotomy can improve some symptoms, including skin discoloration, heart problems, abdominal pain, and diabetes. Symptoms such as cirrhosis and impotence are less likely to improve, but further damage may be prevented. If HH is diagnosed early and managed correctly, it is consistent with a healthy and normal life expectancy.

What if I am found to be a carrier?
If you are a carrier of HH, this means you have one gene that works properly and one gene that does not. Research has shown that carriers do not develop HH; however, they may have increased levels of iron. Environmental factors may also contribute to symptoms in some carriers. A carrier has an increased risk to have a child with HH.

What is genetic testing?
Genetic testing can show whether or not a person carries the gene mutations known to cause HH by analyzing DNA from a small amount of cells. Cells can be obtained through a sample taken from the inside of the mouth by brushing the inner surface of the cheek or through a blood sample. The DNA from these cells can be isolated and used to test for the presence of gene mutations.

Who will benefit from HH genetic testing?
Anyone concerned about their potential risk of having HH can be tested. This test is most useful prior to onset of symptoms so early management of the disease can be started before damage has occurred. If symptoms are already present, genetic testing and follow-up treatment can prevent any further damage from occurring. HH genetic testing is recommended when there is clinical presentation of symptoms due to increased iron levels or a family history of HH. Genetic testing for adult-onset disorders such as HH is not recommended in asymptomatic minors.

How do I pursue genetic testing?
Discussion with your physician, health care provider, or a genetic counselor will help you make an informed decision about whether to have HH genetic testing. Genetic testing can be coordinated through your doctor’s office or the Genetics Clinic at Michigan State University.

For more information you may contact the Michigan State University Human Genetics staff at: (877) TEST DNA [(877) 837-8362] or (517) 353-2032. You are welcome to visit our web page: www.phd.msu.edu/DNA/home.html

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