

## ***HFE*-Related Hereditary Hemochromatosis**

**THE MOST COMMON FORM** of hereditary hemochromatosis (HHC) is caused by alterations in the *HFE* gene. This is an autosomal recessive condition with reduced penetrance causing iron overload. HHC is clinically-suspected when an individual has BOTH persistently elevated fasting ferritin AND elevated transferrin saturation (TS) levels. If untreated, HHC can cause accumulation of iron in various organ systems causing fatigue, arthralgia in the hands and fingers, bronzing of the skin, arrhythmias, low sex drive, male infertility, diabetes, liver cirrhosis, rarely liver cancer and early death. However, compliance to treatment via routine phlebotomies can arrest the disease progression and allow individuals to live relatively symptom free and have a normal lifespan. Molecular testing for the *HFE* gene is available to individuals showing biochemical evidence of HHC.

**MOST INDIVIDUALS** with HHC have two mutations in the *HFE* gene. The chance to develop iron overload depends on the genotype. Most affected individuals have two copies of the C282Y mutation, which is associated with a 50-90% chance of developing biochemical evidence of the disease. Individuals with one C282Y and one H63D mutations have about a 5% chance of developing the disease. Individuals with two H63D mutations have a very low chance of developing the disease (<1%). Heterozygotes (also called carriers) are not likely to have iron overload as a direct result of their *HFE* genotype.

**ELEVATED FERRITIN** in the absence of elevated TS is NOT clinically suggestive of HHC. There are many other causes of elevated ferritin, including fatty liver disease, infection, malignancy, or rheumatologic disease.

### **If Your Patient Has C282Y/C282Y OR C282Y/H63D Genotype:**

Your patient and his/her family members may benefit from genetic counselling. Please refer your patient to genetics. We will discuss familial risks and inheritance of HHC. In the meantime, please refer to **Flow Chart #2** for **Surveillance** and **Management** recommendations.

### **If Your Patient Has H63D/H63D, C282Y/Normal, or H63D/Normal:**

Because these genotypes are associated with very low risk for *HFE*-related HHC, we cannot confirm this diagnosis for your patient. **A genetics referral is NOT indicated.**

**IF** this patient has elevated ferritin, consider investigating other causes as listed above. You may consider consulting the following services:

- ▶ Hematology, if ferritin is elevated but < 1000 ug/L
- ▶ Hepatology, if ferritin is > 1000 ug/L OR if there are signs of abnormal liver function (eg. elevated liver enzymes)

### **General Recommendations for Individuals with Iron Overload**

Individuals who are at-risk for iron overload should avoid ingesting excess iron or vitamin C (ie., avoid multivitamins containing these ingredients). Individuals may also opt to donate blood with Canadian Blood Services. Diet modifications include reducing intake of red meat.

For individuals who are at-risk of abnormal liver function, alcohol consumption should be limited. These individuals should also avoid raw shellfish. Consuming raw shellfish increases the risk of exposure to *Vibrio vulnificans*, a bacterium that can cause life threatening complications in individuals who have liver damage.

**Flow Chart #1**

**ADULT** with family history of hereditary hemochromatosis (HHC)

IS the affected individual's genotype and relation to the current patient known?

**NO**

**ASK PATIENT** to obtain further information. *If affected is a sibling, may consider baseline ferritin & TS. Reassess as needed if new information arises.*

**YES**  
What is the Genotype?

C282Y/C282Y

All Others

C282Y/H63D

**OUR PATIENT** is the \_\_\_\_\_ of the affected individual

The patient is **NOT** likely to be at increased risk for *HFE*-related HHC. **No** further work-up indicated. Reassess if symptoms arise.

**OUR PATIENT** is the \_\_\_\_\_ of the affected

Child or Sibling

Parent

All Others

All Others

Sibling

- Take baseline ferritin & TS if not yet done
- **OFFER GENETIC TESTING**

**TAKE** baseline ferritin & TS

Ferritin > 200,  
TS > 60 or > 45  
twice in 1 mo?

No

Yes

**OFFER GENETIC TESTING**

- Take baseline ferritin & TS if not yet done
- **OFFER GENETIC TESTING**

Refer to **Flow Chart #2**

Refer to **Flow Chart #2**

**If Genetic Testing Is Declined You Can Consider the Following**

**IF Ferritin < 200 & TS < 60**

Monitor ferritin & TS...

- Every 2 years if sibling is C282Y/C282Y
- Every 5 years if sibling is C282Y/H63D

**IF Ferritin > 200 But TS NOT > 45 twice**

Patient's high ferritin cannot necessarily be explained by *HFE*-related HHC

- Refer to hematology if ferritin < 1000 or hepatology if ferritin > 1000

**If Ferritin > 200 & TS >60 or 45 twice**

- You may consider treating your patient with phlebotomy

**Flow Chart #2**  
**ADULT** with DNA test results suggestive of hereditary hemochromatosis (HHC)

Genotype?

**C282Y/C282Y**

**C282Y/H63D**

**All Others:** H63D/H63D  
 H63D/Normal & C282Y/Normal

- **IF** both ferritin & TS are elevated, the patient has evidence of HFE-related HHC. Please arrange for your patient to have **phlebotomy** treatment with ferritin monitoring.
- **IF** only ferritin is elevated, consider other causes of elevated ferritin.
- **IF** iron indices are normal, the patient has **an increased risk** to develop HHC. Monitor ferritin & TS *every 2 years*
- **REFER** to hematology if ferritin < 1000 and hepatology if ferritin > 1000 for management.
- **REFER PATIENT TO GENETICS**
- **FULL SIBLINGS:** Offer genetic testing, ferritin and TS
- **PARENTS:** Offer baseline ferritin
- **ADULT CHILDREN:** Offer genetic testing, ferritin and TS. Note: If there are > 2 children and the partner is available, offer DNA testing to the partner

- **IF** both ferritin & TS are elevated, the patient has evidence of HFE-related HHC. Please arrange for your patient to have **phlebotomy** treatment with ferritin monitoring
- **IF** only ferritin is elevated, consider other causes of elevated ferritin.
- **IF** iron indices are normal, the patient has a **< 5% risk** to develop HHC. Monitor ferritin & TS *every 5 years*
- **REFER** to hematology if ferritin < 1000 and hepatology if ferritin > 1000 for management
- **REFER PATIENT TO GENETICS**
- **FULL SIBLINGS:** Offer genetic testing, ferritin and TS
- **PARENTS & ADULT CHILDREN:** We do **NOT** recommend ferritin / TS screening or genetic testing for HHC

- This genotype is **NOT** sufficient to diagnose HHC.
- **SEE** attached information sheet