Hereditary Haemochromatosis (HH) is a common autosomal recessive disease resulting in excessive absorption of dietary iron from the intestine. Over time, excess iron accumulates in the parenchymal cells of organs including the liver, pancreas, heart and anterior pituitary causing organ damage.

HH is more common in people of Celtic or northern European decent. It is the most common genetic disease in Ireland with approximately 1 in 83 people predisposed to develop HH.

Early diagnosis and treatment of HH prevents complications and results in a normal life expectancy. Phlebotomy is a simple and effective way to both prevent and manage iron overload in patients with HH.

The Genetics of HH

Hereditary Haemochromatosis is caused by mutations in the HFE gene, mainly C282Y. The association with haemochromatosis with HFE variants other than C282Y, such as H63D, is still debated and no established consensus has been published.

Carriers (also known as heterozygotes) have one altered HFE gene and one normal HFE gene and are generally not affected by iron overload. Iron overload arises when both copies of the HFE gene are altered/mutated. Not everyone who inherits two HFE mutations will develop iron overload and fewer will develop the clinical syndrome.

The majority of patients are homozygous for the C282Y mutation in the HFE gene. The prevalence of the C282Y homozygous state in the Irish population has been estimated at 1.2% or approximately 55,000 individuals. However not all patients develop symptoms due to variable clinical penetrance.

C282Y/H63D compound heterozygosity is a risk factor for slightly higher serum iron parameters and mildly increased hepatic iron stores when in association with co-morbidity factors, for example, alcohol or metabolic syndrome.

There are several factors known to influence expression of the disease in those patients who are genetically susceptible. Women tend to have a later and less severe onset because of menstruation and pregnancy. Alcohol, a diet high in iron, obesity and hepatitis B and C increase the chance of clinical symptoms.

A blood based genetic test can be arranged to screen for the HFE mutations. HH is an adult onset disease, and testing of minors is not recommended.
What are the Symptoms?

Symptomatic organ involvement, when it does occur, tends to begin in middle age. No two people are alike and symptoms will vary from person to person.

The most common symptoms noticed by people with HH include:
- Fatigue, general weakness and lethargy
- Joint pain. Knuckle and first joint of the first two fingers are commonly affected
- Abdominal pain
- Sexual dysfunction
- Discoloration of or bronzing of skin
- Mood swings and irritability

The early biochemical signs of HH tend to be:
- Increased serum ferritin and transferrin saturation
- Abnormal liver function tests (LFTs)
- Hepatomegaly (enlarged liver)

Symptoms are often attributed to other causes, leading to delay in diagnosis. Combinations of the symptoms of HH can and should lead to early diagnosis.

If not treated early, people with HH can develop diabetes mellitus, cirrhosis, cardiac problems and hepatocellular carcinoma.

Consider Testing For HH in:
- Patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease.
- Family members of HH patients.
- Chronic unexplained fatigue, weakness and abdominal pain.
- Asymptomatic patients with incidental elevated LFT, ferritin or hepatomegaly.
- Early onset arthralgia (joint pain), atypical arthropathy.
- Early onset male impotency, early menopause and loss of libido in women.
- Early onset arrhythmias and cardiomyopathy.
- Unexplained increasing skin pigmentation or 'permanent tan'.
- Type 2 diabetes mellitus, especially those diagnosed at an early age, with elevated LFT, hepatomegaly, early-onset sexual dysfunction or abnormal iron markers.

Diagnosis of HH

The clinical diagnosis of hereditary haemochromatosis is C282Y homozygosity and increased body iron stores with or without clinical symptoms. Therefore, HH is diagnosed in terms of phenotype (raised serum ferritin and transferrin saturation) and genotype, and is not made by identification of mutated genes alone.

For practical clinical purposes, C282Y/H63D compound heterozygotes and H63D homozygotes are not classified as HFE-associated HH (following the most recent EASL guidelines), and it is recommended that in patients with these genotypes and iron overload, other causes of hyperferritinemia should first be investigated. These patients may be at-risk of developing mild to moderate iron overload in association with comorbid factors and may be appropriate for therapeutic phlebotomy.

See the table overleaf for more details on the interpretation of the genetic result and the risk of developing iron overload.
What are the tests?

**Iron Studies**

Both fasting transferrin saturation (TS) and serum ferritin (SF) are required as patients in the early stages of clinical disease can have normal SF, but raised TS. In addition, SF is an acute phase protein which can be raised during illness.

**Serum Ferritin**

SF reflects body iron stores but, as an acute phase reactant, can be elevated non-specifically on occasions (e.g. through alcohol consumption, chronic inflammation and other liver diseases).

A SF of > 200 µg/L in pre-menopausal women and > 300 µg/L in men and post-menopausal women suggests that the patient may be iron overloaded. This should prompt a test for fasting TS.

Patients with a SF >1000 µg/L should have a referral to gastroenterology/hepatology at the same time the blood test is sent for genetic testing. This is because as SF >1000 µg/L places the individual at increased risk of severe HH related morbidity such as liver cirrhosis and a liver biopsy/fibroscan needs to be done.

**Transferrin Saturation**

Fasting transferrin saturation of >45% is strongly suggestive of HH and should prompt a test for HFE gene testing. Transferrin saturation is the proportion of the iron transport protein transferrin that is saturated with iron. An increased TS reflects increased absorption of iron – the underlying biological defect of this condition.

**HFE Genetic Testing**

If fasting transferrin saturation is >45%, HFE genetic testing should be done. Laboratories should test for C282Y and, according to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing.

If the patient is negative for the HFE mutations, further investigations for hyperferritinemia should be done.

The HFE gene test is performed once, whereas iron studies are performed every time an assessment of current iron overload is required.

<table>
<thead>
<tr>
<th>Genotype (Prevalence in Population)</th>
<th>Interpretation of result and risk of developing Iron Overload</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Homozygous C282Y</strong> <em>(1 in 83)</em></td>
<td>Diagnosis of Hereditary Haemochromatosis is made in the presence of iron overload. Are at risk of developing HH (i.e. not everyone with this genotype will develop HH), therefore are at risk of developing significant iron overload.</td>
</tr>
<tr>
<td><strong>Compound Heterozygous C282Y/H63D</strong> <em>(1 in 60)</em></td>
<td>Excludes the diagnosis of the most common form of Hereditary Haemochromatosis, genotype consistent with mild to moderate iron overload. May be at-risk of developing mild to moderate iron overload in association with other factors (e.g. alcohol consumption, fatty liver disease and/or metabolic syndrome) and may be considered for treatment via phlebotomy.</td>
</tr>
<tr>
<td><strong>Heterozygous C282Y</strong> <em>(1 in 5)</em></td>
<td>At no increased risk of developing Hereditary Haemochromatosis associated iron overload. Is a carrier of Hereditary Haemochromatosis. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Heterozygous H63D</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Homozygous H63D</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
<tr>
<td><strong>Normal Genotype</strong></td>
<td>At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.</td>
</tr>
</tbody>
</table>
Management

Family Screening

Genetic testing of adult siblings and offspring of a patient diagnosed with HH (C282Y homozygous) is recommended. Parents of C282Y homozygotes should be screened after a clinical decision depending on their age, sex and ferritin. If patients with HH are worried about their children, it is useful to perform genetic testing on the other parent to predict whether the children will need to be considered for genetic testing.

Work Up

If SF is elevated, initial evaluation should include fasting blood glucose, HbA1c, serum AST, and ALT activity.

Patients should be referred onto a specialist if:
- SF >1000 µg/L
- Cirrhosis/advanced liver disease
- Abnormal liver function tests
- Non-HFE iron overload
- Contraindications to phlebotomy
- Significant co-morbidities e.g. fatty liver disease
Treatment

HH patients with SF above the upper limit of normal should have treatment to normalise iron indices. Regular **phlebotomy** will achieve this. Phlebotomy should begin when SF is above the normal range (this is typically >200 µg/L in pre-menopausal women and >300 µg/L in men and post-menopausal women).

If there is a raised TS but normal SF, treatment is not required as it is only with raised SF that there is evidence of raised total body iron levels.

Each 500ml of blood contains approximately 250mg of iron. The aim is to keep SF between 50-100 µg/L.

Initially, the treatment can mean weekly or biweekly phlebotomy to rapidly reduce the ferritin levels. After a normal level has been achieved, maintenance may only require three or four sessions per year for the remainder of life. The frequency of phlebotomy depends on initial SF.

### Phase 1. Iron Unloading Phase

- Weekly or every two weeks phlebotomy of ~500 ml whole blood until SF is <250 µg/L. Then monthly until SF has reduced to 50 - 100 µg/L.
- Ensure pre-phlebotomy haemoglobin >12.5 g/dL.
- Monitor haemoglobin every 4-6 phlebotomies. Delay for 1 week if pre-phlebotomy Hb <11 g/dL.
- Monitor SF every 4-6 phlebotomies, until approaching target values (approx. 100 µg/L), then take on each occasion.

### Phase 2. Lifelong Maintenance Phase

- Phlebotomy to maintain SF 50 – 100 µg/L.
- Highly variable between individuals, often in the range 2-6 phlebotomies per year.
- Check Hb and SF before every phlebotomy (do not perform if Hb <11 g/dL).
- If patient is not undergoing phlebotomy monitor SF at least once a year.

It may take many months or even years to unload excess iron. Oral supplements for vitamin B12 (5 µg daily) and folate (500 µg daily) support erythropoiesis during frequent phlebotomy.

Phlebotomy services

Phlebotomy can be performed in the GP surgery. If you are unable to provide phlebotomy in your clinic, please refer the patient onto another phlebotomy clinic. Most clinics are currently based in the hospital but there are aims to move these to the community in the future.

The Irish Blood Transfusion Service (IBTS) has a therapeutic phlebotomy programme for individuals with HH and patients should be referred onto the IBTS if the referral criteria is met. This includes having SF < 600 µg/L. The service is currently available in Dublin and Cork and it is hoped to expand this service nationally. Please see [https://www.giveblood.ie/](https://www.giveblood.ie/) for more details.
Diagnostic flowchart for patients with suspected Hereditary Haemochromatosis

Determine fasting Serum Ferritin (SF) and Transferrin Saturation

SF value above upper limit of reference range
- Check for inflammation, iron loading anaemia, alcohol misuse, metabolic syndrome, cell necrosis

Transferrin Saturation
- Transferrin Saturation > 45%
  - HFE genetic testing
    - C282Y Homozygote
      - Diagnosis with HH
        - SF < 1000 µg/L and normal liver enzymes
          - Phlebotomy until SF 50 - 100 µg/L. Follow up. Screen first degree relatives.
        - SF ≥1000 µg/L or elevated liver enzymes
          - Specialist Referral: Liver biopsy/Fibroscan if SF ≥1000 µg/L to check for fibrosis/cirrhosis and periodic screening for hepatocellular carcinoma
    - C282Y/H63D compound heterozygote H63D homozygote
      - First be investigated for other causes of hyperferritinemia
      - Further investigations for hyperferritinemia. None found then specialist referral

- Transferrin Saturation ≤ 45%
  - HFE genetic testing
    - C282Y heterozygote H63D heterozygote Absence of HFE-gene mutation
      - Haemochromatosis does not explain current symptoms
    - Haemochromatosis does not explain current symptoms. Investigate other causes of iron overload.

SF within reference range
- Haemochromatosis does not explain current symptoms
- Investigate other causes of iron overload.
Monitoring

» Asymptomatic patients with normal SF at diagnosis should have annual TS and SF.
» If cirrhosis is present, surveillance for hepatocellular carcinoma with 6 monthly ultrasound scan and alpha feto protein levels.

Nutrition and Lifestyle

» Patients should be encouraged to eat a well-balanced diet and plenty of water.
» Patients should be advised to avoid iron supplements. There is no need for a patient undergoing phlebotomy to be prescribed a low-iron diet as the amount of iron removed by phlebotomy is far greater than that present in even a high-iron diet.
» Alcohol consumption should be kept to a minimum as moderate to heavy alcohol consumption increases the risk of cirrhosis by 10%. Abstinence is recommended in those with liver cirrhosis.
» Patients with elevated body iron should avoid raw shellfish because of the risk of Vibrio vulnificus (bacterial food poisoning)

Useful Information

This leaflet was produced following development of the Model of Care for Hereditary Haemochromatosis and Model of Care for Therapeutic Phlebotomy

Irish Haemochromatosis Association
http://www.haemochromatosis-ir.com/


Hereditary Haemochromatosis – Diagnosis & Management from a GP Perspective
http://www.icgp.ie/go/library/catalogue/item/486CC79B-01FF-FE00-8856BF5F4EFEE76D