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# GENETIC HAEMOCHROMATOSIS INFORMATION SHEET

## PHYSIOLOGY

Genetic Haemochromatosis (GH) is an inherited condition leading to raised iron absorption from the gut. If untreated there is excessive iron deposition in liver, pancreas, heart, endocrine organs, joints and skin leading to cirrhosis and failure of other organs. Recently the genetic defect responsible for most cases of the disease has been identified.

## PRESENTATION

Genetic haemochromatosis may present with liver dysfunction of any severity, endocrine dysfunction, arthritis, skin pigmentation or cardiac failure. Other common presentations include abnormal pathology tests, particularly iron studies or liver function tests, and following investigation of family members of an affected individual. Occasionally an abnormality in tissue density from an imaging test may suggest the diagnosis.
The clinical findings of the disease do not usually become apparent before the age of 20 with 50% of men showing clinical signs by the age of 40. Women tend to present with clinical findings later, presumably due to protection from iron loss during menstruation and parturition. Changes in some blood parameters precede the clinical feature by some years and genetic abnormalities can be detected at any age.

## GENETICS

The most common genetic defect is the replacement of a cysteine amino acid with a tyrosine at position 282 (C282Y) in the HFE gene. This gene codes for a cell-surface protein present in a wide range of tissues, particularly the liver and the small intestine. With the C282Y defect this protein is not expressed on the cell surface. The disease is autosomal recessive requiring two defective genes for full clinical expression. This genetic defect has been implicated in 80 – 100 % of cases of GH in Caucasians but is rarely the cause in Afro-American. Another defect, a histidine to aspartic acid substitution at position 63 (H63D) has been identified however the risk for persons carrying this gene is very low compared to those with C282Y homozygosity.

## LABORATORY TESTS AND GH

*Iron studies:*

The classic findings of GH are an increased serum ferritin, low transferrin, elevated iron and a raised transferrin saturation. These changes are usually first seen when the patient is in the late teens or early twenties and become progressively more marked with advancing years. These parameters, particularly iron and therefore iron saturation, show a very high random variation within individuals and abnormal results should be repeated on a fasting sample for confirmation. Patients who consume significant amounts of alcohol may give LFT and iron study results similar to patients with GH. Remeasurement after abstinence from alcohol for a period of several weeks may assist in identifying these persons. Patients with a fatty liver may also have disturbed iron studies.

Serum ferritin is recommended for the monitoring of treatment of GH with venesection with the goal to bring the ferritin to the lower end of the reference interval with a target of about 50 ug/L.

*Liver function tests:*

The initial changes seen in GH are raised ALT and AST due to hepatocyte damage following iron deposition in these cells. Advanced disease may show the changes of cirrhosis with low serum albumin and modest elevations of ALP, GGT and bilirubin. As a small rise in ALT may be the first marker of this condition, persistent elevations of ALT, not due to a known infective cause, should be investigated with measurement of iron studies.

*Genetic Testing:*

Tests are currently performed for the two known defects, C282Y and H63D. The Health Insurance Commission limits the performance of this test to the following circumstances:

1. the patient has an elevated transferrin saturation or serum ferritin on testing of repeated specimens.
2. the patient has a first degree relative with haemochromatosis.
3. the patient has a first degree relative with homozygosity for the C282Y genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis.

Homozygosity for C282Y with appropriate clinical findings or other laboratory results is diagnostic for GH. Note however that carrying 2 copies of the C282Y mutation does not always indicate GH, as up to 30% of women and 7% of men with this defect will not show iron overload.
Heterozygosity of C282Y does not lead to clinical disease from progressive iron loading, although abnormal biochemistry tests may be found. Organ damage may occur in these patients if there is co-existing hepatitis, alcoholism or porphyria cutanea tarda.
As indicated above the absence of the C282Y mutation does not fully exclude the possibility of GH, especially in Afro-Americans.
The meaning of finding the H63D gene is currently uncertain.

## LIVER BIOPSY

Liver biopsy maintains an important role in the diagnosis and management of patients with suspected GH. Liver biopsy is recommended for assessment of liver damage secondary to iron overload, particularly if the serum ferritin is greater than 1000 ug/L, in the presence of abnormal liver function tests, there are signs of established cirrhosis, or there is the possibility of multifactorial liver disease.

In addition, a biopsy remains vital for identifying the cause of liver impairment if the diagnosis is in doubt. Along with histological staining for iron, the liver iron concentration is measured. This result is corrected for the age of the patient, and therefore for the amount

of time that the patient has been absorbing iron, to produce the Hepatic Iron Index (HII = liver iron (umol/g) / patient age (years)). An HII greater than 2.0 is a strong indicator of GH.

## SCREENING RELATIVES

All first-degree relatives of patients identified with GH should be screened for the disease. In general, this should be done by measurement of iron studies from the age of 15 with genetic tests performed in response to abnormal results.

## HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is an important sequelae of liver damage secondary to GH. Serum alpha-foetoprotein should be measured regularly in these patients as a screen for this complication.

## REFERENCES

Powell, LW. Hereditary Haemochromatosis. Pathology 2000; 32:24-36.