

# General Guidelines for Health professionals

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# Haemochromatosis

## Introduction

- Hereditary haemochromatosis (HH) now easily screened for as most symptomatic individuals are homozygous for the C282Y mutation in the HFE gene
- 1 in 200 of Caucasian populations are homozygous
- There is variable expression ranging from asymptomatic (often just a raised transferrin saturation) to those with 'bronze diabetes'; many will have subtle symptoms and modest elevation of ferritin
- Penetrance depends on age, iron losses (blood donation or menstruation lessen burden) and alcohol use

## What to look for?

- Symptoms are non-specific and include: fatigue, arthralgia, loss of libido, abdominal pain
- Typical signs: hepatomegaly, diabetes, pigmentation, arthropathy (hips, knees and particularly 2nd and 3rd metacarpophalangeal joints)
- Check iron indices in anyone with raised ALT and in those with combination of above symptoms / signs

## Investigating suspected haemochromatosis

- If raised ferritin and transferrin saturation, send 5mls EDTA blood sample for HFE genotyping to Molecular Genetics Laboratory, Box 143 Addenbrookes Hospital
- If homozygous then family screening as below

## When to refer to hepatology?

- HH with ferritin > 1000mg/L or raised ALT, or non-HH iron overload: refer to Hepatology as may need liver biopsy
- HH with ferritin < 1000 and normal ALT: no biopsy as minimal risk of liver fibrosis but

venesect if ferritin > 400 (refer Hepatology or local venesection service if available, aiming for ferritin of 50)

- NB non-HH genotype + mildly raised ferritin / ALT = likely fatty liver

## **Family screening for relatives of C282Y homozygotes or C282Y/H63D with abnormal iron studies**

- Siblings should have HFE / iron indices checked
- Children tested only when adult but can screen partner/spouse to see if carrier (children only at risk if spouse is carrier = 10% chance)
- Parents if symptoms suggestive of HH (The risk is low otherwise)
- HH genotype + ferritin <200: reassure and monitor 2-5 yearly (less frequent if female, compound heterozygote, or no evidence of iron accumulation)
- HH genotype + ferritin 200-400: reassure and suggest blood donation via NBS up to 4 x year to prevent further iron overload (check iron indices annually)
- HH genotype + ferritin >400 see 'When to refer to hepatology?' points 1 and 2
- Refer to Medical Genetics Dept Box 134, Addenbrooke's Hospital if: 1) index case genetics unknown 2) uncertain re counselling 3) index case not homozygous but family request (these cases may be advised by Genetics Clinic appointment or letter only)

Support group: **British Haemochromatosis Society**

Reference: Bradley-Smith, G., Hope, S., Firth, H.V., Hurst, J.A. 2010. Oxford Handbook of Genetics. Oxford University Press

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# Alpha-antitrypsin deficiency

## Introduction

Alpha1-antitrypsin deficiency (AATD) is a common disorder (1/1600-1/1800) characterized by a predisposition to emphysema and cirrhosis.

Alpha1-antitrypsin is a proteinase inhibitor. PiM is the normal protein. 10% of the European population are carriers for the S or Z variant. Common phenotypes are PiMM, PiMS, PiMZ, PiSS, PiSZ, and PiZZ. Null variants are rare and are only distinguishable from homozygotes by genotyping.

**Carrier status is common in the general population (1/10) with 4% (1/25) of North Europeans carrying the Z allele and 6% carrying the S allele.**

## Genetics

- Inheritance is autosomal recessive.
- If MZ parents have had a child with a ZZ phenotype and severe neonatal liver disease, there is a 1 in 4 risk for a subsequent ZZ child. However, because of the variable expressivity of the phenotype in alpha-1 antitrypsin, the chance that a subsequent ZZ child will also develop severe liver disease is estimated at 20-30%.

## Prenatal diagnosis / Preimplantation Genetic Diagnosis

- In practice, it is rarely requested.
- Where appropriate, refer to Clinical Genetics, Box 134 Addenbrookes Hospital.

## Family members

- The most important message for family members is not to smoke.
- Because carrier status is so common in the general population (10%, 1/10) and because so few ZZ individuals experience severe neonatal liver disease, screening of

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the entire family for carrier status is rarely appropriate.

## **Close relatives of an individual affected with AATD**

- It is appropriate to offer phenotyping to parents and siblings of an affected individual.
- The possibility that apparently healthy parents of a ZZ or SZ child may themselves be ZZ or SZ should be borne in mind when offering phenotyping.
- Clotted sample (serum) for alpha-1 antitrypsin phenotyping could be arranged from primary care after adequate discussion and with appropriate consent, or patient could be referred for specialist advice and investigation. If interpretation of phenotyping is problematic, it may be necessary to proceed to genotyping (seek advice from Clinical Genetics Box 134 Addenbrooke's Hospital).

NB. If alpha1-antitrypsin typing is to be attempted on an individual who has had a liver transplant, the alpha1-antitrypsin phenotype will reflect the genotype of the donor liver (since this protein is made in the liver) and mutation analysis (of DNA from lymphocytes) will be needed to determine the genotype of the transplant recipient.

**The most important message is not to smoke. Smoking greatly accelerates lung disease in AATD and markedly reduces life expectancy.**

Support Group: [Alpha-1 UK support group](#)

Reference: Bradley-Smith, G., Hope, S., Firth, H.V., Hurst, J.A. 2010. Oxford Handbook of Genetics. Oxford University Press