
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 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