



Molecular genetic testing for alpha1-antitrypsin deficiency

Introduction

Alpha1-antitrypsin (A1AT) deficiency (OMIM 613490) is an inherited disorder that may cause lung disease and/or liver disease. It is estimated that around 1 in 2000 people of European ancestry have this condition but many are undiagnosed. The symptoms of the condition and the age of onset are highly variable. Chronic obstructive pulmonary disease (COPD), including emphysema, persistent airflow obstruction and chronic bronchitis, is the most common manifestation in adults. In addition abnormal A1AT protein may cause severe liver disease in children and adults.

A1AT deficiency is characterised by low concentrations of the alpha1-antitrypsin protein in serum and plasma. This protein normally acts to protect tissues of the body from attack by enzymes that breakdown proteins. In particular A1AT controls activity of neutrophil elastase which is released from white blood cells in response to lung irritation. In the absence of A1AT regulation, excess neutrophil elastase disrupts the delicate tissues of the lungs resulting in early onset lung disease. The first signs of lung disease appear between the ages of 20 and 50 years and include shortness of breath, wheezing and persistent symptoms of recurrent respiratory infection or asthma that do not respond to treatment.

In addition certain genetic defects result in production of an insoluble A1AT protein by the liver. This accumulates in liver cells causing obstruction and eventually damages the liver cells resulting in liver disease. Affected neonates may present with neonatal jaundice and hepatitis, older children may present with cirrhosis and liver failure. Liver symptoms are unusual in adults but if cirrhosis is present there is a risk of hepatocellular carcinoma.

Not all patients with reduced A1AT in serum are symptomatic, however life style changes in particular cessation of smoking and the avoidance of dusty and polluted environments may delay onset of symptoms.

Mutations in the *SERPINA1* gene (OMIM 107400) underlie A1AT deficiency. The most common mutations in Northern Europeans are *SERPINA1* c.863A>T (traditionally referred to as *PiS*) which causes the protein change p.Glu288Val and c.1096G>A (traditionally referred to as *PiZ*) leading to the p.Glu366Lys change in the A1AT protein. Liver disease is associated with the

PiZ mutation because its protein product forms insoluble polymers. Individuals with the *PiZZ* and *PiSZ* genotypes are at risk of developing liver disease.

Lung disease associated with A1AT deficiency may be treated with bronchodilators, corticosteroids, aggressive treatment for respiratory infections and flu and pneumococcal vaccination, furthermore life-style changes to prevent lung irritation such as smoking cessation and avoiding environmental pollution are well-documented. Augmentation therapy with inhaled or injected A1AT may be effective at reducing the rate of deterioration in lung function. Aggressive evaluation is recommended for sub-clinical liver complications in patients with the risk genotypes *PiZZ* and *PiSZ*. Patients with severe liver disease may require liver transplantation.

Reasons for referral

Testing for A1AT deficiency is recommended for adult patients with COPD, adult onset diagnosis of asthma, family history of A1AT deficiency and chronic liver disease. In addition patients with bronchiectasis, panniculitis and unexplained vasculitis, particularly Wegener's granulomatosis type, are at increased risk of A1AT deficiency. Newborns, children and adults with unexplained liver disease should also be tested for alpha1-antitrypsin deficiency.

Service offered

Confirmatory diagnostic testing: molecular testing for the two common *SERPINA1* gene mutations, c.1096G>A p.Glu366Lys and c.863A>T p.Glu288Val. Genetic testing for other *SERPINA1* mutations is not currently available.

Target reporting time

5 working days

Sample type

3ml blood in EDTA anti-coagulant