Molecular Test for Alpha1-Antitrypsin Z and S Mutations

The UNC Hospitals Molecular Genetics Laboratory offers genetic testing for alpha1-antitrypsin (A1AT) enzyme deficiency. Mutations in the *Protease Inhibitor 1 (PI)* gene on chromosome 14 are associated with A1AT deficiency leading to lung and liver disease.

Biology of the Disease and Clinical Indications: A1AT deficiency is an autosomal recessive disorder with a prevalence of 1/2500 to 1/5000 in the US Caucasians. The A1AT enzyme is a plasma protein produced by the liver that helps control tissue degradation by complexing with a variety of proteases. In the lungs, the enzyme binds and inhibits elastase, a protease released by neutrophils which degrades elastin in the alveolar walls.

Over 90 genetic variants have been identified in the *PI* gene, the most common of which is the Z mutation resulting in the substitution of lysine for glutamate at position 342 (Glu342Lys). In approximately 15% of homozygous patients (Z/Z), the abnormal protein is not secreted from the liver, thus predisposing to cirrhosis, obstructive pulmonary disease and emphysema. The S variant, resulting in substitution of valine for glutamate at position 264 (Glu264Val), is a less common mutation. Homozygosity and heterozygosity for the S mutation have no phenotypic effect, however, a compound heterozygote for the Z and S mutations may be symptomatic.

Quantitative serum A1AT levels are an effective screen for A1AT enzyme deficiency. Homozygotes (Z/Z) have 15-20% of the normal plasma concentration whereas heterozygotes (Z/M) have 60% of normal levels. When quantitative serum A1AT levels are found to be abnormally low, DNA analysis is indicated to confirm a diagnosis of A1AT deficiency and to detect the specific mutation within the family.

Laboratory Testing for Z and S mutations: The preferred sample is ACD or EDTA anticoagulated blood (pale yellow top or lavender top, 3mls) which may be refrigerated up to 48 hours before analysis. Testing is done by PCR followed by pyrosequencing. Results are reported as homozygous (for S or Z), heterozygous, or normal.

References:

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2. Cox, DW Alpha-1 antitrypsin deficiency. In: Scriver CR, Beaudet AL, Sly WS, et al.,eds. The Metabolic and Molecular Bases of Inherited Disease. Eighth Edition. Volume 4. New York: McGraw-Hill, 2001:5559-5584.

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