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 *SERPINA1* gene, the most common of which is the Z mutation resulting in the substitution of lysine for glutamate at codon 366 (p.Glu366Lys, E366K). 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 codon 288 (p.Glu288Val, E288V), is a less common, milder mutation. Homozygosity and heterozygosity for the S mutation have no phenotypic effect, however, compound heterozygotes 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 *SERPINA1* Z and S mutations:
The preferred sample is 3 mL of blood in an ACD (yellow top) or EDTA (lavender-top), which may be refrigerated up to 48 hours. Molecular testing is performed using a TaqMan genotyping assay (Applied Biosystems). Genomic DNA is extracted from the blood sample, and targeted genomic regions are PCR amplified and detected by a TaqMan allelic discrimination assay.
Results are reported as homozygous (for S or Z), heterozygous, or normal.

References:

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2. Greene CM, Marciniak SJ, Teckman J, Ferrarotti I, Brantly ML, Lomas DA, Stoller JK, McElvaney NG. α1-Antitrypsin Deficiency. Nat Rev Dis Primers [Internet]. 2016 July 28 [cited 2021 Nov 13];2: article 16051. Available from: https://doi.org/10.1038/nrdp.2016.51.
3. Meseeha M, Attia M. Alpha 1 Antitrypsin Deficiency. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan [cited 2021 Nov 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442030/.
4. Online Mendelian Inheritance in Man (OMIM):

https://www.omim.org/entry/107400?search=Alpha%201%20anti&highlight=1%20alpha%20anti

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