Alpha-1 Antitrypsin Deficiency

Genetics

-Gene: SERPINA1 (alpha-1 antitrypsin; 14q32.1)

-AR

Clinical findings/Dysmorphic features

-Adult chronic obstructive pulmonary disease (COPD); lower lobe emphysema (damage to the air sacs (alveoli) in the lungs)

-Childhood and adult liver disease (obstructive jaundice and raised transaminases in kids; cirrhosis and fibrosis in adults)

-Age of onset: 60’s; 40-50yrs in smokers

Etiology

-One of the most common metabolic disorders in individuals with northern European heritage

-1 in 5,000-7,000 in North America and 1 in 1,500-3,000 in Scandinavia

Pathogenesis

-Low concentrations of alpha1-antitrypsin (AAT), a serine protease inhibitor (serpin)

-Lung: AAT expressed in and secreted by liver --> main function is to protect lung from proteolytic damage by binding and inhibiting neutrophil elastase (always in lung and increased in smokers) --> excessive destruction of elastin in the alveolar walls ("toxic loss of function")

-Liver: defective AAT polymerizes in hepatocytes ("loop-sheet polymerization") --> decreased secretion and intra-hepatocyte accumulation of AAT ("toxic gain of function")

Genetic testing/diagnosis

-Diagnosis:

1) Low serum conc. of AAT (most commonly used technique is nephelometry) --> nl: 100-220 mg/dL; in AATD with lung disease usually <57 mg/dL + either 2) or 3)

2) Functionally deficient AAT protein variant by protease inhibitor (PI) typing (by polyacrylamide gel isoelectric focusing (IEF) electrophoresis of serum)

3) Detection of biallelic SERPINA1 pathogenic variants

-PI\*M: most common allele in all populations

-PI\*Z: most common pathogenic allele --> deficient AAT ; homozygous individuals (PI\*ZZ) have severe AATD

-PI\*S: pathogenic --> deficient AAT; clinical consequence in the compound heterozygous state with 2nd pathogenic allele (e.g. PI\*SZ) and when serum AAT level is <57 mg/dL.

-Null alleles (designated PI\*QO) --> Pathogenic alleles --> no mRNA/no protein

-Targeted mutation testing of SERPINA (PI\*Z: 95% E342K)

Others

-AATD should be suspected in individuals with: 1) Chronic obstructive pulmonary disease (i.e., emphysema, persistent airflow obstruction, and/or chronic bronchitis) 2) AND/OR any of the following: liver disease at any age, including obstructive jaundice in infancy; C-ANCA positive vasculitis (i.e., GPA); necrotizing panniculitis