ALPHA-1 ANTITRYPSIN PHENOTYPES

Nomenclature and gene frequency

Alpha-1 antitrypsin (a1aT) exhibits considerable polymorphism and over 90 genetically determined variants of a1AT have been identified, most of which are associated with normal amounts and activity. The predominant normal variant is designated M and the most common variants associated with varying degrees of a1AT deficiency are the Z and S variants. The Z mutation is the most common cause of disease associated with a1AT deficiency.

Allele	Approx. Frequency	Disease susceptibility
M1	0.60 – 0.72	Normal phenotype
M2	0.14 – 0.19	Normal phenotype
M3	Rare	Normal phenotype
F, X, P saint albans	Rare	Normal phenotype
Pittsburgh	Rare	Haematological Disease
S	0.02 – 0.04	Emphysema
Z	0.01 – 0.02	Emphysema, Liver Disease
Mmalton	Rare	Liver Disease
Mprocida, Mheerlan	Rare	Emphysema
Null	Rare	Emphysema

Clinical Aspects

Patients who are homozygous for one of the deficiency alleles or heterozygous for any two deficiency alleles will have a reduction in a1AT levels, but not all are associated with disease.

The Z variants are the most clinically significant . a1AT levels in ZZ homozygotes are about 15% of normal and 10% develop juvenile cirrhosis due to hepatocellular damage. Men over 50 who are ZZ are at particular risk of cirrhosis and hepatoma.