

F PHENOTYPE

Is the PiF allele of alpha 1-antitrypsin associated with pulmonary disease?

Clin Genet. 1984 Jun;25(6):491-5.

Beckman G, Stjernberg NL, Eklund A.

Pulmonary function was studied in thirteen individuals heterozygous for the alpha 1-antitrypsin allele PiF. Respiratory symptoms were present in seven out of twelve individuals with the FM phenotype, of which five had pulmonary function impairment, mostly of the obstructive type. One patient with the phenotype FZ had bronchitic symptoms and a mild obstructive spirometry pattern. The results suggest a relationship between the PiF allele and chronic obstructive pulmonary disease, which is independent of the serum alpha 1-AT level.

PMID: 6610506 [PubMed - indexed for MEDLINE]

Pulmonary emphysema associated with the FZ alpha 1-antitrypsin phenotype.

Can Med Assoc J. 1981 Mar 15;124(6):737-42.

Cockcroft DW, Tennent RK, Horne SL.

In one family three brothers were found to have a moderate deficiency of alpha 1-antitrypsin associated with the unusual Pi (protease inhibitor) phenotype FZ. The Pi phenotypes of their six living siblings were found to be FM (in three), M (in two) and MZ (in one). The three FZ brothers all had moderate to severe obstructive airways disease, and two had at least moderately severe pulmonary emphysema. Additional risk factors included moderate cigarette smoking in two and prolonged exposure to grain dust in all three. The same risk factors applied to the six non-FZ siblings, but they had only mild symptoms and pulmonary dysfunction or no lung problems at all; one, a female smoker with the MZ phenotype, had probable early emphysema demonstrated radiologically. The three FZ men may have had reduced fertility, as they produced only 1 child among them, as compared with 39 among the other eight siblings. This family study thus suggests that individuals with the FZ phenotype are at risk for pulmonary emphysema and chronic obstructive airways disease, particularly in the presence of other risk factors, such as cigarette smoking and grain dust exposure.

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Kinetic characterisation of alpha-1-antitrypsin F as an inhibitor of human neutrophil elastase.

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Patients homozygous for the Z allele of alpha-1-antitrypsin (alpha 1AT) have very low serum levels and are predisposed to emphysema. There have also been reports of emphysema being associated with the heterozygous phenotype FZ. To investigate whether F alpha 1AT was dysfunctional, the inhibitory activity of F alpha 1AT against human neutrophil elastase (HNE) was compared with that of common alpha 1AT phenotypes. Time-dependent inhibition of HNE by alpha 1AT was used to calculate the association rate constant (k_{assoc}) for M, MZ, FM, FZ, F (partially purified from FZ or FS), Z and S alpha 1AT phenotypes in human sera. The results for k_{assoc} at 25 degrees C were 9.1 (SD 0.9), 9.7 (SD 0.9), 8.0 (SD 0.8), 4.0 (SD 0.4), 4.2 (SD 0.8), 5.1 (SD 0.6) and 8.6 (SD 0.6) $\times 10^6 \text{ M}^{-1}\text{s}^{-1}$ respectively. F was found to have reduced activity much like that of Z, the alpha 1AT most commonly associated with emphysema. MZ (low risk for disease) and FZ heterozygotes had similar intermediate alpha 1AT levels. However the in vivo inhibition time for FZ was almost three times longer than for MZ, indicating greater exposure to proteolytic damage from free elastase for FZ than MZ individuals. In conclusion, F alpha 1AT is expressed in serum at low normal levels but is dysfunctional in its ability to inhibit HNE. Individuals who coinherit the F and a deficiency allele such as Z or Null, are likely to have a high risk for the development of emphysema. The disease risk for F homozygotes remains to be determined.

Am J Hum Genet. 1991 Jun;48(6):1154-8

Kinetic characterisation of alpha-1-antitrypsin F as an inhibitor of human neutrophil elastase. Cook L, Burdon JG, Brenton S, Knight KR, Janus ED. Department of Chemical Pathology, St Vincent's Hospital, Melbourne, Vic. Patients homozygous for the Z allele of alpha-1-antitrypsin (alpha 1AT) have very low serum levels and are predisposed to emphysema. There have also been reports of emphysema being associated with the heterozygous phenotype FZ. To investigate whether F alpha 1AT was dysfunctional, the inhibitory activity of F alpha 1AT against human neutrophil elastase (HNE) was compared with that of common alpha 1AT phenotypes. Time-dependent inhibition of HNE by alpha 1AT was used to calculate the association rate constant (k_{assoc}) for M, MZ, FM, FZ, F (partially purified from FZ or FS), Z and S alpha 1AT phenotypes in human sera. The results for k_{assoc} at 25 degrees C were 9.1 (SD 0.9), 9.7 (SD 0.9), 8.0 (SD 0.8), 4.0 (SD 0.4), 4.2 (SD 0.8), 5.1 (SD 0.6) and 8.6 (SD 0.6) $\times 10^6 \text{ M}^{-1}\text{s}^{-1}$ respectively. F was found to have reduced activity much like that of Z, the alpha 1AT most commonly associated with emphysema. MZ (low risk for disease) and FZ heterozygotes had similar intermediate alpha 1AT levels. However the in vivo inhibition time for FZ was almost three times longer than for MZ, indicating greater exposure to proteolytic damage from free elastase for FZ than MZ individuals. In conclusion, F alpha 1AT is expressed in serum at low normal levels but is dysfunctional in its ability to inhibit HNE. Individuals who coinherit the F and a deficiency allele such as Z or Null, are likely to have a high risk for the development of emphysema. The disease risk for F homozygotes remains to be determined.

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