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Genetic aspects of the Pi system

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Summary

α_1-Antitrypsin can be shown to be polymorphic by starch gel electrophoresis. At present 19 different alleles are known which are inherited in an autosomal pattern and constitute the Pi system. In one phenotype called Pi type ZZ there is a virtual deficiency of plasma α_1-antitrypsin and about 230 such babies are expected in England and Wales every year.

α_1-ANTITRYPSIN is a plasma protein of mol. wt. of around 60,000, which contains sialic acid. It has this name because it migrates as an α_1-globulin on paper electrophoresis and because it inhibits trypsin and other proteolytic enzymes *in vitro*. Its function *in vivo* is unknown.

In 1965 Fagerhol and Braend demonstrated by a rather unusual form of starch gel electrophoresis that this protein is polymorphic. That is to say a number of different types of α_1-antitrypsin can be found in the Caucasian population. At about the same time Laurell and Eriksson (1963) noted an association between a deficiency of this plasma protein and emphysema among young adults. More recently an association between this deficiency and neonatal liver disease has been described. There are many reviews of the genetic (Fagerhol and Laurell, 1970), pulmonary (Hutchison, 1973) and hepatic (Sharp, 1971) aspects of this subject.

Fagerhol and Braend found that one electrophoretic pattern on their starch gel was common and this is now called Pi type MM. A pattern with additional bands running faster than usual was called FM and one with bands running slower than usual Pi type MS. Since then at least 19 apparent alleles have been found which have been named **B, D, E, F, F^2, G, I, L, M, P, S, V, W, W^2, X, Y, Y^2, Z** and **null.** These alleles have been named so that their relative order in the alphabet indicates their relative mobilities on a starch gel. These alleles could in theory be combined in 190 ways to give 190 different genotypes. In practice most types are so rare that we have only

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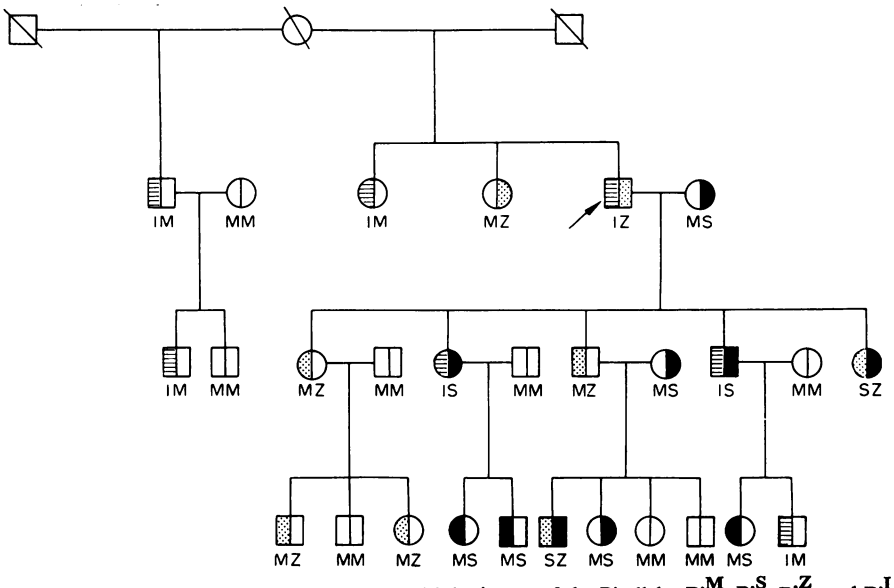

FIG. 1. A family demonstrating the autosomal inheritance of the Pi alleles **Pi^M, Pi^S, Pi^Z,** and **Pi^I.**

seen 25 amongst 10,000 samples during the last 5 years and a further 11 have been found in other countries.

These Pi genes have been shown to be inherited in a straightforward autosomal pattern, as illustrated in Fig. 1. The results of the two commonest types of marriage are:

Parents	Children		
	MM	MS	Exceptions
MM × MM	1185	0	4
MS × MM	124	125	0

These exceptions could be attributed to *in vitro* effects: ageing which increases the electrophoretic mobility and infection which slows the Pi bands. At present we do not know which chromosome carries the Pi genes, but we do know that they are on the same chromosome as the Gm genes which determine the constant part of the heavy chain of IgG (Gedde-Dahl *et al.*, 1972). However, these genes are a long way apart and there is no reason to suspect any functional connection between them.

The majority of the Pi alleles produce normal quantities of α_1-antitrypsin which we think functions normally. Only a few genes produce low levels. Pi^Z produces about 10% of normal, Pi^S, Pi^W and Pi^P produce about 60% of normal and Pi^{null} apparently produces nothing; at least when considered in terms of the plasma concentration. Pi^Z is difficult and Pi^{null} impossible to detect by the usual method of starch gel electrophoresis, so that the distinction between MM, MZ and Mnull is difficult. However, the MZ type can be detected by two dimensional crossed antigen antibody electrophoresis. In the past it has been claimed that Pi MM, MZ and ZZ phenotypes could be distinguished by biochemical or immunological assay alone. This is not so because healthy individuals of other phenotypes such as MS, SS and SZ can give over-lapping assay results as shown in Fig. 2. In addition inflammation, surgery, pregnancy, contraceptive therapy and steroid therapy can double the plasma α_1-antitrypsin concentration in every phenotype. The use of 'hospital controls' can be misleading.

The frequencies of the Pi types at birth in England and Scotland are:

Pi type	% of newborn population	Mean healthy adult plasma α_1-antitrypsin	
		as % of MM	in mg/100 ml
MM	86%	100	257±76
MS	9	80	229±60
MZ	3	65	171±42
SS	0·25	60	150±35
SZ	0·2	35	92±28
ZZ	0·029	10	17±10
Others	1·5	—	—

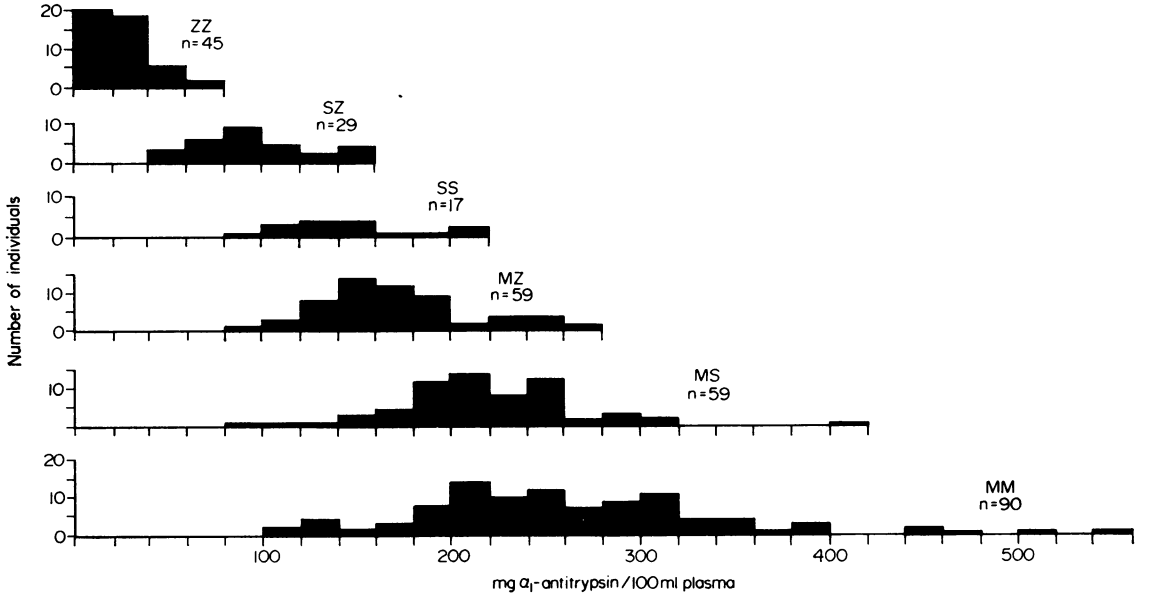

FIG. 2. α_1-Antitrypsin plasma concentrations of individuals classified by Pi type. Assays were carried out by the immunodiffusion method and expressed in terms of a commercial standard (Behringwerke) which had been assayed against a 'partially purified standard'. Thirty-nine of the ZZ samples were from patients, but all other samples were taken from apparently healthy individuals.

Pi ZZ is usually the only type of clinical importance although Pi SZ can sometimes cause confusion on assay and a few (perhaps 2%) SZ individuals can present with a similar clinical picture. We estimate that one baby in 3460 is born with α_1-antitrypsin deficiency (Pi type ZZ), so that in England and Wales about 230 are born each year. We do not think that more than 10–15% of these babies will suffer from liver disease, because of twenty-six Pi ZZ individuals who did not present with liver disease none gave a history of jaundice and none had lost brothers or sisters in childhood with jaundice.

The majority of parents of deficient individuals are of Pi type MZ, but because the gene frequency of $\mathbf{Pi^Z}=0{\cdot}017$ each parent has a 1 in 60 chance of being Pi ZZ. When a Pi ZZ individual is detected it is our normal practice to obtain a repeat sample of blood to confirm the findings and to test blood from the parents, sibs and children of the Pi ZZ individual. The chance of a sib being of Pi type ZZ is usually 1 in 4 (1 in 2 with a deficient parent), but the chance of a second Pi ZZ child suffering from liver disease when a previous sib has had liver disease remains to be quantified.

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