

# Genetic Variants of Serum Alpha 1 Antitrypsin

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## Abstract

Complete absence of data on alpha 1 antitrypsin in this country prompted us to determine serum levels using radial immunodiffusion (RID) and phenotypes by isoelectric focusing (IEF) in 100 healthy adults (52 males and 48 females). Mean serum alpha 1 antitrypsin concentration in healthy subjects was  $2.47 \pm 0.08$  g/l and the main phenotypes MM (70%), M1 M2 (28%) and FM 3(2%) are infrequent in our population (JPMA 45:245,1995).

## Introduction

Alpha 1 antitrypsin (alpha 1 AT), a glycoprotein, displays a high degree of genetic heterogeneity<sup>1</sup> and is referred to as the protease inhibitor (PI) system. More than 70 alleles of alpha 1 AT with a variable prevalence have been identified by isoelectric focusing indifferent populations<sup>2-4</sup>. The most common form of alpha 1 AT is the MM type in most populations<sup>5</sup> and corresponds to a normal amount of alpha I AT in serum. Other common variants include PiS, PiZ and PiF<sup>6</sup>, which are termed as deficient variants. This study was conducted to determine normal serum concentration and to identify alpha 1 AT phenotypes in the local population.

## Subjects and Methods

One hundred healthy adults with no family history of peptic ulcer disease, normal liver function tests and negative endoscopy who gave prior consent to participate in the study were selected. There were 52 males and 48 females. The age range was 18-82 years (mean 33 years). Venous blood samples were drawn with minimum stasis and the clotted blood was centrifuged at 4°C. All sera were stored at -70°C until analysed. Quantitative measurement of serum alpha I AT was carried out by single radial immunodiffusion (RID) technique using M partigen immunodiffusion plates (Behring Diagnostic, Marburg, Germany<sup>7</sup>), Phenotyping was performed by ultrathin layer isoelectric focussing (IEF). Further confirmation of alpha 1 AT phenotyping was done by immunofixation<sup>8</sup>.

## Results

Mean serum alpha 1 AT concentration in healthy controls was  $2.47 \pm 0.08$  (range 0.52-5.0 g/l). Mean values were almost similar in both sexes. The genetic variants were identified in healthy subjects by isoelectric focusing, a procedure of choice in evaluating the various phenotypes in normal population as well as in patients with diseases associated with alpha 1 AT deficiency. Atypical pattern of alpha 1 AT on IEF revealed that most of the normal individuals have a phenotype resembling MM (Figure 1).

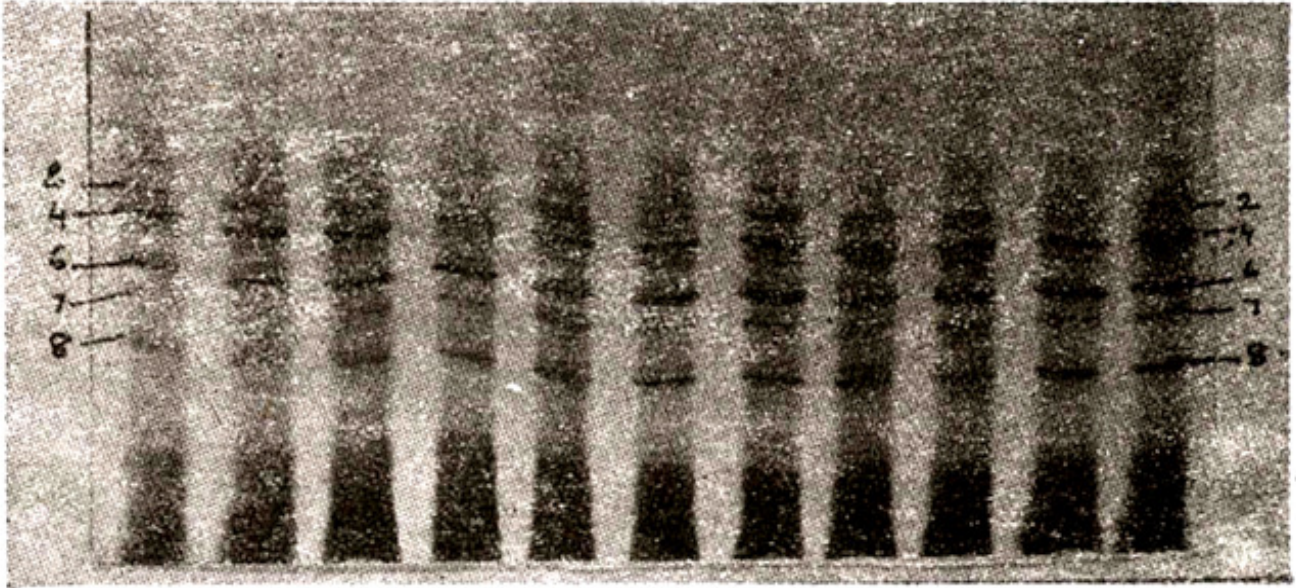


Figure 1. MM Phenotypes in healthy subjects.

All homozygous patterns consisted of two major bands designated as 4 and 6 together with three minor ones i.e., one anodal and two cathodal 7 and 8. - MM subtypes are presented in Figure 2.

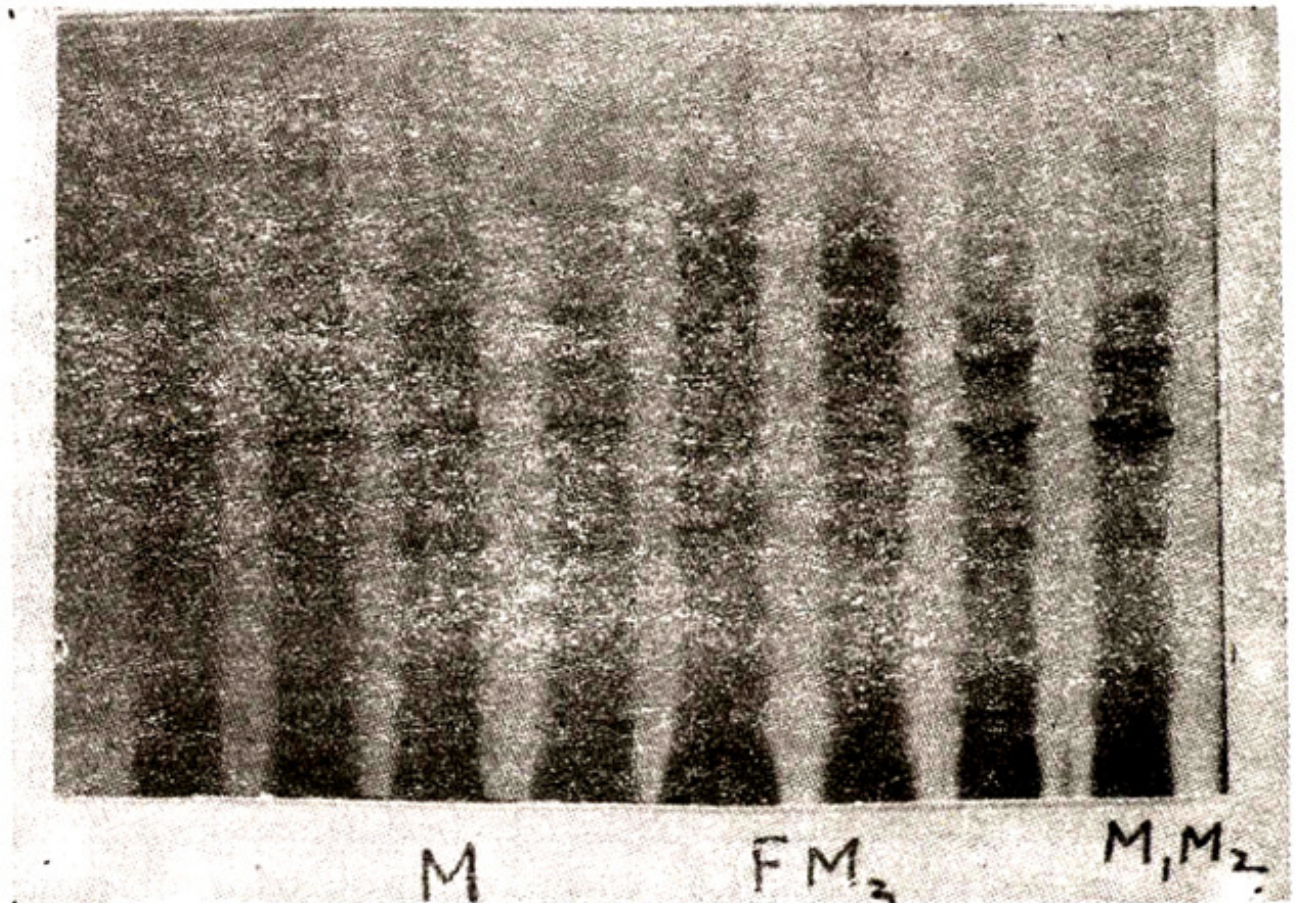


Figure 2. Various phenotypes in healthy subjects

Introduction of IEF with high resolution has revealed at least three subtypes which can be easily differentiated from one another. In the present study, MM was found in 70% of the healthy subjects followed by M1 M2(28%) and FM3 (2%):

## Discussion

Normal serum levels and phenotypes of Alpha 1 antitrypsin were determined in the local population. Quantitative measurement of serum alpha 1 AT in healthy subjects shows that serum values are similar to those reported in other populations<sup>9</sup>. Since alpha 1 AT is an acute phase reactant protein, those characterized by a rapid increase in synthesis during acute inflammation<sup>8</sup>, therefore simple measurements of its blood levels may not provide the effect information regarding the status of its genetic deficiency. It is, therefore, essential to determine the phenotype of alpha 1 AT by their characteristic patterns after isoelectric focusing of serum. We, therefore, performed, isoelectric focusing analysis of each individual sample to identify the most common phenotypes among this small group of population. This study indicates that MM overwhelmingly dominates all other less common phenotypes and thus could be regarded as the normal type in Pakistan. It seems that frequency of phenotypes associated with total and intermediate deficiency of alpha 1 AT is substantially less in this population.

## References

1. Fagerhol, M. K. and Braend, M Serum pre-albumin and polymorphism in man. *Science*, 1965;149:986-87.
2. Cox, D. W., Smyth, S. and Billingsley G. Three new rare variants of alpha 1 antitrypsin. *Hum. Genet.*, 1982;61 :123-26.
3. Cox, D. W, Johnson, A. M and Fagerhol, M. K. Report of nomenclature meeting for alpha 1 antitrypsin. *Hum. Genet.*, 1980;53:429-33.
4. Silverman, E. K., Miletich, J. P., Pierce, J. A. et al. Alpha 1 antitrypsin deficiency. *Am. Rev. Respir. Dis.*, 1989; 140:961-66.
5. Pongawong, P. and Schelp F. P Alpha 1 protease inhibitor phenotypes and serum concentrations in Thailand. *Hum. Genet.*, 1980;54:119-24.
6. Kellermann, G. and Walter, H. Investigations on the population genetics of alpha I antitrypsin polymorphism. *Hum. Genet.* 1970;10:145-50.
7. Mancini, O., Carbonara, A. O. and Heremans, J. F. Immunochemical quantifications of antigens by single radial immunodiffusion. *Immunochemistry*. 1965;2:235-54.
8. Jeppson, J. O. and Franzen, B. Typing of genetic variants of alpha 1 antitrypsin by isoelectric focusing. *Clin. Chem.*, 1982;28:219-25.
9. Perlmutter, D. H. and Pierce, J. A. The alpha 1 antitrypsin gene and emphysema. *Am. J. Physiol.*, 1989;56:147-162.