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The Deficient Alpha-1-Antitrypsin Phenotype PI P Is Associated with an A-to-T Transversion in Exon III of the Gene

To the Editor:

The rare deficient alpha-1-antitrypsin (α_1AT)) phenotype PI P (allele frequency within German population: 0.1%–0.2%) is associated with only 25%–30% of the normal serum concentration of α_1AT in the homozygous form (Fagerhol and Hauge 1968). Therefore, homozygotes of this PI type are at high risk of acquiring chronic obstructive pulmonary diseases. Recently,

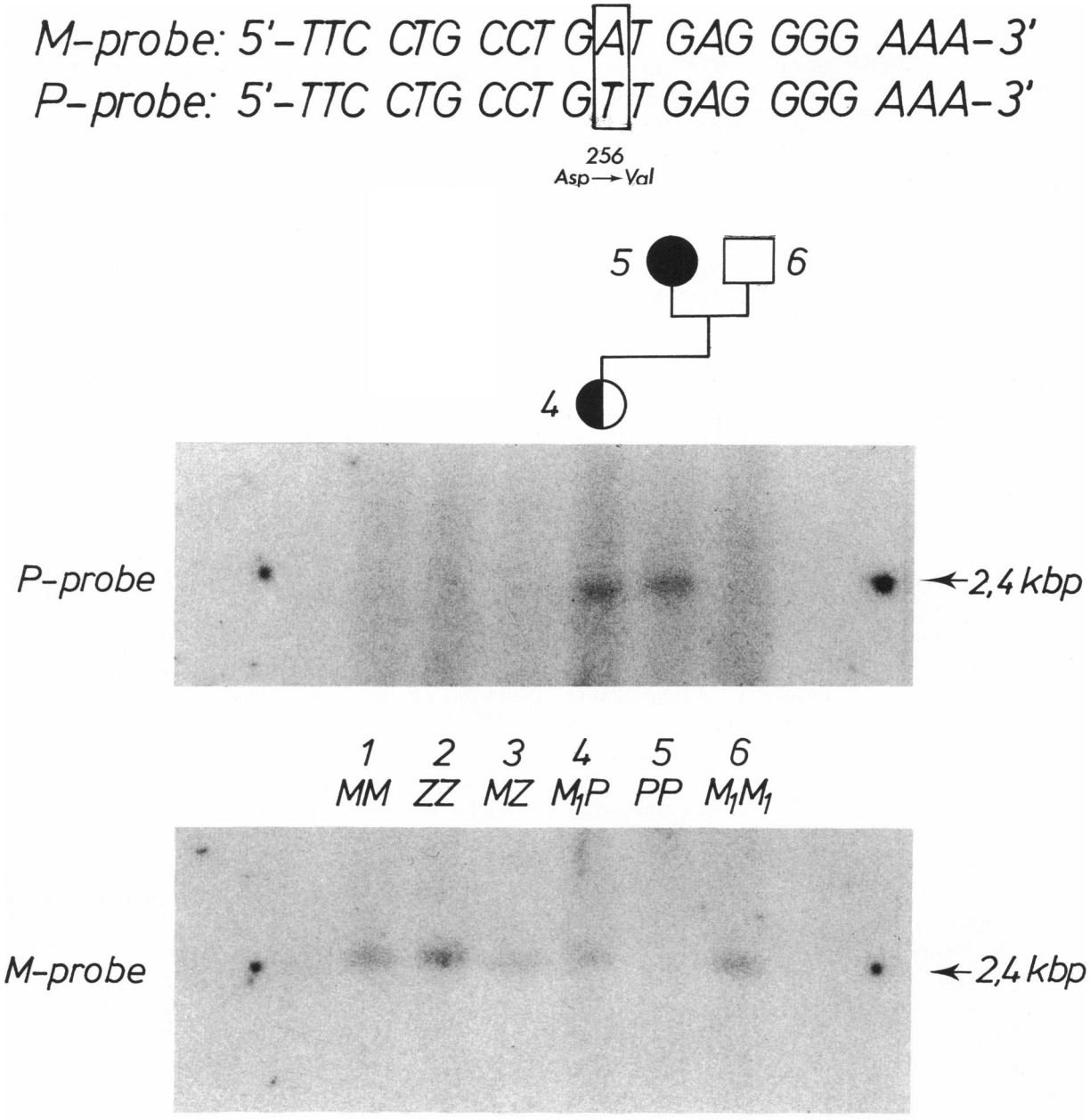

Figure 1 Detection of the exon III sequence difference between the normal M and the deficient P α_1AT genes by oligonucleotide probes. Shown at the top are the oligonucleotide probes used to detect the sequence around residue 256 for the normal M and for the deficient P gene. The sequences of the M/P oligonucleotides are based on data of Long et al. (1984). The mismatching nucleotides are boxed. At the bottom, autoradiograms of individuals homozygous or heterozygous for the M, P, and Z genes are shown. Genomic DNA of three members of a PI P–affected family (see pedigree) and, as control, of three unrelated PI Z and PI M individuals was digested with the restriction enzyme *Pst*I. Within the resulting 2.4-kbp fragment enclosing exons III and IV, the P probe hybridized only to the P gene (lanes 4 and 5). In contrast, the M probe hybridized only to the M and Z genes (lanes 1–4 and 6).

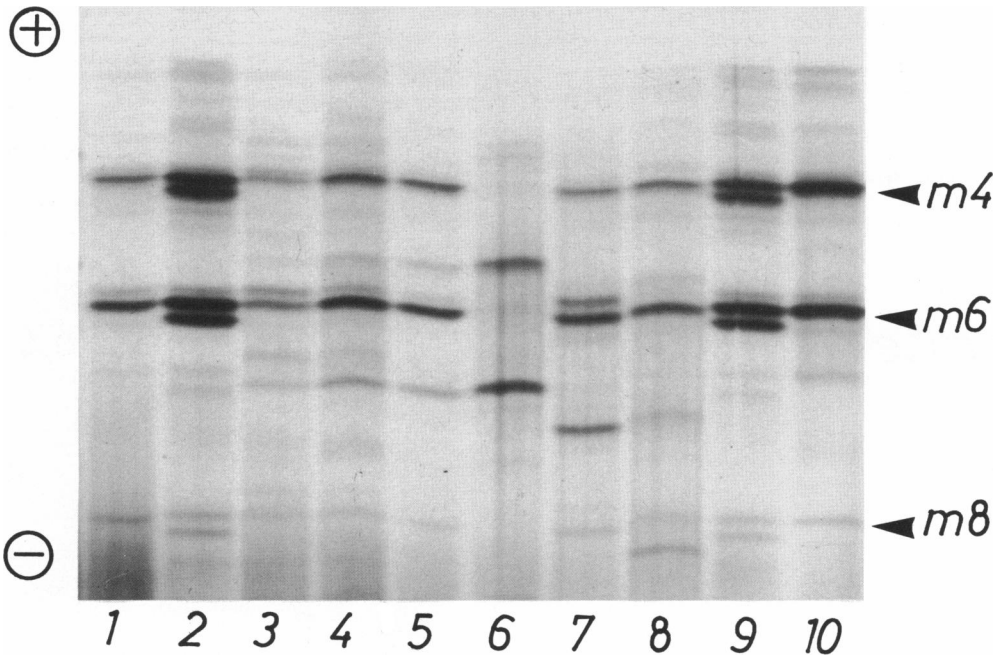

Figure 2 Presentation of PI phenotypes after IEF with pharmalytes in a polyacrylamide gel, pH range 4.2–4.9. Anode is at the top. From left to right, samples were (1) M1, (2) M1M2, (3) M1P, (4) M1P, (5) M1P, (6) P, (7) M3S, (8) M3Z, (9) M1M2, and (10) M1. The major IEF bands (m4, m6, and m8) for the various α_1AT M types are indicated by arrows.

by sequencing the entire α_1AT protein of an individual with the PI P phenotype, an amino acid substitution (Asp to Val) in position 256 of the polypeptide chain has been observed (Weidinger and Jeppson 1986; J.-O. Jeppsson, personal communication). We have tried to determine the precise nature of the mutation responsible for this substitution and to check whether this mutation is, in fact, always related to the PI P type. The only possible explanation for this amino acid substitution is an A-to-T transversion in exon III of the gene (M [GAT Asp^{256}] to P [GTT Val^{256}]). Following this assumption we constructed a pair of 21mer oligonucleotide probes directed at the sequence of interest around residue 256 and homologous to the mutant, as well as at the corresponding normal sequence (fig. 1).

Under experimental conditions as described elsewhere (Meisen et al. 1988), the resulting autoradiograms confirmed our supposition (fig. 1).

The family of the index case demonstrated that the PI P mutation was inherited in an autosomal codominant fashion. The 41-year-old female, being homozygous for the phenotype PI P, suffers from chronic obstructive pulmonary disease. In the case of this female, quantitative determination of serum α_1AT by radial immunodiffusion showed a value of 106 mg/dl during the last examination.

To address the question of whether there is an association between the detected point mutation and the PI P phenotype, we investigated three further, unrelated PI P–affected families. In all cases this A-to-T transversion was observed (results not shown).

When using the routine method of isoelectric focusing (IEF) on polyacrylamide gels (Weidinger et al. 1985) to determine the PI phenotype, it is relatively easy to discriminate between PI Z and PI P types (fig. 2). By use of the described oligonucleotide probes, a clear discrimination between both types is now also possible on the DNA level.

At present we have no explanation of how this mutation is able to produce such low serum α_1AT levels.

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