Intragenic Recombination within the Alpha-1-Antitrypsin Locus

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INTRODUCTION

The alpha-1-antitrypsin (Pi) system displays more than 60 alleles. The M allele is the most frequent with a frequency of 0.9463 in a Swedish population (Hjalmarsson 1988). More unusual alleles are the S, Z and F alleles. Furthermore, the M allele can be split into the suballeles M1, M2, M3 and M4. The amino acid sequences have been determined by DNA sequencing and the following genetic model for the Pi M suballeles has been suggested (Long 1984; Nukiwa 1988; Crystal 1989; Graham 1990).

Allele	Codons/amino acids at positions 101	376	Frequency
M1	Arg CGT	Glu GAA	0.6894
M2	His C<u>A</u>T	Asp GA<u>C</u>	0.1649
M3	Arg CGT	Asp GA<u>C</u>	0.0904
M4	His C<u>A</u>T	Glu GAA	0.0179

The nucleotide substitutions are underlined. The gene frequencies are according to Weidinger (1982).

MATERIAL and METHODS

Blood samples from 1048 families involved in paternity cases in Sweden have been subtyped for the Pi M alleles by isoelectric focusing (Hjalmarsson 1988). The Pi M3 and M4 alleles were not separated due to very small differences in charge.

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RESULTS and DISCUSSION

A mother-child exclusion which could not be explained by the presence of a silent allele was observed in the alpha-1-antitrypsin system (Pi). The mother was typed Pi M1,M2, the child Pi M3 and the father Pi M3,S. In addition to the Pi M system the family members have been typed for all genetic markers available at the institute, including HLA and DNA. The results have been verified after resampling. The probability of maternity is 0.992.

Table 1. Phenotypes of the family

Marker	Mother	Child	Father
ABO	B	O	O
MNSs	MS	MNS	NSs
Rh	CDe	CDe	CcDe
Fy	b	ab	a
Kk	k	k	k
Gm	-1.-2	1.-2	1.2
Hp	2,1	1	2,1
Gc	2,1S	1F,1S	1F,1S
Pi	M2,M1	M3	M3,S
Tf	2,1	2,1	1
F13B	1	2,1	2,1
PGM	a1	a1	a3,a1
EAP	BA	BA	BA
GLO	2	2,1	1
EsD	1	1	2,1
HLA	A2,28;B15,35	Aw19,28;B12,15	A9,w19;B12,27
D2S44	4.11,3.35	4.13,3.36	4.11,3,76

The most plausible explanation to the observed mother-child exclusion is an intragenic recombination in the oogenesis.

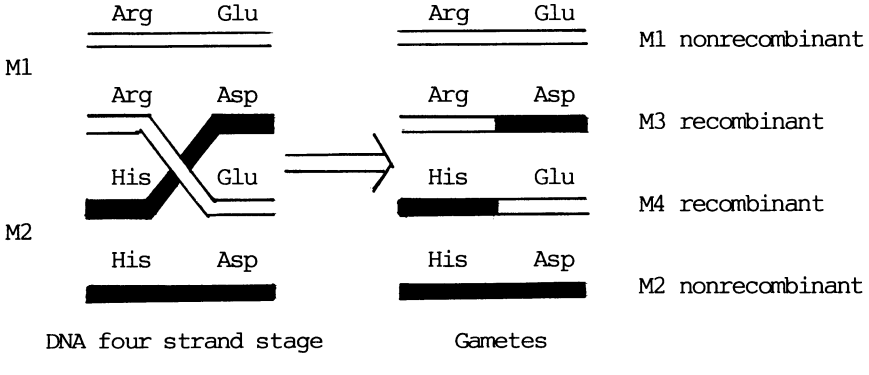

Fig. 1. Recombination scheme. Obviously the child Pi M3 has inherited the M3 (or M4) allele from the Pi M1,M2 mother after a crossover event in the meiosis. As can be seen in the figure new recombinants are only possible when all four amino acids are different, hence only by persons who belong

to the phenotypes Pi M1,M2 and M3,M4. Due to the difficulties in separating the M3 and M4 allele the genotype M3,M4 is defined as M3 by most investigators.

A possible sequence for the recombination events within the Pi M system is:

1. M1 —point mut.→ M3 2. M1 —point mut.→ M4 3. M3,M4 —crossover→ M2

Table 2. Parent-child pairs where a recombination may cause false exclusion (M3 includes M4)

Mother or Father	Child
M1,M2	M1,M3
	M3
	M2,M3
M3(M3,M4)	M1
	M1,M2
	M2

Another recombination within the Pi gene has been described by Bender et al. 1991 due to a crossover in the spermatogenesis.

Intragenic recombination within other genetic markers has earlier only been observed within the PGM 1 gene (Wetterling 1990). In these systems, as well as in others, the risk of false exclusions in paternity cases must be considered, when the alleles include amino acid substitutions at several different sites, distant enough to allow a crossover event.

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