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Transmission of the Pi^Z Allele for α_1-Antitrypsin Deficiency: Population Genetic Considerations

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Summary. It is shown that a simple preferential transmission of the Pi^Z allele by Pi^Z-heterozygous males for α_1-antitrypsin deficiency cannot maintain the observed polymorphism at the locus without invoking any viability or fertility selection against the Pi^Z gene carriers (heterozygotes or homozygotes). From the data on frequencies of Pi^Z alleles in Europe, the estimates of such selection coefficients are shown to be of the order of 5–20%, which seems too large for natural populations. Furthermore, an analysis of 26 nuclear families, each ascertained through a heterozygous Pi^Z or homozygous ZZ child, does not provide statistical evidence for such a hypothesis.

Introduction

Recently there has been considerable debate regarding the suggestion of preferential transmission of the Pi^Z allele by males, but not by females, heterozygous for α_1-antitrypsin (α_1AT) deficiency (i.e., Pi^Z carriers in heterozygous condition) (see, e.g., Iammarino et al. 1979, 1980; Chapuis-Cellier and Arnaud 1979; Cox 1980). While this hypothesis raises an intriguing possibility that a serum protease inhibitor (α_1AT) might be active in or on spermatozoa, it has been suggested more recently with the help of some new data that the apparent segregation distortion may be a result of the bias of sex-ratio and/or genotypes of the probands through which such families are ascertained (Constans et al. 1982). Furthermore, in electrophoretic surveys in various populations it has been demonstrated that the Pi^Z allele is found in low frequencies in a widespread area of Northern and Southern Europe (see the references in Table 3). It is therefore of interest to examine the population dynamic considerations of the segregation distortion hypothesis.

In this paper our object is to demonstrate that a segregation distortion in male heterozygotes (Pi^Z carriers) alone cannot maintain a polymorphism of the Pi^Z allele unless the Pi^Z gene carriers (homozygotes or heterozygotes) are subjected to a viability selection disadvantage to a certain degree. We therefore examine the condition for stable equilibria of genotype frequencies under the joint action of selection and segregation distortion in male heterozygotes. This treatment further indicates that in order to test the hypothesis of preferential transmission of the Pi^Z allele by male heterozygotes only we must estimate the relevant parameters from the family data and test for the significance of their departure from the null values (under the assumption that the Pi^Z allele is maintained in the population by Hardy-Weinberg equilibrium). We conducted such a test by considering the segregation of Pi^Z alleles in 26 families that have been reported by us earlier (Constans et al. 1982).

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Methods and Results

Condition for Stable Equilibrium of Pi^Z Allele under Preferential Transmission Model. At the α_1AT locus several alleles are found by electrophoretic, immunodiffusion, and isoelectric focusing techniques (e.g., M1, M2, M3, S, F, etc. in addition to Z). Since Pi^Z is the only allele involved in the preferential transmission hypothesis, let us consider only the three Pi-type genotypes: Pi^Z-homozygous (ZZ), Pi^Z-carriers (M_1Z, M_2Z, SZ, FZ, etc. jointly called MZ henceforth), and those not involving the Pi^Z allele (e.g., M_1M_1, M_1M_2, M_1S, M_2F, etc. jointly represented by MM). In a large infinite random mating population, let the frequencies of the three types MM, MZ and ZZ at a particular generation be u, v and w, respectively ($u+v+w=1$). From the published data on population frequencies there is no indication of sex differences of genotype frequencies and hence we shall assume that the genotype frequencies are the same in both sexes. Let θ be the probability that a M-gamete (i.e., anything other than Pi^Z gametes) is transmitted by a Pi^Z heterozygote male. The probability that such a male would contribute the Z-gamete is, therefore, $1-\theta$. The preferential transmission of Z-allele would thus translate into a value of θ less than 0.5. Under this hypothesis, the heterozygote females contribute the two gametes in equal frequencies. Furthermore, we assume that the fitness values for the three genotypes, MM, MZ and ZZ are 1, 1 and $1-s$, respectively ($0 \le s \le 1$). Note that by doing so, we are essentially assuming that the selection against the Pi^Z allele operates via a selection disadvantage against Pi^Z-homozygous individuals. In theory, even though an underdominant selection model could be an alternative model of selective disadvantage, since most disease association studies with α_1AT implicate the Pi^Z-homozygous individuals and no significantly increased disease susceptibility is seen among heterozygotes, the above selection model seems to be biologically more relevant (see Vogel and Motulsky 1979, pp. 172–173, for a brief review).

Under this model, the mating types, their frequencies, and the segregation probabilities can then be represented by expressions given in Table 1.

The respective genotype frequencies in the adult population of the next generation are then given by

$$\begin{aligned} Tu' &= (u+\theta v)(u+v/2) \\ Tv' &= u(w+v/2)+(v+w)(u+v/2)+\theta v(w-u) \quad \text{and} \\ Tw' &= (1-s)(w+v/2)[(1-\theta)v+w] \end{aligned} \tag{1}$$

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where T, the average fitness of the next generation is given (so as to make $u' + v' + w' = 1$) by

$$T = \theta v + (u + v/2)(1 - \theta v) + (w + v/2)[u + (1 - s)\{w + (1 - \theta)v\}].$$

Table 1. Mating types, frequencies, and segregation probabilities for the transmission of Pi^Z allele

Mating type[a] and frequency			Children[a]		
Father	Mother	Frequency	MM	MZ	ZZ
MM	MM	u^2	1	0	0
MM	MZ	uv	$1/2$	$1/2$	0
MM	ZZ	uw	0	1	0
MZ	MM	uv	θ	$1-\theta$	0
MZ	MZ	v^2	$\theta/2$	$1/2$	$(1-\theta)/2$
MZ	ZZ	vw	0	θ	$1-\theta$
ZZ	MM	uw	0	1	0
ZZ	MZ	vw	0	$1/2$	$1/2$
ZZ	ZZ	w^2	0	0	1

[a] The M allele represents the collection of all alleles other than the Pi^Z allele. Thus MM, and MZ types in fact comprise collections of several genotypes (see text)

Following Karlin (1968) we can then determine the condition for protected polymorphism (none of u, v or w equal to unity) by examining the eigenvalues of the transmission matrix, $\underline{A}$ which relates the vector of genotype frequencies $\underline{U} = (u, v, w)$ in two successive generations by $\underline{U} = \underline{A}\underline{U}$ at two boundaries $\underline{U} = (0, 0, 1)$ and $\underline{U} = (1, 0, 0)$ which yields $\theta < 1/2$ and $s > 1/2 - \theta$.

Thus, if the preferential transmission of the Pi^Z allele has to operate only through the Pi^Z heterozygote males (i.e., if $\theta < 1/2$), the Pi^Z allele will be found in non-zero frequencies in the equilibrium population only if the ZZ genotypes have a selective disadvantage of magnitude $s > 1/2 - \theta$.

In general, explicit solutions to the set of recurrence equations (1) are difficult to obtain. However, starting with some arbitrary initial values u_0, v_0 (and $w_0 = 1 - u_0 - v_0$) for specific values of s and θ satisfying $(0 < \theta \leq 1/2, 1/2 - \theta < s \leq 1)$ through grid search method we have shown that globally stable polymorphic genotype frequencies can be obtained by iteration using the recurrence relationships as given in equation (1). Table 2 presents the equilibrium genotype frequencies (u_e, v_e) for selected values of θ and s.

As mentioned before, electrophoretic surveys for Pi^Z alleles show that the allele is widespread in its occurrence in Europe, particularly in the northern areas (see references in Table 3).

Table 2. Equilibrium *MM* and *MZ* genotype frequencies (u_e, v_e) for various values of s and θ

θ	s			
	0.01	0.05	0.1	0.5
0.499	(0.809, 0.181)	(0.959, 0.040)	(0.979, 0.021)	(0.995, 0.005)
0.497	(0.490, 0.421)	(0.883, 0.113)	(0.940, 0.059)	(0.988, 0.012)
0.495	(0.250, 0.501)	(0.810, 0.180)	(0.902, 0.095)	(0.980, 0.020)
0.490	[a]	(0.641, 0.321)	(0.811, 0.180)	(0.960, 0.039)
0.450	[a]	[a]	(0.256, 0.513)	(0.814, 0.181)

[a] Inadmissible (s, θ) combination, since $s < 1/2 - \theta$ in these cases

Table 3. Distribution of α_1-antitrypsin phenotypes in 14 European populations

Population	Sample size (n)	Relative genotype[a] frequencies (%)			Source
		MM	MZ	ZZ	
Northern Sweden	1869	98.34	1.66	0.00	Beckman et al. (1980)
Northwestern Finland	300	97.33	2.67	0.00	Beckman et al. (1980)
Finland	136	97.70	2.30	0.00	Frants and Eriksson (1978)
Norway	2830	96.93	3.00	0.07	Fagerhol (1967)
Finland	548	97.26	2.74	0.00	Arnaud et al. (1977)
Finland	223	99.10	0.90	0.00	Fagerhol et al. (1969)
Southern England	926	95.68	4.21	0.11	Arnaud et al. (1979)
Ireland	1000	96.10	3.90	0.00	Blundell et al. (1975)
France (Bretagne)	280	95.35	4.65	0.00	Sesboue et al. (1978)
France (Pyrenean groups)	1386	97.40	2.60	0.00	Constans (unpublished data)
Germany	1474	97.69	2.24	0.07	Hoffmann and van den Broek (1976)
Germany	408	98.78	1.22	0.00	Cleve et al. (1979)
Northern Italy	202	98.02	1.98	0.00	Klasen et al. (1978)
Central and Southern Italy	500	97.20	2.60	0.20	Piantelli et al. (1978)
Pooled	12,082	97.26	2.70	0.04	

[a] The M allele represents a collection of all alleles other than the Pi^Z allele. Thus, MM and MZ types in fact comprise collections of several genotypes (see text)

Table 4. Data on genotypic distribution of 26 nuclear families

Genotype of proband	Genotypes of		No. of families	No. of children in each family	Genotypic distribution of children in each family		
	Father	Mother			MM	MZ	ZZ
MZ	MM	MZ	5	1	0	1	0
MZ	MM	MZ	4	2	1	1	0
MZ	MM	MZ	2	2	0	2	0
MZ	MM	MZ	1	4	2	2	0
MZ	MZ	MM	3	1	0	1	0
MZ	MZ	MM	4	2	0	2	0
MZ	MZ	MM	1	2	1	1	0
MZ	MZ	MM	1	3	2	1	0
MZ	MZ	MZ	1	1	0	1	0
MZ	MZ	MZ	1	6	3	3	0
ZZ	MZ	MZ	2	1	0	0	1
ZZ	MZ	MZ	1	2	0	0	1

Table 3 presents a compilation of α_1AT genotype frequencies in each of 14 population surveys.

As seen from Tables 2 and 3, in order to maintain the observed genotype frequencies at this locus, even with an average preferential transmission of 0.001 of the Z-gamete (i.e., $\theta = 0.499$) by Pi^Z-heterozygous males, the selection coefficient operating against the ZZ individuals has to be rather high—between 5–50%. This result is not surprising in view of the facts that: (1) a preferential transmission of the Pi^Z allele would tend to increase its frequency in the population; whereas, (2) the frequency of the Pi^Z allele in most populations is fairly low; and, therefore, in order to maintain such low frequencies, a strong selection must operate against individuals carrying the Pi^Z allele.

Likelihood Analysis of Family Data. Constans et al. (1982) recently reported data on 26 nuclear families each of which was ascertained through exactly one child (homozygous or heterozygous Pi^Z individuals). The data are summarized in Table 4.

In order to test if the data provide any evidence for the preferential transmission of the Pi^Z allele by Pi^Z heterozygous males we conducted a likelihood ratio test to contrast the two hypotheses: (1) preferential transmission of the Pi^Z allele by Pi^Z heterozygous males ($\theta < 1/2$) with a selection coefficient s ($s > 1/2 - \theta$) operating against the ZZ individuals, and (2) no preferential transmission and no selection hypothesis ($\theta = 1/2$, $s = 0$).

To derive the likelihood expression, let us consider a family with r children where r_1, r_2 and r_3 are the number of children of genotypes MM, MZ and ZZ, respectively ($r_1 + r_2 + r_3 = r$). Let π_i be the probability that an individual of genotype i ($i = 1$ for MM, 2 for MZ and 3 for ZZ individuals) is a proband through which the family is identified. Suppose that the parental genotypes in this family are j and k (j and k also take values 1, 2 or 3 like i as stated above). The likelihood of observing such a family is then given by, following Elandt-Johnson (1971, p. 467)

$$L_i = \frac{r!}{r_1! r_2! r_3!} p_{1jk}^{r_1} p_{2jk}^{r_2} p_{3jk}^{r_3} \frac{[1-(1-\pi_i)^{r_i}] f_{jk}}{\sum_{m,n} f_{mn} [1-(1-\pi_i p_{imn})^r]} \quad (2)$$

where p_{ijk} = probability that an offspring from a parental mating, $j \times k$ is of genotype i ($i, j, k = 1, 2$ or 3), and f_{jk} = probability that the parental mating is of the type, $j \times k$; and the summation $\sum_{m,n}$ is taken over all mating types, $m \times n$ that can potentially produce an offspring of genotype i.

If π_i is much smaller than one (single ascertainment, as in the case of the 26 families being considered here), we can express $(1-\pi_i)^n \cong 1 - n\pi_i$, and $(1-\pi_i p_{ijk})^n \cong 1 - n\pi_i p_{ijk}$ and thus the likelihood, L_i, of equation (2) becomes approximately equal to

$$L_i \cong \frac{(r-1)!}{(r_i-1)! \prod_{j \neq i} r_j!} \frac{f_{jk}}{\sum_{m,n} f_{mn} p_{imn}} p_{1jk}^{r_1} p_{2jk}^{r_2} p_{3jk}^{r_3} \quad (3)$$

where as before $\sum_{m,n}$ is taken over all mating types $m \times n$ which can potentially produce an offspring of genotype i.

For the data presented in Table 4, we can then write the likelihoods of 26 families in three groups (using the segregation probabilities as given in Table 1) as:

Likelihood of the twelve MM × MZ families,

$$L_{MM \times MZ} = \frac{3}{2^{21}} \left(\frac{uv}{A}\right)^{12};$$

Likelihood of the nine MZ × MM families,

$$L_{MZ \times MM} = \theta^3 (1-\theta)^{13} \left(\frac{uv}{A}\right)^9;$$

Likelihood of the five MZ × MZ families,

$$L_{MZ \times MZ} = \frac{5}{2^{10}} \theta^3 (1-\theta)^4 \frac{v^{10}}{A^2 B^3}; \quad (4)$$

where $A = v/2 + u(v + 2w) + \theta v(w - u)$ and $B = w^2 + vw(1-\theta)/2 + v^2(1-\theta)/2$.

Combining the three parts of equation (4), the pooled likelihood of the 26 families is given by

$$L_1 = \frac{15}{2^{31}} \theta^6 (1-\theta)^{17} \frac{u^{21} v^{31}}{A^{23} B^3}. \quad (5)$$

Table 5. Numerical evaluations of the likelihood L_1[a] for various of θ. The values of u and v used in these computations are $u=0.9726$, $v=0.0270$ (weighted average of the 14 population surveys of Table 3)

θ	0.10	0.15	0.20	0.25	0.27	0.30	0.37	0.40	0.49	0.499
L_1	0.33	1.42	2.84	3.62	3.63	3.34	1.96	1.37	0.29	0.24

[a] $[L_1 \times 10^{-54}$, eq. (5)]

Under the preferential transmission with selection model, the likelihood L_1 is a function of θ and s as u, v, A and B are all implicitly functions of the two parameters. Using the weighted averages of the genotype frequencies (over the 14 population surveys of Table 3), $u=0.9726$ and $v=0.0270$, we have computed the value of L_1 [as given by equation (5)] for various values of θ. The results are presented in Table 5, from which it is seen that the likelihood L_1 reaches a maximum of 3.628×10^{-54} for $\theta=0.27$.

On the other hand, under the hypothesis of no preferential transmission and no selection model ($\theta=1/2$, $s=0$), the likelihood of the 26 families as given in equation (5) reduces to

$$L_2 = \frac{15}{2^{47}} p(1-p)^{51} \qquad (6)$$

since in this case $u=(1-p)^2$, $v=2p(1-p)$ and $w=p^2$ where p represents the frequency of the Pi^Z allele in the population. The maximum likelihood solution for p [obtained by taking the derivative of equation (6) and equating it to zero] is given by 0.019 ± 0.005 which agrees fairly well with the pooled gene frequency estimate from the 14 samples of Table 2 ($\hat{p}=0.014 \pm 0.001$). The maximum value of the likelihood is numerically equal to 7.613×10^{-16}. It is, therefore, seen that the likelihood of the 26 families is at least 2.1×10^{38} times higher than that under the hypothesis of no preferential transmission of the Pi^Z allele.

Discussion

From the foregoing analysis it is clear that in order to explain the maintenance of the observed frequencies of Pi^Z genotypes in the 14 different European populations by the hypothesis of preferential transmission of the Pi^Z allele by Pi^Z heterozygous males, the necessary selective disadvantage against the ZZ individuals needs to be rather severe (5–50%). A selection model that would make only the heterozygous Pi^Z-gene carriers selectively disadvantageous will require an even stronger selection coefficient to counter-balance the advantage conferred to the Pi^Z allele by means of the segregation distortion hypothesis. Although the strong association of α_1AT polymorphism and chronic obstructive pulmonary disease and childhood cirrhosis of the liver (see Vogel and Motulski 1979 for a review) may impose some such selective disadvantage for the ZZ homozygotes, the likelihood analysis of the 26 families reported here does not support this preferential transmission hypothesis satisfactorily. In this connection, it must be noted that the likelihood L_2 [as given in equation (6)], which is a function of the Pi^Z allele frequency only, may be supported by some other selective mechanism as well, not involving preferential transmission of the Pi^Z allele. One such mechanism could be a mutation-selection balance. If this is true, then the necessary selective disadvantage, s, to counteract the pressure of recurrent mutations of the order 10^{-5} needs to be of the order 2.77% (since in this case $p=\sqrt{\mu/s}$ and hence $s=\mu/p^2$; μ being the mutation rate at this locus. While there is no direct evidence of recurrent mutations at the α_1AT locus, and even if it is so, the mutation rate could be much smaller than 10^{-5}, this simple computation merely illustrates that for any other selective mechanism that can simultaneously explain the family as well as the population data need not involve the inordinate high value of selective disadvantage against the Pi^Z homozygote individuals.

In this connection the analogy of the α_1AT system in man with other known systems that involve the maintenance of deleterious gene complexes in wild populations by transmission-ratio distortion is worth making. Such examples include mouse *t*-complex (see Bennett 1975 and Silver 1981 for recent reviews), segregation distorter (SD) factors in Drosophila (see Hartl and Hiraizumi 1976; Crow 1979), and the spore killer (SK) complex in Neurospora (Turner and Perkins 1979) etc. In all these systems, along with the observed segregation distortion a strong selective disadvantage of the gene carriers (of the form of viability and/or fertility disadvantage) is well documented in the population at large, without which the maintenance of the genes in polymorphic frequencies in natural populations would be hard to obtain.

A further property that is shared by all these other transmission-ratio distortion systems is the suppression of recombination over the localized region of chromatin encompassing the deleterious genes (Silver 1979). Given the recent discovery of the molecular structure of the variation of α_1AT system in man (e.g., see Carrell et al. 1982), the direct test of the segregation distortion hypothesis may have to be based on molecular data.

It may therefore be concluded that while the present analysis does not favor the preferential transmission of the Pi^Z allele by heterozygous males, the exact nature of the selection mechanism at this locus is not evident from the current findings as well. In this connection it is worthwhile mentioning that Suarez and Pierce (1982) have also reached a similar conclusion on the basis of a different reasoning.

In order to explain the association of the Pi^Z allele with chronic obstructive pulmonary disease and childhood liver cirrhosis and the clinical variation of the Pi^Z allele in Europe, obviously, more detailed study would be needed to understand the nature of the selective mechanism operating at this locus.

Our contribution, therefore, is not so much to arrive at a definite conclusion of the Pi^Z-related preferential transmission hypothesis debate. But we introduced, in our opinion, a more appropriate statistical methodology and our contention is that the previously advocated methodologies are somewhat inappropriate to deal with the controversy.

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