GENE CONVERSION AT THE GRAY LOCUS OF *SORDARIA FIMICOLA*: FIT OF THE EXPERIMENTAL DATA TO A HYBRID DNA MODEL OF RECOMBINATION

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Manuscript received April 27, 1984

Revised copy accepted November 9, 1984

ABSTRACT

A hybrid DNA (hDNA) model of recombination has been algebraically formulated, which allows the prediction of frequencies of postmeiotic segregation and conversion of a given allele and their probability of being associated with a crossing over. The model considered is essentially the "Aviemoore model." In contrast to some other interpretations of recombination, it states that gene conversion can only result from the repair of heteroduplex hDNA, with postmeiotic segregation resulting from unrepaired heteroduplexes. The model also postulates that crossing over always occurs distally to the initiation site of the hDNA. Eleven types of conversion and postmeiotic segregation with or without associated crossover were considered. Their theoretical frequencies are given by 11 linear equations with ten variables, four describing heteroduplex repair, four giving the probability of hDNA formation and its topological properties and two giving the probability that crossing over occurs at the left or right of the converting allele.—Using the experimental data of Kitani and coworkers on conversion at the six best studied gray alleles of *Sordaria fimicola*, we found that the model considered fit the data at a *P* level above or very close (allele *h4*) to the 5% level of sampling error provided that the hDNA is partly asymmetric. The best fitting solutions are such that the hDNA has an equal probability of being formed on either chromatid or, alternatively, that both DNA strands have the same probability of acting as the invading strand during hDNA formation. The two mismatches corresponding to a given allele are repaired with different efficiencies. Optimal solutions are found if one allows for repair to be more efficient on the asymmetric hDNA than on the symmetric one. In the case of allele *g1*, our data imply that the direction of repair is nonrandom with respect to the strand on which it occurs.

GENETIC recombination arises from reciprocal crossing overs and from nonreciprocal gene conversion or postmeiotic segregation (PMS) of at least one of the two recombining alleles. Holliday and Whitehouse (see WHITEHOUSE 1982) have proposed that these three modes of recombination result from a hybrid DNA (hDNA) intermediate forming a half-chromatid chiasma between the two recombining chromatids. On this model, PMS corresponds to unrepaired heteroduplex sites on the hDNA, conversion is due to their repair and crossover is generated by the cleavage of the half-chromatid chiasma lead-

ing to chromatid exchange (HOLLIDAY 1964; MESELSON and RADDING 1975). Alternatively, conversion may be due to some kind of extrareplication rather than to the repair of an heteroduplex site (see SZOSTAK *et al.* 1983 for a revival of this idea). In addition, recent observations suggesting that the crossing over site is not necessarily contiguous to the hDNA cast some doubt on the relation between crossing over and hDNA postulated by the model (SANG and WHITEHOUSE 1983; THEIVENDIRARAJAH and WHITEHOUSE 1983). The present work examines the more widely accepted version of the hDNA model [formulated by MESELSON and RADDING (1975) and generally referred to as the "Aviemoire model"] and asks whether it can account quantitatively for the distribution of PMS, conversion and their associated crossovers at the gray locus of *Sordaria fimicola*. This locus was chosen because of the particularly extensive data available, thanks to the work of Kitani and coworkers (reviewed by KITANI and WHITEHOUSE 1974).

The amenability of the hDNA model to an algebraic analysis has been discussed previously (WHITEHOUSE 1965; EMERSON 1966; PAQUETTE and ROSSIGNOL 1978; FINCHAM, HILL and REEVES 1980). Given a few assumptions on the properties of hDNA formation and of heteroduplex repair, the frequencies of the various classes of conversion and PMS are linear functions of variables such as γ (meiotic probability of having a hDNA at the site considered), α (probability that the hDNA is asymmetric), β (probability that the asymmetric hDNA is formed on the mutant chromatid) and δ (probability that the invading strand generating the hDNA has the 5'3' polarity). Four other variables define the probability that the two mismatches corresponding to a given allele (depending on which chromatid the hDNA is formed) are repaired (p and q) and that this repair generates the wild-type allele rather than the mutant one (r and s). The papers cited above analyzed monofactorial crosses (wild type $\times$ mutant) with only five detectable classes of conversions and PMS. The corresponding equations cannot contain more than four independent variables if 1 d.f. is kept to test the goodness of fit of their solutions. Since four variables would already be needed to describe heteroduplex repair, oversimplifying assumptions must be introduced to limit the number of variables to four (1 d.f.) or five (0 d.f.). This difficulty can be overcome when closely linked flanking markers are present in the crosses because crossovers associated with conversion or PMS become detectable. Consequently, a larger number of different classes of events can be analyzed, allowing the use of a larger number of variables (KALOGEROPOULOS and THURIAUX 1982).

We present a system of 11 linear equations that give the frequencies of 11 types of conversion and PMS in function of ten independent variables which, in addition to the eight variables γ , α , β , δ , p , q , r and s mentioned before, include two variables giving the probability of having a crossing over at the left (G) or the right (D) of the converting allele on the chromosome map of KITANI and OLIVE 1967. Solutions fitting the experimental data at a P level greater than or very close to 5% were found for the six mutants of gray analyzed in more detail by Kitani and coworkers and showed that the model considered essentially accounts for the distribution of conversion, PMS and associated crossovers at that locus.

TABLE 1
Segregation patterns of the gray alleles

Allele	Type of aberrant asci											Total no. of aberrant asci	Total no. of asci
	a	b	c				d				e		
			Ra-1	Ra-2	Rp-1	Rp-2	Ra-1	Ra-2	Rp-1	Rp-2			
<i>g1</i>	400	28	99	73	84	66	23	4	13	10	23	823	405,418
<i>g6</i>	60	5	31	17	18	23	9	4	9	9	17	201	89,334
<i>g7</i>	71	9	42	15	24	32	8	7	12	12	43	271	124,617
<i>h2</i>	40	20	68	29	36	51	63	23	19	42	285	676	323,445
<i>h4</i>	5	16	17	5	7	4	37	12	13	26	49	191	91,607
<i>h5</i>	31	9	31	17	11	21	16	7	3	4	59	209	98,585

Data from KITANI and WHITEHOUSE (1974). Symbols for aberrant segregations (+ = wide type, m = mutant): a = 6+:2m; b = 2+:6m; c = 5+:3m; d = 3+:5m; e = aberrant 4+:4m. Ra-1, Ra-2, Rp-1, Rp-2 as defined by KITANI and WHITEHOUSE (1974). Ra-1 and Ra-2 correspond to genotypes with a parental distribution of the flanking markers, in which the spore pair involved in the conversion event but not showing postmeiotic segregation shows no recombination between the flanking markers and *g* (Ra-1) or recombination on both sides of *g* (Ra-2). Rp-1 and Rp-2 correspond to genotypes in which the same spore pair shows recombination between *g* and M (Rp-1) or *g* and N (Rp-2).

MATERIALS AND METHODS

The conversion and PMS pattern of the six gray alleles considered have been determined by Kitani and coworkers and are summarized in Table 1. Classes a, b and e correspond to the 6+:2m, 2+:6m and aberrant 4+:4m listed in Table 5 of KITANI and WHITEHOUSE (1974). Classes c and d correspond to the 5+:3m and 3+:5m segregations, with Ra-1, Ra-2, Rp-1 and Rp-2 denoting the distribution of associated crossovers as defined by these authors.

Equations (1) to (11) were solved by the method of the least chi-square value using iterative computation. The variables were allowed to vary between 0 and 1, except for γ , *G* and *D*. For γ , the range was between 0.001 and 0.004, since the observed frequencies of aberrant segregation are between 1.9 and 2.3×10^{-3} per meiosis (KITANI and WHITEHOUSE 1974). *G* and *D* were allowed to vary between 0 and 0.6, as the total frequency of crossovers associated with aberrant segregations does not exceed 0.6.

Two iterative computing procedures were used. In one of them (KALOGEROPOULOS and THURIAUX 1982), the variables are allowed to vary simultaneously by steps of 0.3 (0.003 for γ) in the first round of iteration, with increasingly narrow ranges down to 0.01 (0.00001 for γ) in the following ones. In the second procedure, only one variable is allowed to vary at a time by steps of 0.01 (0.00001 for γ). The calculation was made in three phases. (1) Each variable but one received an arbitrary value obtained by a generator of random numbers except for *G* and *D* (initial value 0.25) and for γ (initial value 0.002). The solution giving the lowest chi-square for the variable tested was retained for the following iterations, in which the other variables were tested one after the other. (2) The process was repeated, but this time the initial values were the ones retained at the end of phase 1. These iterations were carried on until a minimal chi-square value was obtained for each variable. (3) Phases 1 and 2 were repeated six times, starting each time from a new set of randomly generated values.

Both procedures gave almost identical best fitting solutions, but the second was more rapid. The chi-square values were calculated against the experimental data of Table 1. A correction for coincidental crossing overs (crossing overs unrelated to the conversion or PMS event considered but occurring between the two flanking markers of gray) was introduced using the method of SANG and WHITEHOUSE (1979) but was found hardly to alter the results (data not shown) because of the small genetic distances involved (see KITANI and OLIVE 1967). Several families of solutions are given in Table 2. This is partly due to symmetric solutions such that, if δ is replaced by $1-\delta$,

there is a permutation between p and q , r and s . In addition, several alleles gave different, nonsymmetric sets of solutions with an almost identical goodness of fit.

RESULTS

Construction of the equations giving the frequencies of the various classes of conversion and PMS in a three-factor cross (wild type $\times$ mutant with two flanking markers): Table 1 lists the 11 classes of conversion and PMS (with or without associated crossing over) analyzed in the present work. Their probability is given by the following equations:

$$a = \gamma N \{ (1 - \alpha)pqrs + \alpha\beta(\delta qs + (1 - \delta)pr) \} \quad (1)$$

$$b = \gamma N \{ (1 - \alpha)pq(1 - r)(1 - s) + \alpha(1 - \beta)(\delta p(1 - r) + (1 - \delta)q(1 - s)) \} \quad (2)$$

$$\begin{aligned} cRa-1 = \gamma N \{ (1 - \alpha)(1 - G - D)(\delta p(1 - q)r + (1 - \delta)q(1 - p)s) \\ + \alpha\beta(1 - G - D)(\delta(1 - q) + (1 - \delta)(1 - p)) \} \end{aligned} \quad (3)$$

$$cRa-2 = \gamma N \{ (1 - \alpha)(1 - G - D)(\delta(1 - p)qs + (1 - \delta)pr(1 - q)) \} \quad (4)$$

$$\begin{aligned} cRp-1 = \gamma N \{ (1 - \alpha) \{ pr(1 - q)(\delta G + (1 - \delta)D) + (1 - p)qs(\delta D + (1 - \delta)G) \} \\ + \alpha\beta G(\delta(1 - q) + (1 - \delta)(1 - p)) \} \end{aligned} \quad (5)$$

$$\begin{aligned} cRp-2 = \gamma N \{ (1 - \alpha) \{ (1 - p)qs(\delta G + (1 - \delta)D) + pr(1 - q)(\delta D + (1 - \delta)G) \} \\ + \alpha\beta D(\delta(1 - q) + (1 - \delta)(1 - p)) \} \end{aligned} \quad (6)$$

$$\begin{aligned} dRa-1 = \gamma N \{ (1 - \alpha)(1 - G - D)(\delta(1 - p)q(1 - s) + (1 - \delta)p(1 - r) \\ \cdot (1 - q)) + \alpha(1 - \beta)(1 - G - D)(\delta(1 - p) + (1 - \delta)(1 - q)) \} \end{aligned} \quad (7)$$

$$\begin{aligned} dRa-2 = \gamma N \{ (1 - \alpha)(1 - G - D)(\delta p(1 \\ - r)(1 - q) + (1 - \delta)(1 - p)q(1 - s)) \} \end{aligned} \quad (8)$$

$$\begin{aligned} dRp-1 = \gamma N \{ (1 - \alpha) \{ (1 - p)q(1 - s)(\delta G + (1 - \delta)D) + p(1 - r) \\ \cdot (1 - q)(\delta D + (1 - \delta)G) \} + \alpha(1 - \beta)G(\delta(1 - p) + (1 - \delta)(1 - q)) \} \end{aligned} \quad (9)$$

$$\begin{aligned} dRp-2 = \gamma N \{ (1 - \alpha) \{ p(1 - r)(1 - q)(\delta G + (1 - \delta)D) + (1 - p) \\ \cdot q(1 - s)(\delta D + (1 - \delta)G) \} + \alpha(1 - \beta)D(\delta(1 - p) + (1 - \delta)(1 - q)) \} \end{aligned} \quad (10)$$

$$e = \gamma N(1 - \alpha)(1 - p)(1 - q) \quad (11)$$

The ten variables used in these equations are defined in the introduction. Equations (1), (2) and (11) are identical with equations (1), (2) and (7) of KALOGEROPOULOS and THURIAUX (1982). Equations (3), (4), (7) and (8) give the frequencies of the 5+:3m and 3+:5m segregations with a parental (non-crossover) distribution of flanking markers. They correspond to the tritypes (Ra-1) and tetratypes (Ra-2) of SANG and WHITEHOUSE (1979) or to the c_r , c_s , d_r and d_s of KALOGEROPOULOS and THURIAUX (1982). They were directly derived from equations (3) to (6) of the latter work by introducing a factor $(1 - G - D)$ denoting the lack of crossing over.

FIGURE 1.—Formation of the cRp-1 class of 5+:3m segregation on symmetric and asymmetric hDNA. The base pairs corresponding to the wild-type and to the mutant information are denoted ab and xy , with a and x being carried on the "5'3'" strand and b and y being carried on the "3'5'" strand. Asymmetric hDNA formation on the wild-type chromatid (probability $\gamma\alpha(1-\beta)$) cannot generate a 5+:3m segregation. Asymmetric hDNA formation on the mutant chromatid with the hDNA initiated from the left of the gray locus cannot generate 5+:3m segregants of the Rp-1 type. The resulting equation is $cRp-1/N = \gamma(1-\alpha)\{\delta(Gpr(1-q) + D(1-p)qs) + (1-\delta)(G(1-p)qs + Dpr(1-q))\} + \gamma\alpha\beta G(\delta(1-p) + (1-\delta)(1-q))$.

The reasoning leading to equations (5), (6), (9) and (10) is illustrated in the case of (5) by Figure 1 [equations (6), (9) and (10) are easily reconstructed by analogy]. Equation (5) gives the frequency of the 5+:3m segregations of the Rp-1 type, that is of those 5+:3m which are associated with a crossover between gray and *mat*, the flanking marker located on the left of gray. The model depicted in Figure 1 is based on two assumptions. First, the "outer" (noncrossed) strands of the half-chromatid chiasma are cut and joined to generate a whole-chromatid exchange, *i.e.*, to form a crossing over (HOLLIDAY 1964). Second, the migration of the hDNA along the chromatid is unidirectional, *i.e.*, if it has been initiated on one side of the converting allele, its resolution and, consequently, the site of the crossing over must be on the other side of the allele, since back migration of the half-chromatid chiasma toward the initiation site is not allowed. Although both assumptions are plausible, they are largely hypothetical and, in particular, there is no strong argument against the occurrence of back migration. Should the latter occur, our system of equations would still hold provided that heteroduplex repair always follows the resolution of the half-chromatid chiasma leading to crossing over.

5:3 segregations are formed either on a symmetric hDNA or on an asymmetric one located on the mutant chromatid. The first term of equation (5) includes a factor $(1 - \alpha)$ giving the probability of having a symmetric hDNA. If the single strands exchanged are the one carrying the b and y information (probability given by the factor δ) and if the hDNA has been initiated from the right of the converting allele, a Rp-1 segregation will require a crossing over on the left side (probability G) combined with the nonrepair of the b/x heteroduplex site (probability $1 - q$) and the repair of the a/y heteroduplex site toward the strand carrying the wild-type information ab (probability pr). If the exchanged strands carry the a and x information (probability $1 - \delta$) with the hDNA initiated from the right of the converting allele, the crossing over on the left side (probability G) must be combined with the nonrepair of a/y (probability $1 - p$) and the repair of b/x toward the strand carrying the wild-type information (probability qs). A mirror situation is observed when the Rp-1 segregation is due to a hDNA initiated on the left of the converting allele (leading with a probability D to a crossing over on the right side). The second term of equation (5) corresponds to the 5:3 generated on the asymmetric hDNA formed on the mutant chromatid (hence, the factor $\alpha\beta$). In that case, an Rp-1 segregation can only be observed if the hDNA has been initiated from the right of the allele (leading with a probability G to a crossing over on the left side) and if there is no repair of the heteroduplex site. Depending on the invading strand, this heteroduplex site will be of the x/b type (probability δ) or of the a/y type (probability $1 - \delta$), with a frequency of nonrepair given by $1 - q$ and $1 - p$, respectively. The sum of all of these terms gives equation (5).

Goodness of fit of a general model (ten variables) and of two simplified ones such that $\beta = 0.5$ (chromatid parity of the asymmetric hDNA) or $\delta = 0.5$ (equal probability of each strand being the invading one): Table 2 gives the best fitting solutions for the ten variables of equations (1) to (11) with the experimental data of Table 1. Three alleles (*g1*, *g6* and *g7*) give fitting solutions at a *P* level greater

TABLE 2

Best fitting solutions for the general model described by equations (1) to (11)

Allele	α	β	δ	p	q	r	s	G	D	γ ($\times 10^{-5}$)	χ^2
<i>g1</i>	0.28	0.50	0.46	0.67	0.93	0.55	0.99	0.32	0.15	298	1.73*
<i>g6</i>	0.34	0.50	0.41	0.41	0.82	0.96	0.78	0.20	0.29	269	1.64*
	0.49	0.96	0.31	0.80	0.32	0.62	0.65	0.20	0.29	276	1.64*
<i>g7</i>	0.17	0.50	0.00	0.52	0.69	0.76	0.78	0.20	0.32	260	3.26*
	0.45	0.99	0.00	0.56	0.49	0.64	0.50	0.20	0.32	262	3.25*
<i>h2</i>	0.19	0.53	0.00	0.33	0.31	0.51	0.66	0.06	0.39	227	6.25
	0.26	0.48	0.50	0.28	0.29	0.64	0.60	0.07	0.38	225	6.29
<i>h4</i>	0.30	0.50	0.25	0.58	0.25	0.14	0.54	0.12	0.30	243	3.89
	0.45	0.26	0.50	0.17	0.50	0.89	0.19	0.12	0.30	234	3.88
<i>h5</i>	0.27	0.70	0.33	0.45	0.44	0.69	0.67	0.00	0.36	243	6.24
	0.22	0.99	0.00	0.50	0.43	0.55	0.66	0.00	0.36	248	6.23
	0.19	0.50	0.00	0.44	0.50	0.69	0.75	0.00	0.36	245	6.24

* Chi-square values correspond to $P \geq 0.05$ (1 d.f.).

than 5%, whereas one allele (*h4*) gives a chi-square value of 3.89, which is very close to the 5% level of sampling error. For each allele, there is always one set of solutions with β close to 0.5 and one with δ close to 0.5, which prompted us to test submodels such that $\beta = 0.5$ (or $\delta = 0.5$). In that case, a second degree of freedom becomes available. For both submodels, the best fitting solutions (Tables 3 and 4) correspond to a P level greater than (*g1*, *g6*, *g7*, *h4*) or close (*h2*, *h5*) to the 5% threshold ($\chi^2 = 5.99$). Their goodness of fit can be improved if one allows for a different efficiency of repair between the symmetric and asymmetric hDNA. This is expressed by multiplying p and q in the terms corresponding to the asymmetric hDNA by a corrective factor E . In that case (Tables 3 and 4), five of the six alleles give fitting solutions at the 5% level, with allele *h4* giving a chi-square value very close (3.88) to the threshold value of 3.84. E is always ≥ 1 , which would imply a more efficient repair on the asymmetric hDNA.

*Inadequacy of simplified models such that $\alpha = 0$ (fully symmetric hDNA), $\delta = 0$ (constant chemical polarity of the invading strand) or $r = s = 0.5$ (random direction of mismatch repair) in explaining the segregation of *g1*.* We have previously found that a model implying a fully symmetric hDNA ($\alpha = 0$) did not at all account for the segregation pattern of *g1*, although it did account for the segregation of the other alleles (KALOGEROPOULOS and THURIAUX 1982, table 9). The model required, however, that $\delta = 0$. With the system of equations (1) to (11), we are now in a position to test a model imposing a fully symmetric hDNA ($\alpha = 0$) as well as a model imposing that the invading strand has always the same polarity ($\delta = 0$) with no constraint on any other variable. Table 5 shows that neither hypothesis can account for the properties of *g1*, since the best

TABLE 3

Best fitting solutions when $\beta = 0.5$

Allele	α	δ	p	q	r	s	G	D	γ ($\times 10^{-5}$)	E	χ^2
<i>g1</i>	0.28	0.46	0.67	0.93	0.55	0.99	0.32	0.15	298		1.73*
	0.37	0.47	0.61	0.92	0.52	0.99	0.31	0.15	288	1.09	0.97*
<i>g6</i>	0.34	0.41	0.41	0.82	0.96	0.78	0.20	0.29	269		1.64*
	0.34	0.41	0.41	0.82	0.96	0.78	0.20	0.29	269	1.00	1.64*
<i>g7</i>	0.17	0.00	0.52	0.69	0.76	0.78	0.20	0.32	260		3.26*
	0.03	0.00	0.56	0.71	0.64	0.81	0.20	0.32	265	1.37	3.20*
<i>h2</i>	0.16	0.00	0.34	0.39	0.49	0.69	0.06	0.39	228		6.25
	0.24	0.07	0.30	0.29	0.48	0.70	0.08	0.37	233	1.63	2.14*
<i>h4</i>	0.30	0.25	0.58	0.25	0.14	0.54	0.12	0.30	243		3.89*
	0.26	0.23	0.59	0.30	0.11	0.64	0.12	0.30	251	1.05	3.88
<i>h5</i>	0.30	0.00	0.39	0.46	0.85	0.70	0.00	0.36	240		6.23
	0.39	0.00	0.32	0.39	0.92	0.72	0.02	0.34	241	1.50	3.25*

For each allele, the first row of numbers correspond to an equal efficiency of repair of symmetric and asymmetric heteroduplexes (2 d.f.) and the second row to an enhanced efficiency of repair for asymmetric heteroduplexes ($E \geq 1$, 1 d.f.). * Chi-square values correspond to $P \geq 0.05$.

TABLE 4

Best fitting solutions with $\delta = 0.5$

Allele	α	β	p	q	r	s	G	D	γ ($\times 10^{-5}$)	E	χ^2
<i>g1</i>	0.35	0.67	0.92	0.66	0.99	0.48	0.32	0.14	298		1.98*
	0.42	0.67	0.92	0.60	0.99	0.50	0.32	0.15	289	1.07	1.38*
<i>g6</i>	0.39	0.71	0.81	0.39	0.73	0.88	0.20	0.29	266		1.64*
	0.39	0.70	0.39	0.81	0.89	0.73	0.20	0.29	267	1.00	1.64*
<i>g7</i>	0.35	1.00	0.57	0.56	0.58	0.68	0.20	0.32	263		3.25*
	0.52	1.00	0.34	0.64	0.02	0.76	0.21	0.31	297	1.48	2.54*
<i>h2</i>	0.26	0.48	0.28	0.29	0.64	0.60	0.07	0.38	225		6.29
	0.32	0.48	0.13	0.35	0.89	0.53	0.08	0.37	228	1.73	1.97*
<i>h4</i>	0.44	0.25	0.22	0.49	0.98	0.12	0.11	0.31	240		3.90*
	0.45	0.25	0.49	0.19	0.18	0.90	0.12	0.30	236	1.00	3.90
<i>h5</i>	0.26	0.68	0.46	0.43	0.70	0.67	0.00	0.36	243		6.25
	0.41	0.69	0.53	0.16	0.85	0.04	0.01	0.35	253	1.88	2.90*

* Chi-square values correspond to a probability of sampling error P above 5% (2 d.f.).

TABLE 5

Best fitting solutions with $\alpha = 0$ or $\delta = 0$ or $r = s = 0.5$

Allele	α	β	δ	p	q	r	s	G	D	γ ($\times 10^{-5}$)	χ^2
<i>gl</i>			0.48	0.80	0.94	0.34	0.97	0.37	0.09	400	10.19
	0.72	1.00		0.78	0.33	0.71	0.01	0.35	0.11	262	27.29
	0.74	1.00	0.12	0.88	0.33			0.30	0.16	316	48.0
<i>g6</i>			0.30	0.73	0.84	0.28	0.97	0.20	0.29	399	1.89*
	0.34	0.99		0.67	0.25	0.57	0.06	0.21	0.28	291	5.10*
	0.60	1.00	0.19	0.79	0.24			0.21	0.27	299	2.76*
<i>g7</i>			0.15	0.56	0.73	0.58	0.84	0.19	0.33	268	4.77*
	0.58	0.99		0.56	0.33	0.65	0.03	0.20	0.32	261	3.25*
	0.53	1.00	0.00	0.60	0.41			0.22	0.30	280	5.83*
<i>h2</i>			0.00	0.40	0.39	0.38	0.76	0.07	0.38	230	6.28*
	0.19	0.53		0.33	0.31	0.51	0.66	0.06	0.39	227	6.26
	0.26	0.71	0.00	0.34	0.23			0.06	0.39	226	6.32*
<i>h4</i>			0.15	0.64	0.45	0.08	0.75	0.11	0.31	265	4.12*
	0.35	0.01		0.37	0.44	0.31	0.61	0.12	0.30	249	5.98*
	0.46	0.13	0.35	0.16	0.49			0.11	0.31	236	5.15*
<i>h5</i>			0.15	0.48	0.59	0.48	0.83	0.00	0.36	253	8.31
	0.44	0.67		0.37	0.32	0.93	0.46	0.00	0.36	240	6.23
	0.35	1.00	0.00	0.50	0.33			0.03	0.33	251	6.76*

For each allele, the first row of numbers corresponds to $\alpha = 0$ (3 d.f.), the second row to $\delta = 0$ (2 d.f.) and the third to $r = s = 0.5$ (3 d.f.). * Chi-square values correspond to $P \geq 0.05$.

fitting solutions obtained for that allele correspond to values of P (0.02 and 0.001) which are well below the 5% level of sampling error.

The solutions of Tables 2 and 3 are such that $p \neq q$. This implies that the two mismatches corresponding to a given allele (depending on which chromatid carries the hDNA) have different probabilities of being repaired. In addition, the values taken by r and s are often fairly different from 0.5, suggesting that the direction of repair of the corresponding mismatch is nonrandom. This is confirmed (Table 5) by the solutions obtained with a model such that $r = s = 0.5$ (equal probability of generating either parental allele from the repair of any mismatch). Such a model may in principle account for most alleles, provided that α , β and δ take appropriate values that strongly differ from one allele to another. It could, however, in no way explain the segregations observed for *gl*.

DISCUSSION

The model of recombination expressed by equations (1) to (11) is in fact the Avimore model (MESELSON and RADDING 1975): it postulates the exchange of copolar strands between the recombining chromatids, allows for an asymmetric phase of hDNA, explains gene conversion exclusively in terms of heteroduplex repair and interprets crossover by a second pair of single-strand cuts

affecting those strands that were not invading during the formation of hDNA. It is not essential for our purpose to assume (as the Aviemore model does) that crossing over is due to a process of strand isomerization, but it is required that, once an hDNA has been initiated, the crossing over site associated with that hDNA (that is, the genetic site where the resolution of the half-chromatid chiasma occurs) is always located opposite to the initiation site with respect to the allele undergoing gene conversion or PMS. This is to say that there is no back migration of the hDNA along the chromatid or, if back migration occurs, that it always precedes heteroduplex repair. HOLLIDAY (1974) has discussed the relevance of this assumption on the interpretation of aberrant segregation in terms of asymmetric hDNA.

Our aim was to examine whether and on what conditions such a model could quantitatively account for the pattern of gene conversion, PMS and associated crossovers observed at the gray locus (see KITANI and WHITEHOUSE 1974). Previous studies of the same locus were based on the five classes of conversion and PMS detected in monofactorial crosses, which limit the number of variables available down to four if 1 d.f. is to be kept. These studies (EMERSON 1966; FINCHAM, HILL and REEVES 1980) were based on a fully symmetric hDNA ($\alpha = 0$). However, even a more general system with six variables and allowing for asymmetric hDNA was inadequate to completely explain the segregations observed at the gray locus (KALOGEROPOULOS and THURIAUX 1982). The 11 equations with ten variables developed here enables us to reexamine this issue without the constraints on the symmetry of the hDNA or on the properties of heteroduplex repair which had to be introduced in the previous studies. We find that two versions of the model both allowing for asymmetrical hDNA and such that either $\beta = 0.5$ or $\delta = 0.5$ give best fitting solutions that, for each allele tested, correspond to chi-square values greater than or very close to the 5% threshold of sampling error. In both cases, the best results are obtained under the somewhat arbitrary but plausible assumption that heteroduplex repair is more efficient on the asymmetric hDNA. Thus, the theoretical frequencies of conversions, PMS and associated crossovers predicted by the Aviemore model coincide (or, in the case of allele *h4*, almost coincide) with the experimental data, allowing for a 5% probability of sampling error.

It is remarkable that the "canonical" hDNA model accounts for the distribution of aberrant segregations at the locus that is by far the more extensively characterized in this respect. This, of course, does not invalidate other interpretations of gene conversion (SZOSTAK *et al.* 1983). More generally, we cannot exclude that the fit observed simply reflects the large number of parameters used to describe the system. In most cases, the best fitting values calculated for a given parameter are allele specific rather than locus specific. Allele specificity is of course expected for parameters related to mismatch repair (p , q , r , s) but not for parameters related to the topology of the hDNA (α , β , δ). Since the intragenic map of gray is only tentative (KITANI and OLIVE 1967) we cannot exclude that the allele specificity observed for the latter parameters is in fact determined by the position of the mutant sites on the gene. Genes with more reliable intragenic maps have been analyzed in *S. cerevisiae* (DICAPRIO and HASTINGS 1976; FOGEL *et al.*, 1979) and *A. immersus* (PAQUETTE and

ROSSIGNOL 1978) but are not amenable to our analysis either because post-meiotic segregations are too rare or because no flanking markers are available.

FINCHAM, HILL and REEVES (1980) have argued that the properties of conversion at gray could be compatible with a fully symmetric hDNA ($\alpha = 0$). We (KALOGEROPOULOS and THURIAUX 1982) have proposed an explanation based on a partly asymmetric hDNA that requires that the invading strand always has the same chemical polarity ($\delta = 0$ or 1) and that the asymmetric hDNA has the same probability of being formed on either chromatid ($\beta = 0.5$). None of these models was entirely consistent with the experimental data of Kitani and coworkers and our present data show that the corresponding assumptions (which had to be introduced to keep 1 d.f. for testing the goodness of fit of the solutions) were indeed ill-founded. At least in the case of allele *g1*, we can reject the hypothesis of a fully symmetric hDNA and the hypothesis that the invading strand always has the same chemical polarity. On the other hand, our results are compatible with the asymmetric hDNA having the same probability of being formed on either chromatid, but the results do not necessarily imply this conclusion, as shown by the equally fitting solutions obtained under the assumption that $\delta = 0.5$ and given the values of β which are fairly different from 0.5. As far as mismatch repair is concerned, our results imply, as might have been anticipated, that the two mismatches corresponding to a given allele have different probabilities of being repaired. They also imply, at least in the case of allele *g1*, but possibly for other alleles, that the direction of repair is nonrandom (r and/or s different from 0.5).

Our equations are based on the assumption that the site of crossing over associated with a given hDNA is located distally to the initiation site of the hDNA, *i.e.*, the converting allele is always between the initiation site and the site of crossover. Consequently, all of the mutant sites (with the possible exception of *h5*) are included on hDNA initiated from either side of the locus, since the values taken by G and D differ from 0. Moreover, if one accepts the fine structure map of KITANI and OLIVE (1967), the mutants located on the right of gray (*h2*, *h4* and *h5*) should predominantly be included on hDNAs initiated from the left of the locus, whereas the opposite is true for *g1*, which is believed to be located on the left of the gene. It is hard to see how this could be achieved without a site for hDNA initiation inside gray itself.

The hypothesis of the crossing over being always distal to the initiation site is inherent to our system of equations. It is a plausible one and is supported by the internal consistency of our results. Yet, WHITEHOUSE (1982, p. 321) has argued that the crossing over can be proximal to the initiation site. His argument (based on the properties of PMS asci leading to intragenic recombination in gray) rests on the assumption that there is no initiation inside gray itself. Similarly, FOGEL *et al.* (1979) in a study of PMS at the *arg4-16* mutant of *S. cerevisiae* reported an excess of crossovers at the high conversion end unlike what would be expected under the hypothesis of a distally located crossing over, granted however that initiation is at the high conversion end. Thus, the adequacy of our equations in explaining the segregation patterns observed at gray does not mean that crossing over is always distal to the site of hDNA initiation. More generally, SANG and WHITEHOUSE (1983) and THEIVENDIRA-

RAJAH and WHITEHOUSE (1983) have evidence that the crossing over may not be contiguous to its associated hDNA. Whereas our system of equations does not strictly require such a contiguity, their data nevertheless suggest that the association between PMS or gene conversion and crossing over may be different from the one postulated so far in the various versions of the hDNA model (see WHITEHOUSE 1982 for a discussion of that point), which would lead to questions concerning equations (5), (6), (9) and (10) of the present study.

We thank V. PONTIKIS and G. MALGOUYRES for their help during this work. This work was supported by a grant from Centre National de la Recherche Scientifique (L.A. 040086).

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Communicating editor: R. C. ULLRICH