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Gene conversion disparity in yeast: its extent, multiple origins, and effects on allele frequencies

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The extent of disparity in gene conversion direction in yeast (*Saccharomyces cerevisiae*) is important for recombination mechanisms and for effects of conversion on allele frequencies in populations. An analysis of published and unpublished data demonstrates that yeast frequently shows significant and extensive conversion disparity, contrary to many published statements. All types of mutation – base-substitutions, frameshifts and longer deletions and additions – can show significant 6:2/2:6 and/or 5:3/3:5 disparity. There was little correlation between the occurrence of 6:2/2:6 and 5:3/3:5 disparities; when both were significant, they were more often in opposite directions than in the same direction. Surprisingly, there was little correlation between a mutation's molecular nature and its disparity properties, which generally seem unpredictable. Disparity in yeast has multiple origins. From the equations discussed, all disparity types can be explained by one or more of: correction direction disparity, chromatid invasion disparity (including cases caused by different frequencies of double-strand breaks or gaps in nonsister homologous chromatids), strand invasion disparity, and different correction frequencies for the two types of mispair for a heterozygous mutation. Levels of overall disparity and of conversion frequency mean that conversion must often change allele frequencies in sexually reproducing yeast populations.

Keywords: allele frequencies, disparity, gene conversion, recombination, *Saccharomyces cerevisiae*, yeast.

Introduction

The extent to which yeast shows disparity in conversion direction for alleles at a locus is important for mechanisms of conversion and crossing-over, and for population genetics and evolution. Parity in conversion direction for yeast was a major line of evidence offered for the original double-strand break-repair (DSBR) model (Szostak *et al*., 1983; Orr-Weaver & Szostak, 1985). Frequent disparity would be good evidence for the modified DSBR model (Sun *et al*., 1991), where most conversions come from hybrid DNA, not from double-strand break-repair. The extent of disparity for various types of mutation is crucial for assessing the influence of gene conversion on allele frequencies in populations (Lamb & Helmi, 1982; Lamb, 1985, 1986). There are now sufficient yeast data to study the origins and influencing factors of different types of disparity, such as 6:2/2:6 and 5:3/3:5 disparity, which can be in opposite directions, say with preferential conversion to wild-type in 5:3 and 3:5 segregations and preferential conversion to mutant in 6:2 and 2:6s.

Firm statements that yeast shows parity in direction of conversion, not disparity, have been made, even in recent reviews (Fogel & Mortimer, 1969; Fogel *et al*., 1971; Orr-Weaver & Szostak, 1985; Nicolas & Petes, 1994; Petes & Pukkila, 1995). Szostak *et al*. (1983) stated that in yeast all classes of mutations and all mutations show parity. Evidence (Lamb, 1986) that disparity was common in yeast has received insufficient attention.

The extent of disparity in yeast has here been re-examined as there are now excellent data with large sample sizes, including mutations of known molecular nature (see references in Tables 1–6). The recent data were obtained for other purposes, not for disparity.

The aims here were: (i) to study the extent, direction and origins of disparity for different molecular

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types of mutation; (ii) to see whether equations for recombination (Lamb, 1996a,b) can account for disparity phenomena, including opposite-direction disparity in 5:3/3:5 and 6:2/2:6 octads; and (iii) to assess the extent to which gene conversion can change allele frequencies. The data of Detloff *et al*. (1991), on nine different base-substitutions in a single *his-4* codon, enable one to study effects of different types of mispair.

Although yeast has unordered meiotic tetrads, not octads, the ability to detect postmeiotic segregation from sectored colonies means that conversion ratios can be given as corresponding octad ratios, e.g. aberrant 4:4 and 5:3. To help understand the causes of disparity, the parameters of conversion are given in Table 1, where α, β, γ_1, γ_2 and δ relate to hybrid-DNA (hDNA) formation, g relates to double-strand gap frequency, and p, q, r and s relate to correction in heterozygotes of mispairs (base-substitutions) or nonpairs (frame-shifts or longer additions or deletions). Allele ratios are given as + (wild-type): *m* (*mutant*). Hybrid DNA could arise as a result of initiation by double-strand breaks or gaps, or by other means, as in the Meselson & Radding (1975) model. Although double-strand gap-repair can cause conversion in yeast, conversion will usually be discussed as arising from hDNA, because results from yeast and filamentous fungi fitted expectations of conversion from hDNA, not from double-strand gaps (Lamb, 1987; Detloff *et al*., 1991), although double-strand breaks probably initiate the hDNA. On the modified DSBR model (Sun *et al*., 1991), most conversions arise from hDNA, not from double-strand gap-repair.

The type of hDNA, symmetric or asymmetric, affects disparity. From symmetric hDNA, 6:2 and 2:6 asci need two corrections in the same direction (both to + or both to *m*), 5:3s and 3:5s need one correction and one noncorrection, and aberrant 4:4s have no corrections. From asymmetric hDNA, 6:2s and 2:6s need one correction and 5:3s and 3:5s have no correction. From symmetric hDNA, preferential correction of mispairs to + produces more 6:2s than 2:6s and more 5:3s than 3:5s, with greater disparity amongst 6:2s and 2:6s than amongst 5:3s and 3:5s (Rossignol *et al*., 1979). From symmetric DNA, the

Table 1 Symbols and definitions for the parameters for gene conversion between two alleles at one locus

The parameters are for meiotic hybrid DNA formation at a given site, using a $+/m$ heterozygote as an example; at the single point of mutation, the + chromatids have base pair *AB* and the mutant chromatids have base pair *XY*. That is for a base-substitution mutant; for a frame-shift, there would be two nonpairs, rather than mispairs. For an *Aa* heterozygote, *A* takes the place of + and *a* takes the place of *m*. Except for γ_1 and γ_2, the terminology is based on that of Kalogeropoulos & Thuriaux (1982).

(i) Hybrid DNA formation

γ_1 The probability of hDNA forming between any two homologous nonsister chromatids at the given site, if no hDNA has already formed in any chromatid at that site in the bivalent.

γ_2 The probability of hDNA being formed at that site in the remaining pair of homologous nonsister chromatids, if hDNA is already formed, or being formed, at that site between the other two nonsister homologues.

α The probability that hDNA formed at that site is asymmetric; $1-\alpha$ is the probability that it is symmetric.

β The probability that the invading chromatid for that site in asymmetric hDNA carries the + allele; $1-\beta$ is the probability that it carries the *m* allele.

δ The probability that the invading single strand in asymmetric hDNA has a given polarity, say 3′5′; $1-\delta$ is the probability that it has 5′3′ polarity.

In symmetric hDNA, *AY* mispairs occur in previously + chromatids by δ events, and in previously *m* chromatids by $(1-\delta)$ events; *XB* mispairs occur in previously *m* chromatids by δ events, and in previously + chromatids by $(1-\delta)$ events. In asymmetric hDNA, *AY* mispairs occur in previously *m* chromatids by $\beta(1-\delta)$ events, and in previously + chromatids by $(1-\beta)\delta$ events; *XB* mispairs occur in previously *m* chromatids by $\beta\delta$ events, and in previously + chromatids by $(1-\beta)(1-\delta)$ events.

(ii) Hybrid DNA mispair (or nonpair) correction

p The probability of mispair *AY* being repaired; $1-p$ are not repaired.

q The probability of mispair *XB* being repaired; $1-q$ are not repaired.

r The probability of *AY* being repaired to +, given that it is repaired; $1-r$ are repaired to *m*, when repaired.

s The probability of *XB* being repaired to +, given that it is repaired; $1-s$ are repaired to *m*, when repaired.

If conversions occur by double-strand gap-repair (Orr-Weaver & Szostak, 1985), an additional parameter is needed, g, for the chance of the heterozygous site being involved in double-strand gap formation and repair. See Lamb (1996a,b) for equations.

direction but not the extent of disparity should generally be the same in 6:2/2:6 asci as in 5:3/3:5 asci when disparity arises by correction direction biases. From asymmetric hDNA, 6:2/2:6 disparity could be produced by correction direction disparity ($r \neq 0.5$, and/or $s \neq 0.5$), but 5:3/3:5 disparity could not result from correction direction disparity. 5:3/3:5 disparity from asymmetric hDNA could arise if there were different frequencies with which + and *m* chromatids invaded the nonsister chromatids ($\beta > 0.5$ or < 0.5; Table 1), which would also affect 6:2/2:6 disparity in the same direction. 5:3/3:5 and 6:2/2:6 disparity could also arise, usually in opposite directions, from asymmetric hDNA when the strand invasion frequency is biased ($\delta \neq 0.5$) and the two types of mispair, *AY* and *XB*, correct with different frequencies, $p \neq q$. Orr-Weaver & Szostak (1985) reviewed evidence that there is little symmetric hDNA in yeast meiotic recombination.

Materials and methods

Details were given in the original papers. Disparity analyses are by the present author using the following formulae.

$$\text{6:2/2:6 disparity as a percentage} = \frac{[(6{:}2 - 2{:}6) \times 100]}{(6{:}2 + 2{:}6)},$$

where 6:2, etc. stand for the numbers of that type of octad.

$$\text{5:3/3:5 disparity as a percentage} = \frac{[(5{:}3 - 3{:}5) \times 100]}{(5{:}3 + 3{:}5)}.$$

$$\text{Overall disparity} = \frac{[(6{:}2 + 5{:}3) - (2{:}6 + 3{:}5)] \times 100}{6{:}2 + 5{:}3 + 2{:}6 + 3{:}5}.$$

Disparity favouring wild-type gives positive disparity values, disparity favouring mutant gives negative values and parity gives zero values. Significance testing was by χ^2, using Yates' correction if any class's expected numbers were five or fewer. Formulae for the effects of conversion on allele frequencies were given by Lamb & Helmi (1982) and Lamb (1986): *c* is conversion frequency as a fraction; *d* is $b - 0.5$, where *b* is the overall fraction of wild-type alleles in asci with aberrant segregation ratios:

$$b = \frac{(8{:}0 \times 8) + (7{:}1 \times 7) + (6{:}2 \times 6) + (5{:}3 \times 5) + (3{:}5 \times 3) + (2{:}6 \times 2) + (1{:}7 \times 1)}{8 \times \text{no. of asci with aberrant segregation ratios}}.$$

The force of gene conversion on allele frequencies, *y*, is *cd*; *d* and *y* have positive values if disparity favours the wild-type allele, negative values if the mutant allele is favoured, and are zero if there is no disparity.

Results

Disparity significance in relation to sample sizes

Finding significant disparity depends on having sufficiently large samples. For 6:2/2:6 disparity in Tables 2 and 3, all eight data sets with fewer than 10 6:2s plus 2:6s had no significant disparity. Of 11 sets with 10–19 6:2s plus 2:6s, only one (9%) had disparity significant at $P \leq 0.05$. Of 18 sets with 50–99 6:2s plus 2:6s, eight (44%) had no significant disparity, five (28%) had disparity significant at $P \leq 0.05$ and five (28%) had disparity significant at $P \leq 0.01$; of eight sets with more than 400 6:2s plus 2:6s, two (25%) had no significant disparity, two (25%) had disparity significant at $P \leq 0.05$ and four (50%) had disparity significant at $P \leq 0.01$. Many cases of no significant disparity in yeast might therefore have had significant disparity had the samples of conversion asci been larger.

Disparity of base-substitutions

Table 2 shows 48 data sets on heterozygous single base-substitutions. Twenty-two (46%) had significant 6:2/2:6 disparity, 14 with disparity to wild-type and eight to mutant. Nine (19%) had significant 5:3/3:5 disparity, three to + and six to *m*. Eighteen (38%) had significant overall disparity, 10 to + and eight to *m*. Twenty-six (54%) out of 48 sets showed one or more of these three types of disparity significant at $P \leq 0.05$ or 0.01. The statements that yeast shows parity in conversion direction are thus incompatible with the evidence.

Where sample sizes of convertant octads were large, even 7% disparity was significant, e.g. *thr1*. In 35 out of 48 data sets, there were fewer than 30 segregations in 5:3s plus 3:5s, when only extreme disparity would be significant. For samples of 30 or more relevant conversion asci, significant 5:3/3:5 disparity occurred in seven out of 13 data sets (54%), significant 6:2/2:6 disparity occurred in 22 out of 43 data sets (51%) and significant overall disparity occurred in 15 out of 43 data sets (35%). Because there were usually many more 6:2s and 2:6s than 5:3s and 3:5s, the different sample sizes make it difficult to determine whether 5:3/3:5 disparity is rarer than 6:2/2:6 disparity: these figures show them to be about equally frequent.

Table 2 Conversion disparity for heterozygous base-substitution mutations, $+/m$

	Numbers in octad classes				5:3/3:5 disparity		6:2/2:6 disparity		Overall disparity	
Mutation	5:3	3:5	6:2	2:6	%†	χ^2_1	%†	χ^2_1	%†	χ^2_1
Fogel *et al*. (1979)										
pet1	0	0	4	27	—	—	−74	17.1**	−74	17.1**
trp1	12	8	62	47	20	0.8	14	2.1	15	2.8
mat1	0	0	93	104	—	—	−6	0.6	−6	0.6
ura3	2	1	10	9	33	0.0	5	0.1	9	0.2
ade6	3	3	4	9	0	0.0	−38	1.2	−26	1.3
his5–2	4	1	14	10	60	0.8	17	0.7	24	1.7
tyr1	5	1	59	44	67	1.5	15	2.2	17	3.3
CUP1	6	3	123	124	33	1.0	0	0.0	1	0.0
gal2	0	0	36	17	—	—	36	6.8**	36	6.8**
leu2–1	0	0	41	25	—	—	24	3.9*	24	3.9*
trp5–48	1	0	23	31	—	—	−15	1.2	−13	0.9
met1	18	6	18	17	50	6.0*	3	0.0	22	2.8
met10	1	0	17	16	—	—	3	0.0	6	0.1
ura1	11	15	331	275	−15	0.6	9	5.2*	8	4.3*
ilv3	9	6	230	239	20	0.6	−2	0.2	−1	0.1
lys1–1	3	7	51	78	−40	1.6	−21	5.7*	−22	6.9**
SUP6	0	0	22	33	—	—	−20	2.2	−20	2.2
thr1	14	22	691	594	−22	1.8	8	7.3*	7	6.0*
his4–4	39	41	411	303	−3	0.1	15	16.3**	13	14.2**
ade8–10	0	0	48	30	—	—	23	4.2*	23	4.2*
met13	1	0	459	474	—	—	−2	0.2	−2	0.2
cde14	1	1	48	39	0	0.0	10	0.9	10	0.9
ade7	11	8	47	27	16	0.5	27	5.4*	25	5.7*
his2	2	0	215	231	100	0.5	−4	0.6	−3	0.4
arg4–4	0	1	5	13	—	—	−44	3.6	−47	4.3*
arg4–3	5	3	28	23	25	0.1	10	0.5	12	0.8
arg4–19	2	6	87	68	−50	1.1	12	2.3	9	1.4
arg4–17	38	20	485	551	31	5.6*	−6	4.2*	−4	2.1
arg4–16, all combinations of other *arg4* alleles, pooled	5	289	508	302	−51	98.0**	25	52.4**	1	0.1
arg4–16, alone	56	170	181	77	−50	57.5**	40	41.9**	−2	0.2
arg4–16 with *arg4–17*/+	19	49	133	79	−44	13.2**	25	13.8**	9	2.1
arg4–16 with *arg4–19*/+	17	55	84	60	−53	20.1**	17	4.0*	−6	0.9
arg4–16 with *arg4–19*/+ and with *arg4–17*/+	3	15	110	86	−67	8.0**	12	3.0	6	0.7
Fink & Styles (1974)										
his4–39	0	0	16	10	—	—	23	1.0	23	1.4
Lawrence *et al*. (1975)										
met3	0	0	30	8	—	—	58	12.7**	58	12.7**
ilv3	0	0	80	61	—	—	13	2.6	13	2.6
Fogel *et al*. (1981)										
arg4–17, ochre	35	19	431	514	30	4.7*	−9	7.3**	−7	4.5*
Detloff *et al*. (1991) The first 10 lines are for different single-base changes in the initiating ATG codon, with the bases shown. The two ATC results are from different diploids.										
his4-CTG	18	15	99	114	9	0.3	−7	1.1	−5	0.6
his4-AAG	11	10	54	58	5	0.1	−4	0.1	−2	0.1
his4-ATC	56	57	113	33	−1	0.0	55	43.9**	31	24.1**
his4-ATC	22	21	46	18	2	0.0	44	12.3**	27	7.9**
his4-ACG	12	25	132	156	−35	4.6*	−8	2.0	−11	4.2*
his4-GTG	8	9	63	88	−6	0.1	−17	4.1*	−15	4.0*
his4-AGG	10	8	55	79	11	0.2	−18	4.3*	−14	3.2
his4-ATT	8	9	31	52	−6	0.1	−25	5.3*	−22	4.8*
his4-TTG	16	18	92	109	−6	0.1	−8	1.4	−8	1.5
his4-ATA	8	6	42	58	14	0.3	−16	2.6	−12	1.7
his4–17	6	12	23	44	−33	2.0	−31	6.6*	−32	8.6**

†In Tables 2–5, disparities with no sign are towards wild-type, +; those with a minus sign are towards mutant. *$P<0.05$, **$P<0.01$.

The two results for *arg4–17* and the five for *arg4–16* clearly showed opposite directions of disparity: for *arg4–17*, 5:3/3:5 disparity was significant and positive, to + (about +30%), whereas 6:2/2:6 disparity was significant and negative, to *m* (about −7%). For *arg4–16* these directions were reversed, with 5:3/3:5 disparity to *m* (−44 to −67%) and 6:2/2:6 disparity to + (+12 to +40%). Opposite-direction disparities reduce overall disparity: in the first four *arg4–16* results, significant disparities in opposite directions for 5:3/3:5 and 6:2/2:6 almost cancelled each other out, with no significant overall disparity.

Disparity in relation to the molecular nature of mispairs

In the *his4* data of Detloff *et al*. (1991) in Table 2, the first 10 lines show the effect of all nine possible heterozygous base-substitutions in the same initiating ATG codon, with ATC from two different diploids giving similar results. Of those transversions giving identical base mispairs when heterozygous with wild-type, AAG and TTG (both giving A/A and T/T mispairs) gave no significant disparity; ATC (giving C/C and G/G mispairs) gave highly significant ($P \leq 0.01$) 6:2/2:6 and overall disparity from both diploids, but no 5:3/3:5 disparity. Of those transversions giving same-type mispairs, purine/purine, A/G, and pyrimidine/pyrimidine, T/C, CTG gave no significant disparity, AGG gave significant 6:2/2:6 disparity only, and ATT gave significant 6:2/2:6 and overall disparity. Of those transitions giving different-type purine/pyrimidine mispairs, G/T and A/C, ATA gave no significant disparity, ACG gave significant 5:3/3:5 and overall disparity, whereas GTG gave significant 6:2/2:6 and overall disparity. There was no correlation between disparity and the position of the mispair within the codon.

Conversion disparity for single-base additions and deletions

The data from Fogel & Lusnak, Williamson *et al*. White & Fogel (all from S. Fogel, pers. comm.) and Detloff *et al*. (1991) are given in Table 3. With only one octad in the 5:3s plus 3:5s, 5:3/3:5 disparity cannot be studied. 6:2/2:6 disparity is not significant for one-base deletion *ade8-H1D*; it is highly significant for one-base addition *his4–519* in data of Detloff *et al*. (1991). The same mutant, *his4–519*, in data of Williamson *et al*. (Fogel, pers. comm.), has 6:2/2:6 disparity not quite significant, but has significant overall disparity. That mutation showed about the same amount of disparity to mutant, −21 to −24%, in both data sets. Malone *et al*. (1992) gave data on *his2*, with additions of one to eight bases, and two base-substitutions; disparities ranged from +26 to −23%, but with samples of only 8–26 in classes 3:1 and 1:3, none was significant.

Conversion disparity for longer additions and deletions

Porter *et al*. (1993) used palindrome additions of 18, 27 or 32 bases (Table 3). None showed significant 5:3/3:5 disparity in samples of 12–45 in either class. With wild-type *RAP1*, two of the three palindromes showed significant 6:2/2:6 disparity to wild-type, with +52 and +64% disparity, whereas the third showed +39%, not quite significant. With mutant *Rap1* present, there was no significant disparity for any of the three palindromes. The data of Gilbertson & Stahl (1996) were for a palindromic insertion of 30 bases in the *arg4* locus, giving a mixture of significant and nonsignificant 6:2/2:6, 5:3/3:5 and overall disparity.

The deletions ranged from 8 to over 1000 bp. Only *ade8–18*, a deletion of 39 bp, had enough 5:3s and 3:5s for testing. It showed highly significant disparity to + for 5:3/3:5 (+12%), 6:2/2:6 (+19%) and overall disparity. Even stronger significant 6:2/2:6 disparities to + were shown by *his4-Δ15*, 400 bp, (+45 and +69% disparity in different data sets) and *ade8-XIF*, 60 bp, (+63%). The other large deletions did not show significant 6:2/2:6 disparity, but sample sizes were often inadequate. For example, *his4-Δ290* (many bp) gave 12 of 6:2 and 23 of 2:6, and *ade8-Kpn-IΔ*, 1200 bp, gave 5 of 6:2 and none of 2:6. Although for longer deletions there were four cases of significant 6:2/2:6 disparity to + and none to *m*, *his4-Δ26*, 300 bp, and *his4-Δ290*, many bp, had −27 and −31% disparity, but neither was quite significant for the sample size.

Conversion disparity in an artificial recombination-initiating region with HO*-induced cutting*

Kolodkin *et al*. (1986) used a plasmid containing the *HO* gene (which specifies an endonuclease making a double-strand break in the *MAT* gene) fused to the *GAL10* promoter, so galactose could induce expression of *HO* to produce double-strand breaks in *MAT*. $MAT\alpha_{inc}$ is not cut by *HO* endonuclease, so only the *MATa* allele is cut by this enzyme in the heterozygote. Without galactose, 429 tetrads showed only three conversions at *MAT*, all 1α:3*a*, which is not enough to test disparity. With galactose, as

shown in Table 4, 1550 tetrads gave the unusual result of far more aberrant segregations (all 4α:0*a*) from conversion events involving both pairs of nonsister chromatids at the same point, than aberrant segregations mainly from events involving one pair of nonsister chromatids (3:1 and 1:3). Disparity was absolute, 100%, and highly significant, for 4α:0*a*/0α:4*a*, but 36% disparity for 3α:1*a*/1α:3*a* was not quite significant. The different sensitivity of two alleles in a heterozygote to an endonuclease can thus cause extreme disparity.

Conversion disparity in relation to a natural recombination-initiation region

Nicolas *et al*. (1989) identified an initiation site for meiotic gene conversion in the promoter region of *ARG4*, using deletion analysis. The conversion frequency of the *arg4-RV* allele was not affected by homozygous deletions upstream of position −316 (Δ1, Δ2, Δ3) or downstream of position +345 (Δ15), but deletions within that interval (Δ4, Δ5, Δ6, Δ7, Δ8 and Δ9) reduced the conversion frequency of heterozygous *arg4-RV* by two- to ninefold, by delet-

Table 3 Conversion disparity for heterozygous frame-shifts and longer insertions and deletions

Mutation	Number of bp deleted (−) or added (+)	Numbers in octad classes				5:3/3:5 disparity		6:2/2:6 disparity		Overall disparity	
		5:3	3:5	6:2	2:6	%	χ^2_1	%	χ^2_1	%	χ^2_1
Fogel *et al*. (1979)											
ade8–18	−39	375	294	351	239	12	9.8**	19	21.3**	15	29.6**
his4-Δ15	−400	0	0	55	21	—	—	45	15.2**	45	15.2**
his4-Δ26	−300	0	0	18	31	—	—	−27	3.5	−27	3.5
Fink & Styles (1974)											
his4-Δ15	−400	0	0	11	2	—	—	69	4.9*	69	4.9*
his4-Δ290	many	0	0	12	23	—	—	−31	3.5	−31	3.5
his4-Δ29	very many	0	0	3	5	—	—	−25	0.1	−25	0.1
Lawrence *et al*. (1975)											
cyc1–1	−300	—	—	2	1	—	—	33	0.0	33	0.0
S. Fogel & K. Lusnak (Fogel, pers. comm.)											
his4–518	+1	0	0	26	40	—	—	−21	3.0	−21	3.0
M. S. Williamson, J. C. Game & S. Fogel (Fogel, pers. comm.)											
his4–519	+1	0	1	27	43	—	—	−23	3.7	−24	4.1*
J. H. White & S. Fogel (Fogel, pers. comm.)											
ade8-X5L	−40	1	1	5	4	0	0.0	11	0.0	9	0.1
ade8-XIF	−60	5	1	17	4	67	1.5	62	6.9**	63	10.7**
ade8-XIE	−60	0	0	9	5	—	—	31	1.1	31	1.1
ade8-H1D	−1	0	0	30	25	—	—	9	0.5	9	0.5
ade8-H1E	−8	0	0	22	19	—	—	7	0.2	7	0.2
ade8-Kpn-IΔ	−1200	0	0	5	0	—	—	100	3.2	100	3.2
Detloff *et al*. (1991)											
his4–519	+ 1	0	0	29	60	—	—	−35	10.8**	−35	10.8**
Porter *et al*. (1993) Palindromic insertions, with the number of base pairs given after 'pal'. The upper three have *RAP1*; the lower three have *Rap1*.											
bik1-IR16	+ pal 32	45	32	27	6	17	2.1	64	13.4**	31	10.5**
his4-IR9	+ pal 18	31	44	16	7	−17	2.3	39	3.5	−4	0.2
his4–3133	+ pal 27	27	31	16	5	−7	0.3	52	5.8*	9	0.6
bik1-IR16	+ pal 32	24	16	7	10	20	1.6	−18	0.5	9	0.4
his4-IR9	+ pal 18	14	19	6	11	−15	0.8	−29	1.5	−20	2.0
his4–3133	+ pal 27	12	17	12	5	−17	0.9	41	2.9	4	0.1
Gilbertson & Stahl (1996) Insertions into *arg4* of a 30 bp LexA operator palindrome, giving *arg4–1691-lop*; the results are from three different diploids, F1216, F1236, F1246, respectively.											
arg4–1691-lop	30	50	78	22	71	−22	6.1*	−53	25.8**	−27	23.5**
arg4–1691-lop	30	28	29	9	33	−2	0.2	−57	13.7**	−25	6.3*
arg4–1691-lop	30	41	27	11	17	21	2.9	−21	1.3	8	0.7

*$P<0.05$, **$P<0.01$.

Table 4 Conversion disparity for heterozygous markers with and without *HO*-induced cutting only in the *MATa* allele

Mutation	Numbers in each octad class				Condition	4α:0*a*/0α:4*a* disparity		3α:1*a*/1α:3*a* disparity	
	4α:0*a*	0α:4*a*	3α:1*a*	1α:3*a*		%	χ_1^2	%	χ_1^2
Kolodkin *et al*. (1986)									
MAT	0	0	0	3	No galactose	–	–	−100	1.3
MAT	215	0	19	9	Galactose	100	213.0**	36	3.6

**$P<0.01$.

ing some or all of the initiation site for conversion in the promoter region. The *arg4-RV* site and its mispairs in hDNA are not changed by these homozygous deletions, offering an opportunity to study its disparity in different locations within the locus. Table 5(a) shows that the same heterozygous mutation can have quite different disparities in different positions, though with no systematic changes with position. Thus with Δ2 there is significant disparity to *m*, −44%, but Δ5 disparity is to +, +31%. The difference between Δ2 and Δ5 is significant ($\chi_1^2 = 7.9$, $P<0.01$).

Nicolas *et al*. (1989) also studied the effects of heterozygous deletions inside and outside the conversion-initiation region: the deletion of an initiation site from one homologue should lead to disparity, as only the wild-type homologue could initiate conversion. Table 5 (b) shows Δ*9HET* having

Table 5 Conversion disparity for heterozygous markers with mutations inside or outside a recombination initiation region in *ARG4* (Nicolas *et al*., 1989)

(a) Effect of homozygous deletions in different parts of the locus on disparity for the same heterozygous *RV* site

Mutant	Deletion length (bp)	3+:1RV	1+:3RV	3+:1RV/1+:3RV disparity		Location of the deletion relative to RV
				%	χ_1^2	
Δ*1*	6000	13	11	8	0.2	Upstream
Δ*2*	800	7	18	−44	4.8*	Upstream
Δ*3*	1500	21	25	−9	0.3	Upstream
Δ*4*	204	2	7	−56	1.8	Upstream
Δ*5*	177	21	11	31	3.1	Upstream
Δ*6*	261	11	7	22	0.9	Upstream
Δ*7*	1500	5	1	67	1.5	Upstream
Δ*8*	815	2	2	0	0.0	Upstream
Δ*9*	142	6	5	9	0.1	Upstream
Δ*10*	319	32	33	−2	0.2	Upstream
Δ*15*	1200	24	17	17	1.2	Downstream

(b) Disparity of heterozygous deletions inside or outside the recombination initiation region

Mutant	Deletion length (bp)	3+:1Δ	1+:3Δ	3+:1Δ/1+:3Δ disparity		Location of the deletion relative to initiation region
				%	χ_1^2	
Δ*9HET*	142	7	28	−60	12.6**	Inside
Δ*5*/Δ*6*	84	1	22	−91	17.4**	Inside
MGD386	84	14	29	−35	5.2*	Outside
MGD366, *SUP3a* insert	137	6	9	−25	0.6	Outside

*$P<0.05$, **$P<0.01$.

highly significant disparity (−60%) to *m* as expected; the seven conversions to + were perhaps initiated from another region. An even stronger disparity (−91%), highly significant, arose in a heterozygote for deletions 5 and 6, with an 84 bp heterozygosity. The homologue retaining the sequences from −140 to −56 was the preferred recipient in conversion. As controls, they had two heterozygous deletions outside the initiation region: *MGD368* had significant disparity to *m* (−35%), but the small sample for *MGD366 SUP3a* had no significant disparity.

Conversion as a force changing allele frequencies

This force, *y*, is the product of the conversion frequency as a fraction, *c*, and disparity measure *d* (see Materials and methods). The earlier yeast data were analysed for *c*, *d* and *y* by Lamb (1984, 1985, 1986), so only newer data are covered in Table 6, using only cases with 20 or more conversion asci. Conversion frequencies were high, with *c* of 0.156–0.548, for *bik1* and the nearby *his4*, and for *MAT*, but lower for *ARG4 RV* with different homozygous deletions, 0.036–0.091. Disparity, *d*, has the highest value for any organism at +0.4527 for *MAT* with the galactose-stimulated *HO*-cutting. The also unnatural situation of a heterozygous deletion in a recombination-initiating region in *ARG4*, for Δ*9HET* and Δ5/Δ6, gave very high disparity, +0.1501 and +0.2283. In more normal situations, *d* varied from −0.0851 to +0.1052 for base-substitutions at *his4*, *d* was −0.0806 for a single-base-addition frameshift, and ranged from −0.0375 to +0.0694 for palindromic insertions in *bik1* and *his4*. Conversion force values, *y*, were most extreme for *MAT*, +0.0711, and *his4* base-substitutions, −0.0354 to +0.0463. Although *ARG4* had some strong disparities, the lower *c*-values reduced the extremeness of *y* compared to other loci. Disparity and conversion force values could be positive or negative, varying from strong to none for different mutants or even for the same heterozygous mutation in different conditions.

Discussion

Disparity extent

It is clear from Tables 2–5 that significant disparity often occurs in yeast for all types of mutation. An increasing proportion of sites had significant disparity as sample sizes increased. The mean absolute value of disparity parameter *d* for yeast was 0.06, a little lower than those of 0.10–0.13 for *Ascobolus* and *Sordaria brevicollis* (Lamb, 1985). The newer yeast data (Table 6) gave a mean absolute *d*-value of 0.07 from 31 samples, showing slightly less disparity than those filamentous fungi.

Mechanisms of recombination

The frequent disparity shown in yeast favours the modified DSBR model of Sun *et al*. (1991) rather than the original DSBR model of Szostak *et al*. (1983). In the modified model, compared to the original model, lengths of double-strand gap-repair, which probably do not give disparity, are absent or much shorter in relation to lengths of hDNA, which can easily give disparity.

Types of disparity

In the present yeast data, there are significant cases of 5:3/3:5 disparity with no 6:2/2:6 disparity, e.g. *met1*; of 6:2/2:6 disparity with no 5:3/3:5 disparity, e.g. *his4-ATC*; of disparity in the same direction for 6:2/2:6 and 5:3/3:5s (*ade8–18* was the only example); and of opposite directions for 6:2/2:6 and 5:3/3:5 disparity, e.g. *arg4–16* and *arg4–17*. For *arg4–16* in a monohybrid cross, the 5:3/3:5 disparity was strongly to *m* (−50%, $P \leq 0.01$) but 6:2/2:6 disparity was strongly to + (+40%, $P \leq 0.01$).

These disparity patterns in yeast resemble those found in *Ascobolus immersus* by Lamb & Ghikas (1979), except that in *Ascobolus* 6:2/2:6 disparity was usually, but not always, in the same direction as 5:3/3:5 disparity; sometimes 6:2/2:6 disparity was stronger than 5:3/3:5 disparity, sometimes weaker and sometimes equal. In the *Ascobolus* data of Lamb & Zwolinski (1992) for *w1*, hDNA was roughly one-third symmetric, and two-thirds asymmetric, in contrast to nearly all asymmetric hDNA in yeast. This partly accounts for disparity usually being in the same direction for 5:3/3:5 and 6:2/2:6 in *Ascobolus*, as symmetric hDNA with biased correction direction affects both types of disparity in the same direction.

Monohybrid or dihybrid (heteroallelic) crosses, coupling or repulsion

Some yeast data were from heteroallelic crosses, where co-conversion could affect disparity at both heterozygous sites. Suppose two heteroallelic mutations, *m1* and *m2*, preferentially convert in the same direction in monohybrid crosses, say to +, but with

m1 having more disparity than *m2*. In coupling, $+,+/m1,m2$, co-conversions will retain the direction of disparity, but with *m2* having more disparity than *m1*. In repulsion, $+,m2/m1,+$, co-conversions will reverse the direction of disparity for each mutant. Mixing data from repulsion and coupling crosses could therefore reduce the amount of disparity found, and disparities from monohybrid and

Table 6 Values of *c*, *d* and *y*, for the force of conversion on allele frequencies

Mutation†	Numbers of conversion asci	Conversion frequency, *c*	Overall disparity measure, *d*	Force of gene conversion, *y*
Porter *et al*. (1993). Palindromic insertions, with the number of base pairs given after 'pal'. The upper three have *RAP1*; the lower three have *Rap1*.				
bik1-IR16, +pal 32	119	0.391	0.0694	0.0272
his4-IR9, +pal 18	126	0.384	0.0063	0.0024
his4–3133, +pal 27	88	0.285	0.0278	0.0079
bik1-IR16, +pal 32	58	0.197	0.0044	0.0009
his4-IR9, +pal 18	50	0.169	−0.0375	−0.0064
his4–3133, +pal 27	46	0.156	0.0245	0.0038
Gilbertson & Stahl (1996). Three diploids with *arg4–1691-lop*, see Table 3.				
(i) +pal 30	221	0.105	−0.0712	−0.0075
(ii) +pal 30	99	0.111	−0.0619	−0.0069
(iii) +pal 30	98	0.083	0.0026	0.0002
Detloff et al. (1991). The first 10 lines are for different single-base substitutions in the initiating ATG codon, with the bases shown. The two ATC results are from different diploids.				
his4-CTG	313	0.489	−0.0307	−0.0149
his4-AAG	173	0.548	−0.0363	−0.0199
his4-ATC	302	0.439	0.1052	0.0463
his4-ATC	134	0.523	0.0857	0.0449
his4-ACG	371	0.473	−0.0391	−0.0185
his4-GTG	189	0.467	−0.0575	−0.0269
his4-AGG	179	0.527	−0.0403	−0.0212
his4-ATT	124	0.416	−0.0851	−0.0354
his4-TTG	279	0.466	−0.0114	−0.0053
his4-ATA	137	0.441	−0.0182	−0.0081
his4–17	90	0.331	−0.0562	−0.0186
Detloff *et al*. (1991). Single base-addition frameshift.				
his4–519	90	0.289	−0.0806	−0.0233
Kolodkin *et al*. (1986). Conversion for a heterozygous marker with *HO*-induced cutting only in the *MATa* allele.				
MAT	243	0.157	0.4527	0.0711
Nicolas *et al*. (1989). Deletions in *ARG4*.				
(i) Effects of homozygous deletions in different parts of the locus on disparity for the *RV* site.				
Δ*1*	24	0.071	0.0208	0.0015
Δ*2*	25	0.091	−0.1101	−0.0098
Δ*3*	46	0.081	−0.0217	−0.0018
Δ*5*	32	0.036	0.0781	0.0028
Δ*10*	65	0.087	−0.0038	−0.0003
Δ*15*	41	0.078	0.0427	0.0033
(ii) Disparity of heterozygous deletions inside or outside the recombination initiation region.				
Δ*9HET*	35	0.032	0.1501	0.0048
Δ*5*/Δ*6*	23	0.031	0.2283	0.0071
MGD368	43	0.053	0.0872	0.0047

†Mutations with fewer than 20 conversion asci have been omitted, as have those included in previous surveys.

dihybrid crosses could differ. Fogel *et al*. (1979) used pooled repulsion (e.g. *arg4 16*,+/+,*17*) and coupling (*16*,*17*/+,+) heteroallelic crosses. If the two mutations had opposite disparity directions, say *m1* converting mainly to + and *m2* converting mainly to *m*, then in coupling, co-conversions would change the direction of disparity of both sites, whereas in repulsion they would not change the direction but could change the strength of disparity at each site. In a heteroallelic cross, conversions at any site are usually a mixture of conversions involving only that site, with its own conversion properties, and of co-conversions in which correction could be triggered by the other nearby heterozygous site, possibly reducing overall disparity for that site: in Table 2, *arg4–16* in a monohybrid cross had +40% 6:2/2:6 disparity, but this was reduced in heteroallelic crosses with either or both *arg4–17* and *arg4–19 to* +12, +17 or +25%. Data from filamentous fungi were nearly all from monohybrid crosses (Lamb, 1984).

Base-substitutions

Table 2 shows that base-substitutions with large samples often have significant 6:2/2:6 disparity, such as *pet1*, *his4–4* and *arg4–16*, but some show no significant disparity, such as *CUP1*, *met13* and *his2*.

Is disparity controlled by a mutation's molecular nature?

One might expect that heterozygous transversions giving mispairs with identical bases (e.g. C/C) would not give disparity unless neighbouring bases differed and affected which strand was excision-repaired; that transversions giving unlike purine/purine (e.g. A/G) and unlike pyrimidine/pyrimidine (e.g. C/T) mispairs would have disparity if excision repair had preferences among purines and/or among pyrimidines; and that transitions giving purine/pyrimidine mispairs would have disparity for each mispair, in opposite directions for the two mispairs, if excision repair had preferences for cutting out purines or pyrimidines. For example, in an A/T (+) to GC (*m*) transition giving A/C and G/T mispairs, a tendency to excise preferentially the purine would give disparity to mutant for A/C but disparity to wild-type for G/T. Disparity could occur if the degree of preferential excision differed between the two mispairs, or if the mispairs were formed with different frequencies.

The results of Detloff *et al*. (1991) in Table 2 do not follow any of those predictions. Two mutants giving A/A and T/T mispairs had no 6:2/2:6 disparity but the one giving C/C and G/G had highly significant disparity. Of the mutants giving purine/pyrimidine mispairs, G/T and A/C, one had no disparity, one had 5:3/3:5 disparity and one had 6:2/2:6 disparity. Of the mutants giving purine/purine, A/G, and pyrimidine/pyrimidine mispairs, T/C, one gave no disparity and two gave 6:2/2:6 disparity. The neighbouring base sequences should have been identical for all these mutations, so differences in nearby bases would not explain these results. For 6:2/2:6 disparity, four of the base-substitutions had significant disparity to *m*, −17 to −31%; two repeats of one (giving G/G and C/C) had highly significant disparity to +, +44 and +55%; and five had no significant disparity from samples of 100–288 of 6:2s plus 2:6s. Only one gave significant 5:3/3:5 disparity, −35%, but it gave insignificant 6:2/2:6 disparity, −8%.

From European strains of *Ascobolus immersus*, Leblon (1972a,b) reported that conversion properties were closely related to a mutation's molecular nature, with frame-shift deletions giving low frequencies of asci with postmeiotic segregation (p.m.s.) and conversion strongly to +; frame-shift additions also gave low frequencies of p.m.s. asci but disparity was strongly to *m*; base-substitutions gave a high proportion of p.m.s. asci, and disparity favoured either + or *m*. Later results showed a less good correlation, e.g. frameshift *A4* usually had over 90% of p.m.s., with no conversion disparity (Rossignol & Haedens, 1980). Yu-Sun *et al*. (1977) found a less good correlation between a mutation's molecular type and its gene conversion spectrum in *Sordaria brevicollis*. In Pasadena strains of *A. immersus*, Lamb & Ghikas (1979) found only a weak correlation between a mutation's molecular nature and its conversion properties for frequency of p.m.s. asci and amount and direction of disparity. When they crossed the same mutation to a number of strains with the same wild-type allele but differing in alleles for certain linked or unlinked conversion control factors, the conversion properties sometimes differed remarkably in p.m.s. frequency and/or in disparity amount or even in disparity direction, although the mispairs were the same in each cross.

The yeast results of Detloff *et al*. (1991) confirm the lack of any consistent disparity pattern in relation to the molecular nature of the mispairs. Such a lack of pattern was also shown in the results of Nicolas *et al*. (1989) in Table 5 for *arg4-RV*. The mispairs and their neighbouring bases remained constant, but were moved in relation to surrounding genetic regions by homozygous deletions. In some positions, the *RV* mutation had no disparity; in one

position it had significant disparity to *m*, and in another position it had nonsignificant disparity favouring +, +31%, a highly significant difference from the −44% result for the same heterozygous mutation.

Lamb (1975) pointed out that unknown heterozygous cryptic mutations near to the known mutations could affect a correlation between a mutation's molecular nature and its conversion properties. Co-conversions triggered by the cryptic mutation's mispairs could alter the perceived properties of conversion, including disparity, of the known mutations.

Additions and deletions

In Table 3, the two single-base-addition frameshifts showed some disparity towards *m*, with −21, −23, and −35% in the three data sets; only the last value is significant. The longer additions were all palindromes, of 18, 27 or 32 bases, giving 6:2/2:6 disparity to +, with +64, +39 and +52% in a *RAP1* strain, where two of the biases were significant. With the same palindromes in a *Rap1* strain, lacking a transcription-activating factor, the disparities were not significant, −18, −29 and +41%, from fairly small sample sizes. It is not clear why the binding of a protein to a site near the 5′ end of *HIS4* and the 3′ end of *BIK1* should affect disparity in the two genes, nor why the longer palindromic addition should have the opposite direction of disparity to the single-base-addition.

The two single-base deletions, *ade8-H1D* and *ade8-H1E*, had no significant disparity. Of 10 longer deletions, five had only three to 13 conversion asci, but one of these had +69% disparity, which was significant. The other five included three with highly significant disparity to wild-type, whereas the other two had disparity to *m*, but neither was significant. Although the *Ascobolus* and *Sordaria* results referred to above usually had strong conversion disparity to + for single-base deletions, that is, preferential cutting of the shorter, unlooped strand, the two yeast single-base deletions had no strong disparity, and longer deletions varied in disparity amount and direction. Yeast deletions converted to + and to *m*, so both the looped or unlooped strands could be cut in mismatch repair. Fogel *et al*. (1981) concluded that in yeast, 'deletions convert at near-normal frequency and with approximate parity, but do not display p.m.s.', but the data in Table 3 show strong disparity for a high proportion of deletions with large samples, and some deletions had a high proportion of p.m.s. segregations. In *A. immersus*, Girard & Rossignol (1974) and Paquette & Rossignol (1978) studied two deletions of much of the *b2* gene. Both had highly significant disparity to mutant, with 11–14% p.m.s., but in crosses heterozygous for a conversion control factor, p.m.s. were 67–75%, with much less disparity.

Causes of disparity

Parameter definitions are in Table 1 and equations for gene conversion were given by Lamb (1996a,b). Hybrid DNA in yeast is generally accepted as occurring very largely from asymmetric hDNA, in which 6:2/2:6 disparity can arise from correction direction disparity (r and/or $s \neq 0.5$) but 5:3/3:5 disparity cannot be caused by correction direction disparity, as no correction occurs in their production from asymmetric hDNA. 5:3/3:5 disparity having a separate cause from 6:2/2:6 disparity would explain why the two types of disparity have little correlation and can be in opposite directions. If nearly all hDNA is asymmetric, then one way 5:3/3:5 disparity can arise is from one chromatid invading the nonsister chromatid with a higher frequency than it is itself invaded by the nonsister chromatid, at the point of heterozygosity. If 5:3/3:5 disparity in a heterozygote favours +, say, then the chromatids carrying the + allele could invade the *m*-bearing chromatids more often than the *m*-bearing chromatids invade the + chromatids, so $\beta > 0.5$. Chromatid invasion disparity cannot be the usual sole cause of 5:3/3:5 and/or 6:2/2:6 disparity, because it would then cause both kinds of disparity together, in the same direction, which rarely occurred in the present yeast data. Thus preferential invasion by the + chromatid in asymmetric hDNA formation should cause 6:2 > 2:6 and 5:3 > 3:5, unless correction direction disparity favoured *m*, when the 5:3 > 3:5 relation is unaltered, but the 6:2 > 2:6 relation could be reduced or reversed. A second possible cause of 5:3/3:5 disparity, and a third cause of 6:2/2:6 disparity, is if strand invasion frequency is biased ($\delta \neq 0.5$) and the two types of mispair, *AY* and *XB*, correct with different frequencies, $p \neq q$.

The frequent occurrence of 6:2/2:6 disparity without 5:3/3:5 disparity in yeast is easily explained by disparity in correction direction in asymmetric hDNA, that is, correction parameters r and s have values departing from 0.5, with values for one or both of them being > 0.5 for disparity to + or < 0.5 for disparity to *m*. As many heterozygous mutants had a low proportion of asci with p.m.s, p and q must often be close to 1.0. Some mutants did have appreciable frequencies of p.m.s. asci, e.g. *met1*,

arg4–16, *arg4–17*, *ade8-Δ18*, *his4-ATC*, *ade8-XIF*, *bik1–1R16*, etc. (Tables 2 and 3).

In Tables 2 and 3, cases of significant 5:3/3:5 disparity generally occurred for mutants having higher frequencies of p.m.s., but usually only mutants with high p.m.s. frequencies had enough 5:3 and 3:5 segregations for significant differences. Significant or highly significant 5:3/3:5 disparity favoured + (*met1*, *arg4–17*, *ade8-Δ18*) or *m* (*arg4–16*, *his4-ACG*) about equally. It occurred for base-substitutions and a deletion of 39 bp. The data of Detloff *et al*. (1991) on different base-substitutions within the same codon show that 5:3/3:5 disparity is allele-specific, shown by *his4-ACG* but not by the other eight base-substitutions, even ones with adequate numbers of p.m.s. asci.

From the equations of Lamb (1996a,b), if one ignores less frequent events involving more than one pair of nonsister chromatids in a single meiosis (γ_2 events), then from asymmetric hDNA the ratio of 6:2/2:6 asci is $\beta[\delta qs+(1-\delta)pr]/(1-\beta)[\delta p(1-r)+(1-\delta)q(1-s)]$. 6:2/2:6 disparity thus increases with any of the following: increasing difference between β and $(1-\beta)$ (chromatid invasion preference); increasing difference between r and $(1-r)$ and between s and $(1-s)$, giving correction direction differences. If r differs from $(1-r)$ in the opposite direction from which s differs from $(1-s)$, that reduces total correction direction disparity.

From asymmetric hDNA, the ratio of 5:3/3:5 asci is $\beta[\delta(1-q)+(1-\delta)(1-p)]/(1-\beta)[\delta(1-p)+(1-\delta)(1-q)]$. This disparity increases as β differs from $(1-\beta)$. Unless strand invasion parameter $\delta=0.5$, this disparity increases as correction frequency p differs from q; unless $p=q$, this disparity increases as δ departs from $(1-\delta)$. The evidence from *Ascobolus* (Lamb & Zwolinski, 1992) for *w1* is for extreme strand invasion disparity, with $\delta=0.0$ or 1.0. If $\delta=(1-\delta)$ and/or $p=q$, 5:3/3:5 disparity from asymmetric hDNA will depend solely on $\beta(1-\beta)$. The *Ascobolus* data all showed a bias in chromatid invasion frequency ($\beta\neq0.5$), some differences in correction frequency between the two types of mispair (p for *AY*, q for *XB*) at a site, and very large differences in direction of repair (r for *AY*, s for *XB*). Unlike 6:2/2:6 disparity, 5:3/3:5 disparity does not depend at all on correction direction parameters r and s, unless there is a significant amount of symmetric hDNA.

One way to get 5:3/3:5 disparity without chromatid invasion preference would be if the strand invasion parameter δ had an extreme value, say 0.0 as in *Ascobolus* (Lamb & Zwolinski, 1992), and the two mispairs corrected with different frequencies, say $p>q$. In asymmetric hDNA, *AY* mispairs arise in formerly *m* chromatids from $\beta(1-\delta)$ events and have correction frequency p and correction direction r. *XB* mispairs arise in formerly + chromatids from $(1-\beta)$ $(1-\delta)$ events and have correction frequency q and correction direction s. With no chromatid invasion preference and complete strand invasion preference, $\delta=0.0$, there would be equal numbers of +,+,*AY*,*m*, (type 1) and +,*XB*,*m*,*m*, (type 2) tetrads before any correction. Type 1 gives 5:3 if not corrected, and if corrected (frequency p) gives 6:2 or correction 4:4, depending on r. Type 2 gives 3:5 if not corrected, and if corrected (frequency q) gives 2:6 or correction 4:4, depending on s. If p is high, type 1 gives few 5:3s and mainly 6:2s and correction 4:4s; if q is low, type 2 gives mainly 3:5s and a smaller number of 2:6s and correction 4:4s. The 3:5s would greatly exceed 5:3s, giving strong 5:3/3:5 disparity to *m*. The 6:2s would probably greatly exceed the 2:6s, giving strong 6:2/2:6 disparity in the opposite direction, to +, but the proportions of 6:2s to 2:6s (but not of 5:3s to 3:5s) would depend on r and s, which determine the proportions of *AY* and *XB* going to 6:2, 2:6 and correction 4:4s. One can therefore understand how opposite directions of 6:2/2:6 and 5:3/3:5 disparity can occur from asymmetric hDNA. The statement of Lamb (1996a), that 5:3/3:5 disparity without 6:2/2:6 disparity is not expected on any recombination model, is wrong and is withdrawn.

With symmetric hDNA (Lamb, 1988), $5:3/3:5=[p(1-q)r+(1-p)qs]/[p(1-q)\quad(1-r)+(1-p)q(1-s)]$, so this kind of disparity depends only on correction parameters p, q, r and s, not on any of the hDNA formation parameters such as β or δ, and $6:2/2:6=rs/(1-r)$ $(1-s)$. The common dependence of both types of disparity on correction direction parameters r and s suggests that both types of disparity will usually occur together, in the same direction, from symmetric DNA.

In yeast, restoration corrections (to the original allele) and substitution corrections (replacement of the original allele by the the invading allele) have been found to be unequal — see Lamb (1996a, p. 1044) for findings and references. Whether such a bias affects overall disparity depends on the relative frequencies of the two types of invasion in asymmetric hDNA (by DNA carrying the + or the *m* allele) and on the degrees of preference for one type of correction, which might differ for the two types of mispair. Parameters p, q, r and s might have different values for restitutions and for substitutions, but without affecting how disparity can arise.

The double-strand break-repair (DSBR) model

On this model (Szostak *et al*., 1983; Orr-Weaver & Szostak, 1985; Sun *et al*., 1991), g is the chance of the heterozygous site being in a region of double-strand gap and repair. In the original model it was assumed that the two types of nonsister chromatid were gapped with equal frequency, to explain the supposed parity in yeast. If different chromatids were gapped or broken at different frequencies, it would cause 6:2/2:6 disparity, but the usual expectation is for the two strands to be affected at equal frequencies. The *HO*-induced cutting at the *MAT* locus (Kolodkin *et al*., 1986) was so efficient that 4α:0*a* tetrads were produced rather than 3α:1*a*. It is strange, however, that there was complete 4:0/0:4 disparity, but incomplete and nonsignificant 3:1/1:3 disparity, which had a much smaller sample size.

If there is gapping of the two types of chromatid (bearing + and m) with unequal frequencies, and the gap is repaired, then as gap repair results in asymmetric hDNA formation, this gives $\beta \neq 0.5$. If the endonuclease results in a break but no gap, and leads to hDNA formation on the DSBR model, β is affected. The data of Kolodkin *et al*. (1986) show an extreme value of β, because of the extreme disparity between conversion to α and to a, and a high value of γ_2 as conversions were nearly all 4:0, not 3:1.

In complicated variations on the DSBR models, as in Gilbertson & Stahl (1996), the quantitative treatment of disparity given here does not accommodate all their details, and attempts to do so would prove unwieldy. The present treatment is to show the main principles of how disparity can arise, but it is not exhaustive.

Effects of disparity on allele frequencies in populations

The force of conversion on allele frequencies, y, is the product of c and d. Petes & Pukkila (1995) stated that meiotic conversion occurs at all loci with frequencies from 1 to 50%, but some c-values in yeast are lower than 0.01 (Lamb, 1984) and Detloff *et al*. (1991) recorded conversion frequencies up to 55% ($c = 0.55$) in yeast. Overall disparity is what matters for allele frequencies, not separate 6:2/2:6 and 5:3/3:5 disparities.

In yeast data previously analysed, for deletions and frameshifts, c ranged from 0.029 to 0.131, d from -0.079 to $+0.139$, and y from -0.0049 to $+0.0063$ (Lamb, 1986). For 62 observations mainly from base-substitutions, c ranged from 0.0016 to 0.181, mean 0.043, SD 0.038; d varied from -0.25 to $+0.17$, with a mean absolute value of 0.06, SD 0.08; y varied from -0.005 to $+0.020$, mean absolute value 0.002, SD 0.003 (Lamb, 1984, 1985). For the newer data (Table 6), excluding small samples, conversion frequencies were generally higher than in the previous data, with c from 0.031 to 0.548. Disparity was very high in the newer data in special situations, such as *HO*-cutting or heterozygous deletions in a recombination-initiating region, $+0.1501$ to $+0.4527$, and ranged from none to high in more normal situations. For newer data, y-values were most extreme for *MAT*, $+0.0711$, and varied from -0.0354 to $+0.0463$ for base-substitutions, a frameshift and palindromic additions. The mean absolute value of y in the newer data (Table 6) was 0.012, compared with 0.002 in the earlier yeast data, 0.004 in *S. brevicollis*, 0.004 in Pasadena strains of *A. immersus*, and 0.011 in European strains of *A. immersus*. The high average value in the newer data is partly because some loci used had unusually high conversion frequencies.

In a population polymorphic for alleles A (frequency p) and a (frequency q), with random mating and no selection, the change in p in one generation because of gene conversion disparity is $\Delta p = 2pqy$ (Lamb & Helmi, 1982). The present and previous y-values for yeast will thus often make conversion an important factor in allele frequencies, capable of driving populations to fixation for whichever allele is favoured by conversion disparity. If there is selection and mutation, conversion can still be important, given these yeast values for y: see numerical examples in Lamb & Helmi (1982) and Lamb (1985), including how y can affect allele frequencies for different dominance conditions, mutation frequencies and selection levels.

Meiotic gene conversion disparity could thus often affect allele frequencies in sexually reproducing yeast colonies. The typically large numbers of individuals in such colonies would increase the importance of conversion relative to genetic drift. Disparity in direction of mitotic gene conversion in heterozygous diploids could also affect allele frequencies.

Conclusions

Gene conversion disparity is widespread for all kinds of mutation in yeast: base-substitutions, frameshifts, longer additions and deletions, and palindrome additions, when sample sizes are adequate for its detection. The occurrence of frequent disparity supports recombination models in which conversion comes largely from hDNA, not largely from double-

strand gap-repair. Disparity can be for 5:3/3:5 and/or for 6:2/2:6 classes; there is little correlation in yeast between these two types of disparity, which were more often in opposite directions than in the same direction.

There was little correlation between a mutation's molecular nature (or that of the mispairs in the heterozygote) and the amount or direction of disparity. Disparity sometimes depended on a mutation's position within a locus, but not systematically. It can also depend on mutations at other loci, such as *RAP1*. It is not usually possible to predict when disparity will occur, nor its direction or extent. Disparity results from heteroallelic crosses can be misleading because of co-conversion effects.

Conversion disparity has a number of different origins. The most frequent cause of 6:2/2:6 disparity from asymmetric hDNA is correction direction disparity, as that does not cause simultaneous 5:3/3:5 disparity. 6:2/2:6 disparity could also be caused by unequal invasion frequencies of the two types of nonsister chromatid in asymmetric hDNA, either directly or as a consequence of different frequencies in double-strand gaps or breaks in the two types of chromatid.

5:3/3:5 disparity has two possible origins. One is from unequal invasion frequencies of the two types of nonsister chromatids in asymmetric hDNA, but that is unlikely to be the major origin in these yeast data as it should tend to give 6:2/2:6 disparity in the same direction as 5:3/3:5 disparity, which only happened once in these data. A more likely origin is bias in strand invasion frequency ($\delta \neq 0.5$) and a difference in correction frequency of the two mispairs, *AY* and *XB*, ($p \neq q$). That will usually give opposite directions for the two kinds of disparity, unless affected by correction direction bias for the 6:2/2:6 disparity. Correction direction disparity does not affect 5:3/3:5 disparity from asymmetric hDNA, but would from symmetric hDNA.

The high conversion frequencies and large amounts of disparity frequently shown here in yeast mean that gene conversion could often be a powerful force in changing allele frequencies, especially in large microbial populations when genetic drift is relatively less important. Sometimes the wild-type allele is favoured, sometimes the mutant allele.

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