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Evolution

Effects of linkage on rates of molecular evolution

(substitution rate/neutral mutations/selected mutations/recombination/Hill–Robertson effect)

C. WILLIAM BIRKY, JR.†‡, AND J. BRUCE WALSH§

†Department of Molecular Genetics, The Ohio State University, 484 West 12th Avenue, Columbus, OH 43210; and §Department of Ecology and Evolutionary Biology, Biological Sciences West, The University of Arizona, Tucson, AZ 85721

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ABSTRACT **When an advantageous mutation is fixed in a population by selection, a closely linked selectively neutral or mildly detrimental mutation may "hitchhike" to fixation along with it. It has been suggested that hitchhiking might increase the rate of molecular evolution. Computer simulations and a mathematical argument show that complete linkage to either advantageous or deleterious mutations does not affect the substitution of selectively neutral mutations. However, the simulations show that linkage to selected background mutations decreases the rate of fixation of advantageous mutations and increases the rate of fixation of detrimental mutations. This is true whether the linked background mutations are advantageous or detrimental, and it verifies and extends previous observations that linkage tends to reduce the effects of selection on evolution. These results can be interpreted in terms of the Hill–Robertson effect: a locus linked to another locus under selection experiences a reduction in effective population size. The interpretation of differences in evolutionary rates between different genomes or different regions of a genome may be confounded by the effects of strong linkage and selection. Recombination is expected to reduce the overall rate of molecular evolution while enhancing the rate of adaptive evolution.**

It is generally accepted that different kinds of sequences, including closely linked genes or parts of a single gene, may have different evolutionary rates. This principle is widely used by molecular biologists to identify functional sequences by their relatively high degree of evolutionary conservation. Moreover, significant differences in evolutionary rates are found between the three positions in individual codons, and these differences are generally attributed to relatively weak, or no, selection operating on base pair substitutions that do not result in amino acid replacements or that replace one amino acid with another similar one (1).

The body of evolutionary theory on which these ideas are based includes a number of assumptions that make the mathematics tractable. In particular, it is usually assumed that different sites in a genome, or even in a gene or codon, evolve independently. This assumption would be valid if all mutations were neutral. Watterson (2) showed that complete linkage does not affect the rate of base pair substitution when all mutations are completely neutral. But plausible suggestions have been made that closely linked mutations might affect each other's fixation if some of them were subject to selection. For example, Brown *et al.* (3) suggested that the rate of fixation of neutral mutations might be accelerated by hitchhiking along with advantageous mutations. Rice (4) argued that the evolution of the inactive animal Y chromosome involved the accelerated fixation of mildly detrimental mutations linked to advantageous mutations. These suggestions were evidently based on the intuition that the fixation probability of a neutral or detrimental mutation, which is normally quite low, might be increased by linkage to an advantageous mutation. When linkage is complete, the unit of selection is a whole chromosome. Then a chromosome carrying a neutral or mildly detrimental mutation together with a strongly advantageous mutation will have a positive selection coefficient and a high probability of fixation. By the same reasoning, detrimental mutations should slow the rate of substitution of linked neutral and weakly advantageous mutations (hitchhiking with a driver going backward). In contrast, Schaeffer and Aquadro (5) and Cann *et al.* (6) felt that it is unlikely that linkage would affect the fixation probability of a neutral mutation, but the latter proposed that the accumulation of detrimental mutations might be increased in the absence of recombination.

There has been no rigorous theoretical treatment of any of these cases. In contrast, there is extensive literature on the evolutionary advantage of recombination, in which it has been shown that the accumulation or fixation of advantageous mutations is decreased by linkage to other advantageous mutations, and the accumulation or fixation of detrimental mutations is increased by linkage to other detrimental mutations (7–16). Thus, it is clear that at least some combinations of linked sites do not evolve independently. It is important to know what effects selection at one site will have on the rate of evolution of a linked site, since this will affect our interpretation of the sequence data used to study evolution at the molecular level. The possible effects of linkage might be particularly important in the genomes of mitochondria and chloroplasts, where biparental inheritance and recombination are often reduced or undetectable (17). In those plants in which both mitochondrial and chloroplast genes are inherited only from the female parent, the two genomes behave as if they are linked to each other. However, linkage effects in organelle genomes may be reduced by random drift of gene frequencies within heteroplasmic cells (10).

Analytic Results

We wished to evaluate the effects of linkage for all combinations of advantageous, detrimental, and neutral mutations. We asked first if neutral substitutions are affected by linked mutations under selection. For the extreme case of complete linkage, this problem can be treated analytically by the following simple argument. The rate of base pair (or amino acid) substitution in the course of evolution is given by

$$E = MF, \qquad [1]$$

where E is the expected per generation substitution rate (Et is the expected number of substitutions in t generations, ignoring time to fixation), M is the per generation mutation rate, and F is the expected probability of fixation of a newly

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‡To whom reprint requests should be addressed.

arising mutant. Eq. 1 demonstrates the connection between fixation probability and rates of substitutions. For a neutral allele A at starting frequency x, $F = x$. If this fixation probability remains unchanged when completely linked to a selective background, rates of substitution at the neutral locus are unchanged.

Let the frequency of allele A at a neutral locus be x. Hence, the frequency of all remaining alleles (collectively referred to as allele a) is $(1 - x)$. This locus is completely linked to a locus at which selected mutants arise. To gain insight into the general case, first consider an extreme case—the newly arising selected mutant is infinitely advantageous and immediately goes to fixation. With probability x, the selected mutant is linked to A and hence A is fixed. Otherwise it is linked to a and A is lost. For this case, the probability of fixation for A is x, as it would be if there were no hitchhiking.

For the general case, let A^* (or a^*) denote the specific copy of A (or a) to which the newly arising selected mutation is linked. Thus, the neutral gene linked to the selected mutation is counted as a different allele. With probability x the linkage is to A, and the starting allele frequencies are $\text{freq}(A^*) = 1/2N$, $\text{freq}(A) = x - 1/2N$ (one copy of A is linked to the selected site), $\text{freq}(a) = 1 - x$. Likewise, with probability $(1 - x)$, the linkage is to a and the starting frequencies are

$$\begin{aligned}\text{freq}(A) &= x,\\ \text{freq}(a) &= 1 - x - 1/2N,\\ \text{freq}(a^*) &= 1/2N.\end{aligned}$$

Let F^* be the probability of fixation of the selected allele. The probability that A is fixed is the sum of three conditional probabilities:

$$\begin{aligned}\text{Prob}(A \text{ fixed}) = x[&\text{Prob}(A^* \text{ is fixed})\\ &+ \text{Prob}(A \text{ is fixed} \mid A^* \text{ is lost})]\\ &+ (1 - x)\text{Prob}(A \text{ is fixed} \mid a^* \text{ is lost}).\end{aligned}$$

If the selected allele is lost, the probabilities of fixation for the remaining two neutral alleles are their relative frequencies:

$$\begin{aligned}\text{Prob}(A \text{ fixed} \mid A^* \text{ is lost}) &= \text{freq}(A)/[\text{freq}(A) + \text{freq}(a)]\\ &= (x - 1/2N)/(1 - 1/2N)\\ &= (2Nx - 1)/(2N - 1).\end{aligned}$$

Likewise,

$$\begin{aligned}\text{Prob}(A \text{ fixed} \mid a^* \text{ is lost}) &= \text{freq}(A)/[\text{freq}(A) + \text{freq}(a)]\\ &= 2Nx/(2N - 1),\end{aligned}$$

giving

$$\begin{aligned}\text{Prob}(A \text{ fixed}) &= xF^* + x(1 - F^*)[(2Nx - 1)/(2N - 1)]\\ &\quad + (1 - x)(1 - F^*)[2Nx/(2N - 1)]\\ &= xF^* + [(1 - F^*)/(2N - 1)][x(2N - 1)]\\ &= xF^* + x(1 - F^*) = x.\end{aligned}$$

Thus, the fixation probability, and hence the rate of evolution, of neutral alleles is not changed by the occurrence of a linked mutation under selection. The mathematical treatment shows that although a neutral allele may hitchhike to fixation with an advantageous mutation, the increased likelihood of its fixation is exactly balanced by a decrease in the fixation probability of the other neutral allele(s) segregating in the same population. The same argument in reverse holds for effects of detrimental mutations on the fixation of neutral alleles. The exact form of selection appears only in F^*, which cancels. Thus, our results hold for any selection scheme, provided alleles A and a remain neutral.

Simulation Results

We used computer simulations (Macintosh Turbo Pascal source can be obtained from J.B.W. upon request) to verify this result and to examine the effects of selection with complete linkage on the fixation of mutations under selection. We use "site" to refer to the locus at which substitutions were followed, and "background genome" to refer to the rest of the genome. Site and background genome mutation rates are denoted by μ_s and μ_g, respectively. Background selection coefficients (and site selection coefficients, where appropriate) were drawn from an exponential distribution and were either restricted to $s \geq 0$ (with mean denoted by $s+$) or $s \leq 0$ (denoted $s-$). Fitnesses were assumed to be additive—i.e., the genome fitness is simply the sum of the fitness of the site plus fitness of the background. Mean fitness was normalized each generation to remove scale effects. Quantities scaled by population size ($N\mu_s$, $N\mu_g$, $Ns+$, $Ns-$) were used, with a population size $N = 50$, simulated for $100/\mu$ generations. The mean number of substitutions (k) in each of 20 replicate populations was computed. For strictly neutral mutations, the expected number $k = 100$.

Table 1. Mean number of substitutions (k) at a neutral site

Selective background		Site mutation rate $N\mu_s = 1.0$	Site mutation rate $N\mu_s = 10.0$
Neutral		$k = 101.1$	$k = 99.0$
		$\text{Var}(k) = 100.8$	$\text{Var}(k) = 64.0$
$Ns+ = 1.0$	$N\mu_g = 0.1$	$k = 99.5$	$k = 100.7$
		$\text{Var}(k) = 75.1$	$\text{Var}(k) = 52.5$
	$N\mu_g = 1.0$	$k = 100.3$	$k = 100.6$
		$\text{Var}(k) = 59.6$	$\text{Var}(k) = 90.9$
	$N\mu_g = 10.0$	$k = 99.2$	$k = 100.0$
		$\text{Var}(k) = 96.7$	$\text{Var}(k) = 104.1$
$Ns+ = 10.0$	$N\mu_g = 0.1$	$k = 99.4$	$k = 101.4$
		$\text{Var}(k) = 110.1$	$\text{Var}(k) = 63.3$
	$N\mu_g = 1.0$	$k = 104.3$	$k = 101.9$
		$\text{Var}(k) = 91.2$	$\text{Var}(k) = 141.1$
	$N\mu_g = 10.0$	$k = 104.3$	$k = 97.0$
		$\text{Var}(k) = 91.2$	$\text{Var}(k) = 91.5$
$Ns- = 1.0$	$N\mu_g = 0.1$	$k = 99.6$	$k = 101.2$
		$\text{Var}(k) = 88.8$	$\text{Var}(k) = 97.6$
	$N\mu_g = 1.0$	$k = 104.0$	$k = 100.4$
		$\text{Var}(k) = 166.7$	$\text{Var}(k) = 99.4$
	$N\mu_g = 10.0$	$k = 98.5$	$k = 98.5$
		$\text{Var}(k) = 140.2$	$\text{Var}(k) = 69.7$
$Ns- = 10.0$	$N\mu_g = 0.1$	$k = 101.6$	$k = 101.7$
		$\text{Var}(k) = 145.3$	$\text{Var}(k) = 139.2$
	$N\mu_g = 1.0$	$k = 101.0$	$k = 99.8$
		$\text{Var}(k) = 92.6$	$\text{Var}(k) = 66.2$
	$N\mu_g = 10.0$	$k = 98.0$	$k = 97.6$
		$\text{Var}(k) = 143.0$	$\text{Var}(k) = 113.4$

Mean number of substitutions at a selectively neutral locus after $100/\mu$ generations, under a variety of selective backgrounds. Fitnesses were drawn from an exponential distribution with mean $Ns+$ (for selection coefficients restricted to $s \geq 0$) or $Ns-$ (s restricted to $s \leq 0$). k is the mean number of substitutions, averaged over 20 replicates, and $\text{Var}(k)$ is the variance in replica means. None of the means differs significantly from 100, the expected number of substitutions in a neutral background. The expected variance in a neutral background (from the Poisson) is also 100. Only one of the variances is slightly significantly different from 100, $\text{Var}(k) = 52.5$ (for $N\mu_s = 10.0$, $Ns+ = 1.0$, $N\mu_g = 0.1$), probability = 0.047 (by χ^2). However, in 26 trials, it is not unexpected that one of the values deviates at the 0.05 level.

Table 2. Mean number of substitutions (k) at a negatively selected site

Selective background		Site mutation rate $N\mu_s = 1.0$	Site mutation rate $N\mu_s = 10.0$
Neutral		k = 50.8 (a)	k = 65.8 (a)
		Var(k) = 36.6	Var(k) = 45.5
$Ns+ = 1.0$	$N\mu_g = 0.1$	k = 53.7 (ab)	k = 62.7 (a)
		Var(k) = 66.3	Var(k) = 57.2
	$N\mu_g = 1.0$	k = 61.8 (c)	k = 64.4 (a)
		Var(k) = 61.7	Var(k) = 20.4
	$N\mu_g = 10.0$	k = 70.7 (d)	k = 74.3 (b)
		Var(k) = 62.2	Var(k) = 54.4
$Ns- = 1.0$	$N\mu_g = 0.1$	k = 53.2 (abe)	k = 62.5 (a)
		Var(k) = 54.8	Var(k) = 37.5
	$N\mu_g = 1.0$	k = 58.4 (bcef)	k = 63.3 (a)
		Var(k) = 34.6	Var(k) = 70.9
	$N\mu_g = 10.0$	k = 61.3 (cf)	k = 67.4 (a)
		Var(k) = 51.6	Var(k) = 40.2

Mean number of substitutions at a locus where all new alleles are negatively selected. Fitnesses are drawn from an exponential distribution mean $Ns- = 1.0$. Background fitnesses drawn from independent exponential distribution with means indicated on the table. Lowercase letters (a–f) adjacent to k indicate significance of pairwise comparisons. Within each column ($N\mu_s$ value), means not significantly different (at the 0.01% level) share the same letter; means with no common letters are significantly different from each other. Data are plotted in Fig. 1.

We first simulated the case with complete linkage between site and genome. Means and between-replicate variances with complete linkage are given in Tables 1–3, and results for selected sites are plotted in Fig. 1. These results verify previous studies, which showed that advantageous mutations interfere with each other's accumulation or fixation when linkage is strong, while detrimental mutations facilitate each other's accumulation or fixation. They further show that detrimental mutations also interfere with the fixation of advantageous mutations and verify the suggestion of Cann *et al.* (6) that advantageous mutations enhance the fixation of detrimental mutations. The magnitude of these effects depends on the total mutation rate in the background, which is a function of the mutation rate per site, and also of the total number of sites that are subject to selection. The effect is also a function of the mean selection coefficient of the mutations.

We next simulated partial linkage between site and background genome (Table 4). With no linkage (i.e., free recombination; $r = 0.5$), selection in the background genome still interferes with selection at the site to some extent as was originally demonstrated analytically by Robertson (14) for advantageous mutations. Decreasing recombination (i.e., increasing linkage) increases the extent to which selection in the background genome interferes with selection at the site. Our results agree with those of Pamilo *et al.* (13), who found that the rate of accumulation of advantageous mutations was higher, and the rate of accumulation of deleterious mutations was lower, for breeding systems with increasing degrees of sexual reproduction and outcrossing.

Felsenstein (7–9) has argued that these phenomena can be explained by noting that selection at a locus increases the variance in the number of offspring produced by different individuals. This increased variance is equivalent to a reduction in the (variance) effective population size (14–16). The reduced effective population size in turn increases the effectiveness of random genetic drift while decreasing the effectiveness of selection. This phenomenon is enhanced by linkage. Following Felsenstein (7), we call this the Hill–Robertson effect.

There is no rigorous general analytic treatment of the Hill–Robertson effect. Thus, it is not possible to decide whether it is sufficient to explain all of the simulation results. However, Felsenstein's interpretation makes two predictions. First, if the effect of selection on linked genes is entirely due to reduced effective population size, then selection should not affect the fixation of linked neutral mutations because their fixation probability is independent of the effective population size (18). Second, selection of either

Table 3. Mean number of substitutions (k) at a positively selected site

Selective background		Site mutation rate $N\mu_s = 1.0$	Site mutation rate $N\mu_s = 10.0$
Neutral		k = 184.1 (a)	k = 151.0 (a)
		Var(k) = 135.9	Var(k) = 66.2
$Ns- = 1.0$	$N\mu_g = 0.1$	k = 189.8 (a)	k = 149.1 (a)
		Var(k) = 170.1	Var(k) = 86.7
	$N\mu_g = 1.0$	k = 186.5 (a)	k = 144.7 (a)
		Var(k) = 199.6	Var(k) = 58.7
	$N\mu_g = 10.0$	k = 166.2 (b)	k = 145.3 (a)
		Var(k) = 182.6	Var(k) = 74.1
$Ns+ = 1.0$	$N\mu_g = 0.1$	k = 175.0 (b)	k = 147.2 (a)
		Var(k) = 88.2	Var(k) = 53.8
	$N\mu_g = 1.0$	k = 172.4 (b)	k = 148.1 (a)
		Var(k) = 210.7	Var(k) = 71.8
	$N\mu_g = 10.0$	k = 150.2 (c)	k = 132.0 (b)
		Var(k) = 131.1	Var(k) = 80.2

Mean number of substitutions at a locus where all new alleles are positively selected. Fitnesses are drawn from an exponential distribution mean $Ns+ = 1.0$. The remainder are the same as for Table 2.

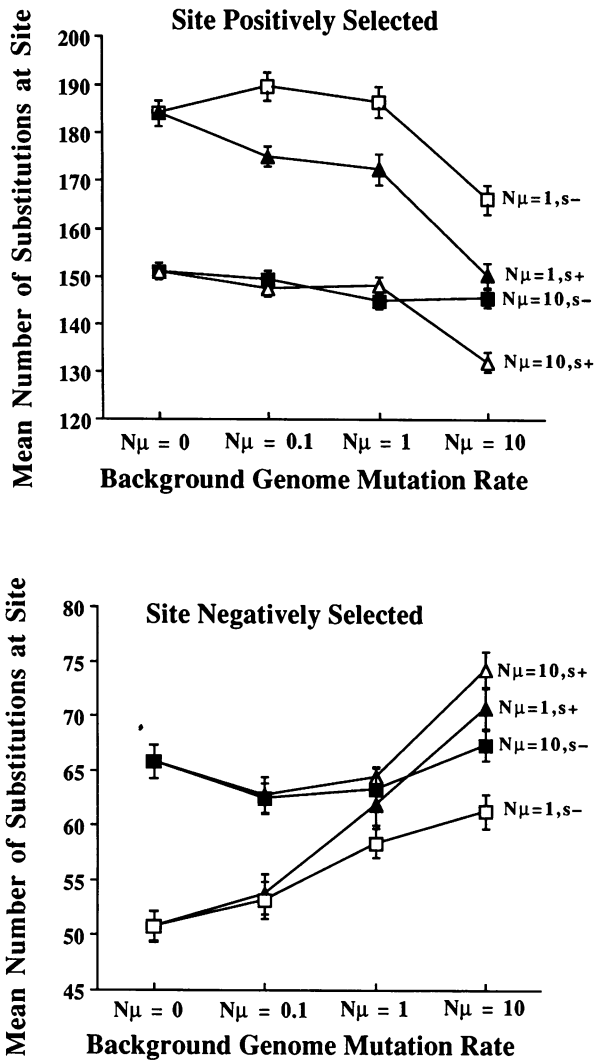

FIG. 1. Mean number of substitutions in $100/\mu$ generations for sites either positively or negatively selected, under different site and background mutation rates, and different background fitnesses. Error bars denote ±1 SEM. Fitnesses are drawn from an exponential distribution. For new alleles at the site positively selected, exponential distribution has mean $Ns+ = 1$, and for the site negatively selected, mean $Ns- = 1$.

detrimental or advantageous genes should have the same qualitative effects on the fixation of selected linked loci—namely, reducing the effect of selection on the fixation of mutations. However, the effect of detrimental mutations should be weaker than the effects of advantageous mutations having the same selection coefficient, because on average the detrimental mutations do not persist as long, or reach as high frequencies, in the population, resulting in a smaller decrease in effective population size. Our results verify both of these predictions, extending previous studies to include effects of advantageous mutations on neutral and detrimental mutations, and of detrimental mutations on neutral and advantageous mutations. While this does not prove that the Hill–Robertson effect is a sufficient explanation, or is the only possible explanation, for the effects of linkage on substitution rates, it strengthens the argument substantially.

The observed variance of evolutionary rates is greater than expected from a simple Poisson distribution (19, 20). For neutral sites linked to a selective background, our simulation results did not detect any variances significantly different from the expected Poisson variance of 100 [from the χ^2, the 95% confidence interval for a true variance of 100 is (46.9, 172.9), which encloses all our observed variances]. Thus, our data do not suggest that linkage to a selected background, by itself, can account for excess variances in rates of neutral substitutions. This is consistent with the findings of Gillespie (19) in which the ratios of the observed variance to the mean are not consistently greater for mitochondrial genes than for nuclear genes in mammals, even though there is no recombination in mammalian mitochondrial genes.

Table 4. Effect of recombination on mean number of substitutions (k) at a selected site

Recombination rate, r	Site positively selected ($Ns+ = 1.0$)	Site negatively selected ($Ns- = 1.0$)
0	150.2 ± 2.6 (a)	70.7 ± 1.8 (a)
0.001	147.7 ± 2.8 (a)	69.5 ± 1.6 (a)
0.01	160.4 ± 2.9 (b)	68.0 ± 1.9 (a)
0.02	163.2 ± 2.4 (b)	64.5 ± 1.6 (b)
0.1	171.9 ± 2.7 (c)	57.4 ± 1.9 (c)
0.5	173.6 ± 2.7 (c)	57.2 ± 1.9 (c)
Background neutral	184.1 ± 2.7 (d)	50.8 ± 1.4 (d)

The effect of partial recombination on rates of evolution. The two sets of parameters chosen correspond to the two most extreme cases seen in simulations assuming no recombination. r is the recombination frequency between the site being followed and the selected locus in the background genome. Within a column, means not significantly different from each other share the same letter, while means with different letters are significantly different. Mean number of substitutions ± 1 SEM. Scaled mutation rates at genome and site, respectively, were $N\mu_g = 10.0$ and $N\mu_s = 1.0$. For all cases but "Background neutral," the genomic background was positively selected, with $Ns+ = 1.0$.

We simulated a single evolutionary line of descent. In real life, evolutionary rates are not measured along a single line of descent, since ancestral sequences are not available for comparison. Instead, a gene is sequenced from two (or more) extant species and divergence rates are calculated on the assumption that the sequences began to diverge when the species diverged from a common ancestral species. This is not strictly true because the founding populations of the species being compared share gene lineages that diverged τ generations earlier within the population of the ancestral species. This increase, τ, in time back to a common ancestral DNA molecule is geometric with mean $2N$ generations for a diploid in the absence of selection (21, 22). Ignoring τ introduces a bias, inflating the substitution rate because the true divergence time is underestimated. This effect is negligible if τ is small relative to the time of isolation of these populations from each other. Directional selection reduces τ, hence reducing the bias, while balancing selection increases τ (relative to a neutral allele), hence increasing the bias in the estimated substitution rate. Thus, our results for substitution rates of neutral alleles on selected backgrounds are not strictly applicable to real data because selection influences τ. But as noted above, the effect is likely to be negligible except for very recently diverged species.

Implications

Our data on evolutionary rates have several important consequences for evolutionary studies of base sequences and amino acid sequences. First, if a class of mutations can be shown to be neutral on physiological evidence, then their evolutionary rate accurately estimates their mutation rate, regardless of the presence of closely linked mutations under selection. For example, the rate of evolutionary divergence of the base sequence of a pseudogene will be equal to the mutation rate (ignoring any effects due to shared polymorphisms as discussed previously), even if the pseudogene is closely linked to other nuclear genes that are subject to strong selection (e.g., see ref. 1). There have been no evolutionary

studies of pseudogenes in organelles, but these could also be used to estimate mutation rates even though they are completely linked to other organelle genes that are under stringent selective constraints.

Second, since there is some linkage in all genomes of all organisms, the substitution rate of advantageous mutations will always be lower, and the substitution rate of detrimental mutations will always be higher, than predicted by existing theory. In other words, the substitution rates of selected mutations will be closer to that of neutral mutations than predicted. Further analysis is required to determine the conditions under which linkage effects are negligible.

This poses a problem for the detection and interpretation of differences in evolutionary rates between different genes or regions of the genome (see ref. 23 for a possible example). These are presumably due to differences in selection pressures between the different regions in many cases, but the difference in substitution rates may actually underestimate the differences in selection intensity. When two adjacent regions are compared (e.g., see ref. 23), the boundaries between them may be blurred by linkage. And of course strong linkage will make it difficult to detect small differences in evolutionary rates.

Differences in selection intensities among different genes or genomes can also be evaluated by comparing the substitution rates of synonymous and nonsynonymous mutations. Selection on the former is generally thought to be weak, so the difference between synonymous rates and the lower nonsynonymous rates provides a minimum estimate of the intensity of selection. These comparisons may be fairly safe when different genes under similar recombination conditions are compared. But when genomes (or parts of genomes) having different recombination frequencies are compared, such as nuclear and organelle genomes, this comparison is compromised. For example, mitochondrial genomes have larger ratios of synonymous/nonsynonymous rates than do nuclear genomes in animals (24–26). The effect of linkage will be to cause these ratios to underestimate the effects of selection for both genomes. But it is not clear whether the error introduced by linkage will be greater for the mitochondrial genomes, in which linkage is complete and the mutation rate is high, or for the nuclear genomes, which have weaker linkage and lower mutation rates per gene but many more genes and larger effective population sizes. Again, more analysis is needed.

Finally, recombination provides yet another explanation for the frequently observed uncoupling of evolution at the molecular and phenotypic levels (27). Recombination increases the rate of substitution of advantageous mutations, decreases the rate for detrimental mutations, and does not affect neutral substitution rates. Thus, recombination enhances the rate of phenotypic evolution, to the extent that phenotypic evolution is driven by the fixation of advantageous mutations. But since detrimental mutations are more common than advantageous mutations, recombination may have the net effect of reducing the total number of substitutions as fixation probabilities for detrimentals increase with decreasing linkage. This reduction with increased recombination occurs provided

$$u_d/u_a > \Delta F_a/\Delta F_d,$$

where u_d and u_a are the total mutation rates to detrimental and advantageous alleles, respectively; ΔF_a is the difference in fixation probabilities of an advantageous mutation with and without recombination; and ΔF_d is the same for a detrimental mutation.

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