Selection on a Modifier of Recombination Rate Due to Linked Deleterious Mutations

S. Pálsson

Several models have been suggested to explain the origin and maintenance of recombination. Here I present the results from computer simulations of multilocus haploid and diploid genotypes in small populations. Each chromosome consisted of 1001 loci where deleterious mutations occurred. At "equilibrium" for mutation-selection-genetic drift balance a single recombination variant was introduced to the population in the middle of a chromosome. On average 75,000 replicates for each combination of parameters were followed to fixation or loss of the modifier allele. The results show that, in a small population, increased recombination can be selected, even in the absence of epistasis or beneficial mutations. The effect of the mutation rate for deleterious mutations depends on the ploidy level and the recessiveness of deleterious mutations. A higher deleterious mutation rate is required for an increase in recombination rate to be favored in haploid populations. Increased recombination could not evolve in the case of strong associative overdominance.

Different models have been proposed to explain the origin and maintenance of recombination. Several models, relying on large population size, have shown that modifiers that increase recombination are not favored except under some patterns of epistasis or environmental change (Feldman et al. 1997; Kondrashov 1993). However, by considering the stochastic behavior of new mutations and the Hill–Robertson effect (Hill and Robertson 1966) among selected loci with beneficial mutations and no epistatic effects, Otto and Barton (1997) found that a neutral modifier allele that increased recombination increased in frequency, on average, because linked beneficial mutations had a higher chance of fixation. The Hill–Robertson effect refers to a buildup of negative linkage disequilibrium, so that deleterious or positive mutations are in repulsion and the efficacy of selection of a site linked to other sites undergoing selection is weakened. The advantage or disadvantage of recombination follows the sign of the disequilibrium, negative linkage disequilibrium rendering an advantage to mixis, positive linkage disequilibrium to linkage. Recent studies by Gessler and Xu (1999) and Hey (1998) on haploid organisms have confirmed these predictions.

Selection in small diploid populations is not simply directional against chromosomes carrying harmful mutations (Pálsson and Pamilo 1999; Pamilo and Pálsson 1998). Chromosomes that are most divergent from each other carry different harmful mutations, and selection depends not only on the number of such mutations but also on how often they are expressed as homozygotes. This can result in frequency-dependent selection favoring rare variants at the level of chromosomes, with alleles at linked loci for deleterious alleles being in repulsion equilibrium, and in balancing selection when recombination is restricted. Such selection will promote neutral variation at linked loci by associative overdominance (Frydenberg 1963), opposite to the effect of background selection (Charlesworth et al. 1993), when linkage is tight and the product of population size (N), dominance (h), and selection (s) coefficients, Nhs, is small, that is, close to or lower than one (Pálsson and Pamilo 1999).

Heterozygote advantage, whether maintained by associative or functional overdominance, results in a segregational load (Crow 1970), which can be considerable if there are many deleterious mutations at linked loci (Franklin and Lewontin 1970; Pálsson 2001). As crossing over breaks down such chromosomal blocks and prevents the accumulation of harmful mutations, one might expect that a modifier fa-

From the Department of Conservation Biology and Genetics, Uppsala, Sweden. S. Pálsson is currently at the Institute of Biology, University of Iceland, Grensásvegur 12, 108 Reykjavík, Iceland. I thank Daniel Falush, Martin Lascoux, Pekka Pamilo, and Philip Hedrick for useful comments. This study was supported by the Icelandic Research Counsil and the Royal Swedish Academy of Sciences. Address correspondence to Snæbjörn Pálsson at the address above or e-mail: snaebj@hi.is.

 93:22–26

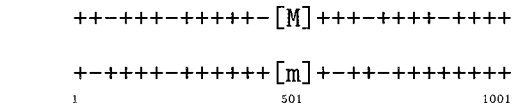

Figure 1. The simulated chromosome in the diploid model. Each chromosome consisted of 1001 loci with + and − alleles, denoting their effects on fitness (w). The fitness values of three possible genotypes at each loci were +/+ = 1, +/− = 1 − hs, and −/− = 1 − s. The fitness of the whole genotype was determined using a multiplicative model (see text). At the center of the chromosome was a locus determining the recombination rate: M/M = r, M/m = r', m/m = r'.

voring increasing recombination would be favored even further in diploid populations than in haploid populations.

Here I look particularly at the situations when the product of Nhs is close to one and explore whether the evolution of recombination rate, determined by a neutral modifier, depends on conditions resulting in associative overdominance (tight linkage) or in background selection at a neutral loci (Pálsson and Pamilo 1999), and in comparison, whether the evolution of recombination rate differs in diploid and haploid genotypes. The study is based on computer simulations of populations of individual chromosomes where the fate of a mutation modifying the recombination rate is studied; on average, 75,000 replicates for each combination of parameters were simulated.

Model

I simulated diploid genotypes consisting of a single pair of chromosomes carrying 1001 loci spread uniformly along the chromosome (as in Pálsson and Pamilo 1999) (see Figure 1). The number of new deleterious mutations per gamete in each generation was selected randomly from a Poisson distribution (with a mean of U), the sites at which deleterious mutations occurred being sampled from a uniform distribution. Mutation rates used in the simulations varied (2^*U = 1.0, 0.1, 0.05, 0.01 per diploid genome per generation, and U = 0.5, 0.05 per haploid genome per generation). These values are equal to or lower than mutation rates used by Hey (1998) and Pálsson and Pamilo (1999). Mating was random.

The range of parameters was selected both to allow comparisons with previous studies on haploid populations by Hey (1998) and diploid populations by Pálsson and Pamilo (1999), where the same parametric conditions as studied here led either to increased heterozygosity at a neutral marker due to associative overdominance or to a reduction in heterozygosity due to background selection (Charlesworth et al. 1993). Certain combinations were selected to explore whether mutation rates could alter the result. A higher mutation rate causes an increased mutational load, which can favor the effect of associative overdominance. At low mutation rates (U = 0.025 and 0.005) I present results with dominance and no recombination to study whether associative overdominance can arise. Simulations with no dominance (h = 0.5) allow comparison between haploid and diploid cases, as under diploidy no overdominance should be expected and are studied for U = 0.5 and 0.05.

The fitness of an individual was determined using a multiplicative model: $w_{yz} = (1 - s)^y(1 - hs)^z$, where y and z are the number of homozygous and heterozygous loci in its genome, respectively. The coefficient of selection (s) was equal to 0.1, and the dominance coefficient (h) was set to 0.1 or 0.5. The population size (N) was set to 100 or 500.

Haploid genotypes were modeled in the same way, except that they consisted of a single chromosome and the individual fitness was calculated as $w_y = (1 - s)^y$. The population size (N) was set to 200 or 1000 to keep the total number of chromosomes equivalent to the diploid model.

The model was first run for 2000 generations, with mutations and selection occurring at the background loci, after which a single neutral modifier mutation (in the frequency of 1/2N) was introduced at a locus in the middle of a chromosome sampled randomly from the population. The simulation was continued until the mutation was either fixed or lost. The recombination rates between adjacent loci were r = 0, 10^{-5}, 10^{-4}, or 10^{-3}. For each initial recombination rate (r) a dominant mutation was introduced which gave the same recombination rate or modified it to r' = 0, 10^{-5}, 10^{-4}, 10^{-3}. On average, 75,000 replicates were done for each parametric combination (replicates of each run are given in Table 1). Additional runs were done with tight initial linkage (r = 0) and with $h = s$ = 0.1 by introducing the modifier mutation after 500 generations (as the strength of associative overdominance may increase during the initial period) and then increasing the population size to 2000 individuals to test whether the effects of associative overdominance were still detectable in larger populations.

To follow the effects of linked selected loci on variation at the modifier locus I calculated the cumulative heterozygosity caused by a new neutral mutation as $H_c = 2\Sigma x_i(1 - x_i)$, where x_i is the frequency of the modifier allele in generation i before its fixation or loss. The expectation of cumulative heterozygosity is proportional to the expected nucleotide diversity and is equal to 2 under a strict neutral model without background selection (Charlesworth et al. 1993; Kimura 1969, 1971). H_c values greater than this expectation demonstrate the presence of associative overdominance. The heterozygosity (H_c) together with the probability of fixation P_o and number of generations to fixation (F_o) or loss (L_o) adds information on whether the modifier allele can invade the population and how well it persists. If the modifier allele sweeps through the population the number of fixations can be high and the heterozygosity low. If its selected against, both the number of fixations and heterozygosity will be low, and if it experiences frequency-dependent selection due to associative overdominance it can show high heterozygosity without being fixed.

To relate the fate of the modifier allele

Table 1. The ratio of the number of fixations of a modifier allele in diploid genotypes to the expected number of fixations with no background selection

h	U	r	$r' = 0$	$r' = 10^{-5}$	$r' = 10^{-4}$	$r' = 10^{-3}$
0.5	0.5	0	0.99 (75)	1.21* (75)	2.84* (88)	4.30* (65)
		10^{-3}	0.24* (88)	0.22* (100)	0.33* (75)	0.94 (75)
	0.05	0	1.05 (75)	1.08 (75)	1.12* (75)	1.07 (75)
		10^{-3}	0.74* (88)	0.69* (75)	1.07 (75)	1.01 (75)
0.1	0.05	0	0.00* (40)	0.00* (35)	0.00* (105)	0.00* (105)
		10^{-5}	0.00* (37)	0.00* (52)	0.43* (105)	0.53* (170)
		10^{-4}	0.09* (110)	0.30* (105)	1.03 (105)	1.19* (105)
		10^{-3}	0.14* (115)	0.22* (110)	0.66* (140)	0.94 (120)
	0.025	0	0.15* (40)	0.24* (31)	0.33* (85)	0.19* (85)
		10^{-5}	0.16* (40)	1.07 (71)	1.75* (75)	1.56* (75)
	0.005	0	0.93 (75)	1.07 (75)	1.07 (75)	1.00 (75)

r and r' are the recombination rates of the unmodified and modified chromosomes, respectively.
N = 100, s = 0.1.
The number of replicates (×1000) for a given observation is presented in parentheses.
* Denotes significant deviations from the neutral expectation ($P < .05$).

Table 2. The heterozygosities at the modifier locus

h	U	r	$r' = 0$	$r' = 10^{-5}$	$r' = 10^{-4}$	$r' = 10^{-3}$
0.5	0.5	0	0.4 (0.01)	0.43 (0.01)	0.70 (0.01)	1.60 (0.04)
		10^{-3}	0.23 (0.00)	0.22 (0.00)	0.28 (0.01)	0.79 (0.02)
	0.05	0	0.89 (0.02)	0.98 (0.02)	1.30 (0.04)	1.89 (0.06)
		10^{-3}	0.92 (0.02)	0.93 (0.02)	1.36 (0.04)	1.79 (0.05)
0.1	0.05	0	14.00[a] (0.61)	8.85[a] (0.49)	0.23[a] (0.02)	0.04 (0.00)
		10^{-5}	24.97[a] (0.96)	16.67[a] (0.65)	1.00[a] (0.06)	0.89 (0.03)
		10^{-4}	1.78[a] (0.08)	1.68[a] (0.09)	1.65 (0.04)	1.99 (0.05)
		10^{-3}	0.95 (0.03)	1.05 (0.03)	1.33 (0.03)	1.75 (0.04)
	0.025	0	16.06[a] (1.45)	10.73[a] (0.79)	0.62 (0.03)	0.31 (0.02)
		10^{-5}	16.59[a] (0.97)	6.39[a] (0.45)	2.03 (0.05)	2.10 (0.06)
	0.005	0	1.65 (0.06)	1.81 (0.05)	2.03 (0.06)	1.94 (0.06)

r and r' are the recombination rates of the unmodified and modified chromosomes, respectively. The results are based on the same simulations as presented in Table 1.

Standard errors are in parentheses.

[a] Estimated values are underestimates, see text.

with its genetic background at the same chromosome I noted the sign of the linkage disequilibrium ($p_{ij} - p_i p_j$) and calculated the test statistic Z_{nS} developed by Kelly (1997). Z_{nS} averages the values of linkage disequilibrium (d_{ij}), the squared correlation of allelic identity between loci i and j (see Hartl and Clark 1989) across all polymorphic sites in a region. I selected 10 polymorphic sites distributed uniformly along the chromosome.

A source code for the simulation program was written in C. Pseudo-random numbers were generated using procedures from Press et al. (1988).

Results

The proportion of modifier mutations that were fixed without background selection ($s = 0$) agrees well with the expectation of the neutral model ($P_n = 1/2N$). When $N = 100$, 256 fixations occurred in 50,000 replicates (0.0051), which is not significantly different from the expectation ($1/2N = 0.005$). The observed heterozygosity of the introduced alleles ($H_o = 2.049$) and the number of generation times to fixation or loss ($F_o = 421.7$ and $L_o = 10.1$, respectively) are also close to the neutral expectations of heterozygosity ($H_n = 2.0$), and to the number of generations to fixation ($F_n = 4N_e = 400$) and to loss ($L_n = (2N_e/N)\ln(2N) = 10.6$).

Diploid Model

The number of fixations at the modifier locus when recombination is not altered ($r = r'$) is in agreement with the expectation of the neutral model, except in some cases when linkage is tight (Table 1). Increased recombination is generally favored unless there is tight linkage, and recombination is favored more strongly at the high mutation rate in the case of no dominance ($h = 0.5$). When the deleterious mutations are recessive ($h = 0.1$), no fixations are observed at the modifier locus when $U = 0.05$, and when there is no recombination, at a low frequency of recombination ($r = 10^{-5}$), the modifier has a lower probability of being fixed than expected with no selection, but it more often gets fixed if it increases the recombination rate. If the modifier is introduced into a background with tight linkage ($r' = 0$ or 10^{-5}) at the mutation rate $U = 0.025$, recombination is favored, but at a still lower mutation rate ($U = 0.005$) the probability of fixation is not or is only slightly affected by the recombination rate determined by the modifier.

Heterozygosities at the modifier locus, as well as the probabilities of fixations, increased generally with increased recombination, except in cases when the variation exceeded the neutral expectation and when linkage was tight ($r = 0$ or 10^{-5}) (see Table 2 and Figure 2 which presents comparisons of the statistics for $N = 100$ and 500). The numbers of generations to loss (Figure 2c,f) were affected in a similar way as heterozygosity, although the average numbers never exceeded the neutral expectation. The number of generations to fixation (results not shown) generally increased with an increased recombination rate of the modifier allele r' and were close to the neutral expectation when $r' = 10^{-3}$, but a different behavior was observed in cases when the original linkage (r) was tight, that is, when $r = 0$, $r' > 0$, and $N = 500$, the number of generations to fixation decreased when r' increased.

The average amount of linkage disequilibrium (Z_{nS}) when the modifier was lost decreased with recombination rate, as expected. As an example, when $s = h = 0.1$ and $N = 100$, the linkage disequilibrium was 0.41, 0.21, 0.05, and 0.02 when recombination rate (r) was 0.0, 10^{-5}, 10^{-4}, and 10^{-3}, respectively. When a modifier allele for a higher recombination became fixed,

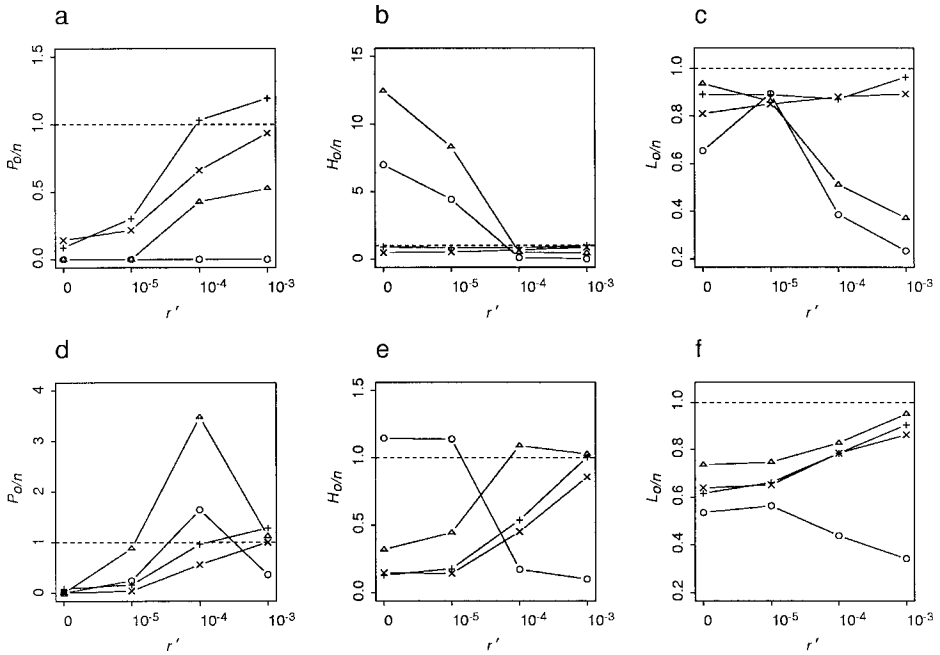

Figure 2. The effects of background selection at a neutral modifier locus. The upper row presents results of the simulations with $N = 100$ (also presented in Table 1) and the lower row with $N = 500$ based on 25,000 replicates for each simulation. $h = s = 0.1$. x axis: the recombination rate (r') caused by an introduced mutation. y axis: (a,d) ratio $H_{o/n}$ of the observed cumulative heterozygosity to the expected neutral heterozygosity; (b,e) ratio $P_{o/n}$ of the observed number of fixations to the expected neutral number of fixations; (c,f) ratio $L_{o/n}$ of the observed number of generations to loss to the neutral expectation of the number of generations to loss. The symbols {cir}, {utri}, +, and × denote the recombination rates (r) 0.0, 10^{-5}, 10^{-4}, 10^{-3}, respectively.

the linkage disequilibrium decreased, for example, when $r' = 10^{-3}$, Z_{nS} was one-third of the linkage observed when $r = 10^{-4}$, whereas when $r = 10^{-3}$, linkage disequilibrium increased by a multiple of three, and increased by a multiple of eight when modifiers were fixed that lowered recombination ($r' = 10^{-4}$, 10^{-5}). A negative disequilibrium (repulsion) was observed in all cases when selection favored increased recombination rate; a positive disequilibrium (coupling) was only observed when the modifier got lost, and it reduced the recombination rate, $r' < r$ and $r = 1.0$.

The number of segregating deleterious mutations increased and exceeded the allowed number of 150 mutations per gamete in some cases when linkage was tight. In such cases the simulations were stopped and the heterozygosity and other statistics are therefore underestimated. At a population size of 100 this occurred mainly when $r = 0.0$ or 10^{-5}, and $r' = 0.0$ or 10^{-5}, and when $N = 500$ the increase was observed when $r = 0.0$ and $r' = 0.0$ or 10^{-5}. The average frequency of the modifier allele fluctuated around 0.5 when the simulations were stopped (with most values close to the average), reflecting a balanced equilibrium maintained by frequency-dependent selection due to associative overdominance, as described in Pálsson and Pamilo (1999), where deleterious mutations accumulate within linked segments. Such cases, when accumulation of deleterious mutations occurred, are characterized by a cumulative heterozygosity (H_c) for neutral alleles well above the expectation of 2.0, varying from 6.4 to 25.0, whereas in the other cases (when the number of deleterious mutations did not accumulate), heterozygosities were less than or equal to 2.0, as expected under background selection (Table 2).

In the cases when the simulations were stopped, average linkage disequilibrium increased as well and became 1.3–2.5 times larger than when the modifier was lost, ranging from 0.48 to 0.78 (SE = 0.08 − 0.18). The increase was lowest when the modifier increased recombination from 0 to 10^{-5}.

Haploid Model

An increased recombination rate was favored when the mutation rate per gamete was high ($U = 0.5$; Table 3); however, at a lower mutation rate ($U = 0.05$), the number of fixations of the modifier was not significantly different from the expectation.

Table 3. The ratio of the number of fixations of a modifier allele to the number expected with no background selection in the haploid model

N	U	r	$r' = 0$	$r' = 10^{-3}$
200	0.5	0	0.96	1.27*
		10^{-3}	0.71*	0.99
	0.05	0	1.00	1.05
		10^{-3}	1.02	1.02
1000	0.5	0	1.00	2.40*
		10^{-3}	0.47*	1.04

r and r' are the recombination rates of the unmodified and the modified chromosomes, respectively.

The results are based on an average of 60,000 replicates each, $s = 0.1$.

* Denotes significant deviation from the neutral expectation ($P < .05$).

Discussion

Deleterious mutations can favor increased recombination rate if a genetic variation exists for such modifiers and resist an invasion of a modifier reducing recombination rate. In addition to the effect of increased mutation rate to favor recombination, a breakup of linked segments harboring deleterious mutations in diploid organisms can contribute further to the evolution of recombination.

The probability of fixation of a modifier allele that increases recombination increases above neutral expectations in the haploid model under a high mutation rate. In a study by Hey (1998) of small haploid populations, a neutral modifier increasing recombination was favored when mutations at the background loci were beneficial, but only slightly when background mutations were deleterious. A more recent study by Gessler and Xu (1999) showed a clear advantage of recombination in a haploid population with deleterious mutations. They interpreted their results in terms of Muller's ratchet, as increasingly favorable conditions were created for the spread of recombination as the ratchet proceeded faster forward with an increased mutation rate. This study shows a more complex dynamic in a diploid model with recessive mutations, as a larger number of mutations segregate within a population and increased recombination is favored at lower mutation rates than in a haploid model.

The fate of a modifier of recombination rate can be understood by considering the effects of background selection and associative overdominance. Selection against deleterious mutations leads to a stronger selection against the modifier allele if it reduces the recombination frequency, resulting in lower heterozygosity at the modifier locus, and it becomes more difficult for the modifier allele to invade the population. If the allele favors recombination, background selection will act more strongly against the original allele and the modifier allele will increase in frequency, resulting in an increase in both the average heterozygosity at the locus and in the fixation probability of the modifier allele.

A different behavior was observed in the diploid model, when linkage was tight and mutations were partially recessive, than in the haploid model. The heterozygosity of the modifier marker can be elevated due to strong associative overdominance, when selection favors heterozygous segments, and such a heterozygosity increasing effect would be strengthened by true overdominance at linked loci. In such cases the number of segregating deleterious alleles can accumulate. Since homozygous modifier locus may have an increased probability of being homozygous for a number of deleterious mutations, the modifier has a low or zero probability of being fixed and is strongly selected against, as seen with low heterozygosity values, even though it favors recombination. Increased recombination may in addition generate homozygous deleterious segments linked to the modifier when it is heterozygous and reduce further its probability to invade the population. One should note that increased recombination was favored compared to the case when the introduced mutation at the modifier locus did not alter the recombination rate when the effect of associative overdominance was weaker. Such results were observed when the recombination rate was $r = 10^{-5}$ but not at $r = 0$ when $U = 0.05$, and for $r = 0$ at a lower mutation rate of $U = 0.25$ (Table 1). The inertia toward increased recombination requires a sufficient number of segregating mutations; when the mutation rate is low or if the modifier mutation occurs before mutations start to accumulate, the modifier can be favored. When the modifier mutation is entered after 500 generations, increased recombination could evolve, although it has a lower chance of being fixed than with no background selection.

The results are similar for the two population sizes studied. However, a noteworthy difference is observed in cases where there is an accumulation of deleterious mutations, which occur under more stringent conditions when the population size is larger. Although the populations are of small size, the effects of associative overdominance are likely to hold in large diploid populations when the recombination

rate is close to zero. Additional runs with $N = 2000$ and no recombination resulted in accumulation of segregating mutations and elevated heterozygosity at the modifier locus compared to the neutral expectation. Whether the effect of associative overdominance can be of any importance in large populations, such as in *Drosophila,* may be questioned, but it is important to keep in mind that the effective population sizes are often only 10% of the actual size (Frankham 1996).

A more complex model than was studied here may be needed to explain selection for the evolution of reduced recombination if recombination already exists, which is known as the reduction principle (see Feldman et al. 1997). The reduction principle has been shown to apply with infinite populations and when there is stabilizing selection or overdominance at multiple loci with multiplicative selection but low recombination rate (Bergman and Feldman 1990; Maynard-Smith 1988), or any other model where linkage disequilibrium is maintained at equilibrium [Feldman et al. (1997), who present a extensive review of the studies on the evolution of recombination].

Several experiments have shown genetic variation for recombination rate [e.g., Korol and Iliadi (1994), and a recent review by Burt (2000)]. Variation in recombination rate has been found among species (Burt and Bell 1987) and individuals (Broman et al. 1998), among and along the chromosomes (e.g., True et al. 1996), and between the sexes with crossing over being more frequent in the homogametic sex, in accordance with a rule proposed by Haldane (1922). Such differences have been found in humans (Broman et al. 1998), and an extreme example is found in *Drosophila,* where crossing over is generally entirely suppressed in males. The recombination rate tends to be higher in domestic animals than in other animals (Burt and Bell 1987), who suggested that high rates of recombination could be indirectly selected in breeding programs because of their effect in removing negative correlations between favored traits.

This study suggests that it can be difficult for a modifier favoring an increased recombination rate to invade a population where associative overdominance has evolved. One example of such a situation may be found in crested newts (*Triturus cristatus carnifex* and *Triturus marmaratus*) (Macgregor and Horner 1980), where heteromorphism for chromosome 1 is a requirement for normal development; another one could be the evolution of the sex chromosomes. Self-incompatibility loci, major histocompatibility complex (MHC) loci, and sex-determining loci (where heterozygous loci may determine the development of one of the sexes) may be candidates for loci where any linked effects can be strengthened, and which would in turn affect the evolution at a modifier loci. Beye et al. (1999) found a hotspot of recombination in the sex locus region in the honeybee (*Apis mellifera*), which is characterized by a strong heterozygotic advantage possibly due to antagonistic selection. Whether such heterozygous loci may favor increased recombination, to uncouple the overdominant locus from the rest of the chromosome where harmful mutations could start to increase in frequency, appears to depend on the strength of the associative overdominance effect across the region. A response in increased recombination rate may result in mismatches between a physical map and a genetic map, and reduce any effects of deleterious mutations on linked neutral loci.

References

Bergman A and Feldman MW, 1990. More on selection for and against recombination. Theor Popul Biol 38:68–92.

Beeye M, Hunt GJ, Page RE, Fondrk MK, Grohmann L, and Moritz RFA, 1999. Unusually high recombination rate detected in the sex locus region of the honey bee (*Apis mellifera*). Genetics 153:1701–1708.

Broman KW, Murray JC, Sheffield VC, White RL, and Weber JL, 1998. Comprehensive human genetic maps: individual and sex specific variation in recombination. Am J Hum Genet 63:861–869.

Burt A, 2000. Perspective: sex, recombination and the efficacy of selection—was Weismann right? Evolution 54:337–351.

Burt A and Bell G, 1987. Mammalian chiasma frequencies as a test of two theories of recombination. Nature 326:803–805.

Charlesworth B, Morgan MT, and Charlesworth D, 1993. The effect of deleterious mutations on neutral molecular variation. Genetics 134:1289–1303.

Crow JF, 1970. Genetic loads and the cost of natural selection. In: Mathematical models in population genetics (Kojima K-I, ed). Berlin: Springer; 128–177.

Feldman MW, Otta SP, and Christiansen FB, 1997. Population genetic perspectives on the evolution of recombination. Ann Rev Genet 30:361–295.

Frankham R, 1996. Effective population size/adult population size ratios in wildlife: a review. Genet Res 66: 95–107.

Franklin I and Lewontin R, 1970. Is the gene the unit of selection? Genetics 65:707–734.

Gessler DDG and Xu S, 1999. On the evolution of recombination and meiosis. Genet Res 73:119–131.

Haldane JBS, 1922. Sex ratio and unisexual sterility in hybrid animals. J Genet 12:101–109.

Hartl DL and Clark AG, 1989. Principles of population genetics, 2nd ed. Sunderland, MA Sinauer Associates; 53–54.

Hey J, 1998. Selfish genes, pleiotropy and the origin of recombination. Genetics 149:2089–2097.

Hill WG and Robertson A, 1966. The effect of linkage on limits to artificial selection. Genet Res 8:269–294.

Kelly JK, 1997. A test of neutrality based on interlocus associations. Genetics 146:1197–1206.

Kimura M, 1969. The number of heterozygous nucleotide sites maintained in a finite population due to steady flux of mutations. Genetics 61:893–903.

Kimura M, 1971. Theoretical foundations of populations genetics at the molecular level. Theor Popul Biol 2:174–208.

Kondrashov AS, 1993. Classification of hypotheses on the advantage of amphimixis. J Hered 84:372–387.

Korol AB and Iliadi KG, 1994. Increased recombination frequencies resulting from directional selection for geotaxis in *Drosophila.* Heredity 72:64–68.

Macgregor HC and Horner HA, 1980. Heteromorphism for chromosome 1 is a requirement for normal development in crested newts. Chromosoma 76:111–122.

Maynard-Smith J, 1988. Selection for recombination in a polygenic model. Genet Res 51:59–63.

Otto SP and Barton N, 1997. The evolution of recombination: removing the limits to natural selection. Genetics 147:879–906.

Pálsson S, 2001. The effects of deleterious mutations in cyclically parthenogenetic organisms. J Theor Biol 208: 201–214.

Pálsson S and Pamilo P, 1999. The effect of deleterious mutations on linked, neutral variation in small populations. Genetics 153:475–483.

Pamilo P and Pálsson S, 1998. Associative overdominance, heterozygosity and fitness. Heredity 81:381–389.

Press WH, Flannery BP, Teukolsky SA, and Vetterling WT, 1988. Numerical recipes in C. The art of scientific computing. New York: Cambridge University Press.

True JR, Mercer JM, and Laurie CC, 1996. Differences in crossover frequency and distribution among three sibling species of *Drosophila.* Genetics 142:507–523.

Received February 20, 2001
Accepted September 5, 2001

Corresponding Editor: Philip Hedrick