REVIEW

The conversion of variance and the evolutionary potential of restricted recombination

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Genetic recombination is usually considered to facilitate adaptive evolution. However, recombination prevents the reliable cotransmission of interacting gene combinations and can disrupt complexes of coadapted genes. If interactions between genes have important fitness effects, restricted recombination may lead to evolutionary responses that are different from those predicted from a purely additive model and could even aid adaptation. Theory and data have demonstrated that phenomena that limit the effectiveness of recombination via increasing homozygosity, such as inbreeding and population subdivision and bottlenecks, can temporarily increase the additive genetic variance available to these populations. This effect has been attributed to the conversion of nonadditive to additive genetic variance. Analogously, phenomena such as chromosomal inversions and apomictic parthenogenesis that physically restrict recombination in part or all of the genome may also result in a release of additive variance. Here, we review and synthesize literature concerning the evolutionary potential of populations with effectively or physically restricted recombination. Our goal is to emphasize the common theme of increased short-term access to additive genetic variance in all of these situations and to motivate research directed towards a more complete characterization of the relevance of the conversion of variance to the evolutionary process.
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Introduction

Genetic recombination is traditionally regarded as a mechanism that aids adaptive evolution. The link between recombination and adaptation can be traced to Weismann (1904), who proposed that the advantages of recombination lie in its ability to unite favorable alleles from separate lineages into one lineage more quickly than mutation alone (also see Fisher, 1930; Muller, 1932). Recombination also allows selection to operate more effectively on individual beneficial alleles segregating on a polymorphic genetic background (Hill and Robertson, 1966; Birky and Walsh, 1988). These lines of reasoning underlie the widely held assumption that recombination facilitates the evolutionary response to selection. Recombination, however, also breaks up complexes of interacting genes and disrupts favorable gene combinations (Maslin, 1968; White, 1973). Theory and empirical research suggest that these consequences of recombination can act as a constraint upon adaptive evolution. Here, we review and synthesize evidence that a phenomenon associated with limits on recombination, the conversion of nonadditive, epistatic genetic variance to additive genetic variance, may help explain why evolutionary responses can be different from predicted and short-term adaptive evolution can occur more

efficiently than expected when recombination is restricted.

Introduction of concepts

Additive and nonadditive variance

The additive or average effect of an allele is defined as the expected deviation from the population mean genotypic value caused by a single copy of an allele (Fisher, 1918; Lynch and Walsh, 1998). The sum of the additive effects of alleles across all loci is the breeding value of an individual. This breeding value represents the expected genotypic value of offspring of the individual. Given random mating, the additive genetic variance for a trait is simply the variance of breeding values of individuals for that trait in a population (Falconer and Mackay, 1996; Lynch and Walsh, 1998).

The genotypic value of an individual, however, is not merely the sum of the additive effects of its genes, because each allele can also have nonadditive, interaction effects. These nonadditive effects include interactions with other alleles at the same locus (ie dominance), or interactions with alleles at other loci (ie epistasis) (Falconer and Mackay, 1996; Lynch and Walsh, 1998). The deviation of the genotypic value of two alleles at the same locus from the expected genotypic value based on the average effect of each allele is the dominance deviation. In a randomly mating population, the variance in dominance deviations across all loci is the dominance variance. Similarly, the deviation of the genotypic value of two alleles at different loci from the expected genotype

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is the interaction deviation. The variance of interaction deviations is the epistatic variance (Falconer and Mackay, 1996; Lynch and Walsh, 1998).

It is important to note that just because two alleles at the same locus display physiological dominance, meaning that they interact nonadditively such that one allele is dominant and the other recessive, does not mean that the population will exhibit any dominance variance. Similarly, just because alleles at different loci show physiological epistasis (interact nonadditively) does not mean that the population will exhibit epistatic variance (Cheverud and Routman, 1995; Wade et al, 2001). Allelic interaction will only contribute to genetic variance if there is allelic polymorphism at the interacting loci (Goodnight, 1988). Furthermore, deviations from additivity due to dominance and epistasis may occur at particular sets of loci, but dominance variance and epistatic variance are based on the sum of dominance and epistatic deviations across all loci (Phillips et al, 2000).

Sexually produced diploid offspring only inherit one allele per locus from each parent, and unrestricted recombination disrupts the coinheritance of interacting alleles at different loci. This means that neither dominance deviations nor interaction deviations are reliably transmitted from parents to offspring (Wright and Cockerham, 1985; Falconer and Mackay, 1996; Gibson, 1996; Wade, 2001). Rather, it is only the additive effects of alleles that are predictably inherited by sexually derived offspring. Accordingly, evolutionary responses to individual level selection are expected to occur only when there is additive genetic variance.

Just as single-locus genotypes can be described in terms of additive and dominance genotypic values, so can multiple-locus genotypes. For example, two-loci epistatic systems are often described in terms of additive-by-additive epistasis, additive-by-dominance epistasis, dominance-by-additive epistasis, and dominance-by-dominance epistasis. Epistatic systems involving more than two loci are described analogously as additive-by-additive-by-additive epistasis, etc. These terms are used because they fit well into the existing quantitative genetic theory (Crow and Kimura, 1970), though they ultimately remain statistical constructs. In reality, allelic and genic interactions are likely to include combinations of these types of epistasis (Cheverud, 2000; Carlborg and Haley, 2004). In this review, we will focus mainly on a simple system of additive-by-additive epistasis (Figure 1) because such a system is most conducive to the conversion of epistatic to additive variance, as we detail below. Furthermore, conversion dynamics in systems of additive-by-additive epistasis have been well-described analytically (eg Goodnight, 1987; Cheverud and Routman, 1995; Cheverud, 2000).

Conversion of variance by restricted effective recombination

The additive effects and interaction deviations of alleles, and hence the additive and nonadditive genetic variance of populations, are dependent on the allele frequencies of populations. As allele frequencies change, so do additive effects, interaction deviations, and the amount of additive and nonadditive genetic variance. For example, as selection or drift causes the loss or fixation of alleles,
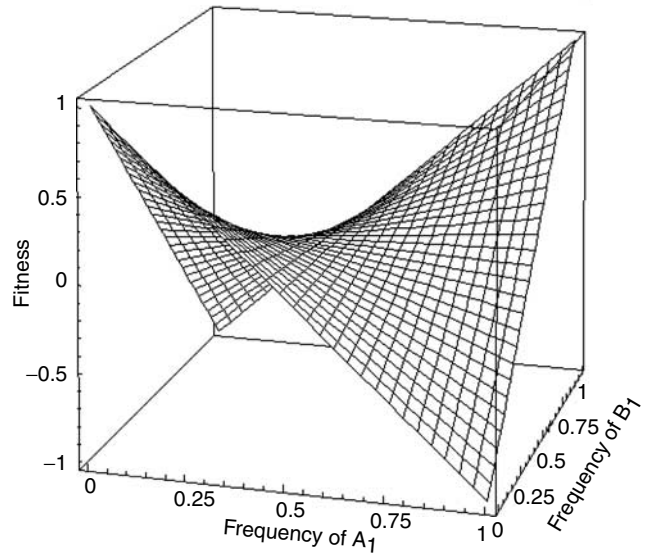

Figure 1 Fitness landscape showing pure additive-by-additive epistasis. The horizontal axis shows the allele frequencies at loci A and B, and the vertical axis shows the mean fitness of a population with those allele frequencies. Note that neither allele at either locus is unconditionally favored at all allele frequencies; the effect of alleles at the A and B loci depends on the frequency of alleles at the alternate locus. In the flat central region of the fitness surface, $p_{A1} \approx p_{B1} \approx 0.5$, the fitness of all genotypes is approximately 0 and neither allele at either locus is favored, but as the allele frequencies tend away from this region, one allele becomes favored. For example, as p_{A1} tends towards 1.0 (right side of figure), locus B acts more additively, and B_1 is strongly favored over B_2. This corresponds to a conversion of epistatic to additive variance (after Whitlock et al, 1995).

heterozygosity decreases and levels of additive genetic variance are also expected to decrease. Changes in allele frequencies can also alter the magnitudes of dominance and epistatic deviations, consequently affecting the relative amounts of nonadditive and additive variance (Goodnight, 1988; Cheverud and Routman, 1995; Barton and Turelli, 2004). One example of this phenomenon is provided by dominance deviations, which decrease as recessive alleles become more common and the proportion of heterozygotes decrease. Loci that formerly had large dominance deviations then act more additively (Wang et al, 1998b). Similarly, when one or more of the epistatic partners of an allele in epistatic systems with additive-by-additive components approach loss or fixation, the interaction deviation decreases and the allele acts more additively (Figures 1 and 2; Goodnight, 1988). In general, the effect of an allele is more predictable (ie is more additive) when the genetic background with which it interacts is more nearly constant.

Changes in allele frequencies, and consequently, the amount of dominance and interaction deviation, can cause a 'conversion' of dominance or epistatic variance to additive variance (Goodnight, 1987, 1988; Whitlock et al, 1993; Figure 2). For example, whenever the ratio of additive-by-additive epistatic variance to additive variance in a panmictic ancestral population exceeds 1:3, the average within-deme amount of additive variance will increase for all values of F_{ST}, Wright's measure of population genetic subdivision, due to conversion (Goodnight, 1988). In this way, as homozygosity in-

creases, the conversion of nonadditive to additive variance may slow the expected decline in additive variance.

Populations that have undergone inbreeding, population bottlenecks, or population subdivision will be increasingly homozygous and there may be substantial

a

b

c

conversion of nonadditive to additive variance (Wade and Goodnight, 1998). The response to selection in these populations may be different from or greater than under purely additive expectations (Lynch, 1984b; Carson, 1990; Wade, 1996, 2001; Willis, 1996; Barton and Turelli, 2004). Mechanistically, the increased homozygosity caused by allelic loss and fixation decreases the effects of recombination, because recombination between homozygous loci does not increase genotypic diversity. Rather, it merely swaps identical alleles. Thus, the ability of recombination to inhibit the co-inheritance of sets of interacting alleles is diminished by inbreeding, population bottlenecks, and population subdivision (Wade, 1996), all of which increase homozygosity in the population.

While all forms of epistasis can increase the average additive genetic variance through conversion, the conversion of additive-by-additive variance results in a greater boost in additive variance than other types of epistasis (Cheverud and Routman, 1996; Naciri-Graven and Goudet, 2003). Moreover, unlike epistatic variance with dominance components, additive-by-additive epistatic variance cannot contribute to inbreeding depression (Falconer and Mackay, 1996). Thus, conversion of additive-by-additive variance seems more likely to facilitate adaptive evolution than the conversion of other types of nonadditive genetic variance.

Conversion of variance by physical restriction of recombination

The physical inhibition of recombination, as in apomictic asexual reproduction and some types of chromosomal rearrangements, can be considered to effectively convert epistatic to additive genetic variance. When recombination becomes physically restricted, groups of interacting genes that had previously been disrupted every generation by recombination are now 'seen' by selection as single alleles because recombination does not break them up. This is analogous to the situation described above, where increased homozygosity decreases the effectiveness of recombination at disrupting the coinheritance of interacting genes. In this way, phenomena that physically restrict recombination across previously freely recombining genomic regions may also convert nonadditive to additive variance. In the following sections, we will expand our discussion of how the appearance of chromosomal inversions and transitions from sexual to asexual reproduction can result in the conversion or release of nonadditive to additive variance that may facilitate adaptive evolution.
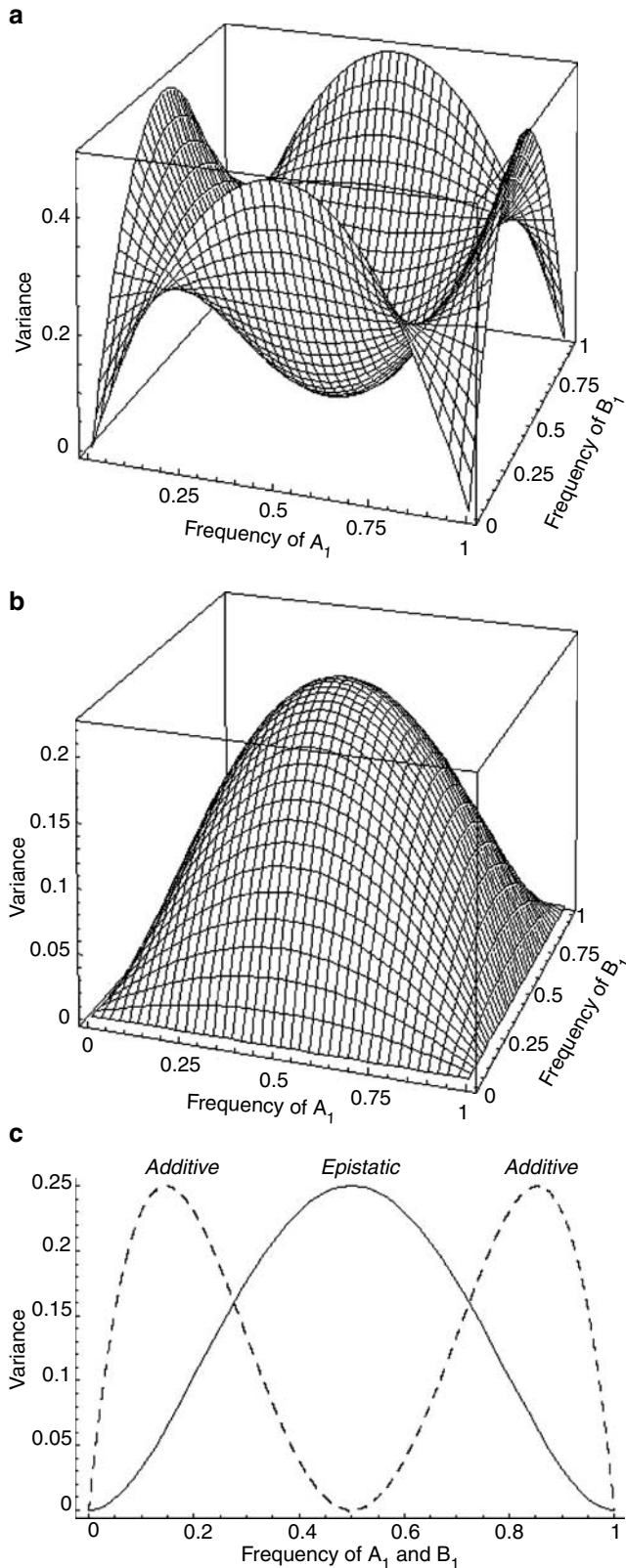
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Figure 2 The additive and epistatic variance for an additive-by-additive epistatic system. In (**a**) and (**b**), the horizontal axes show the allele frequencies at loci A and B, and the vertical axis shows the additive (**a**) or epistatic (**b**) variance for those allele frequencies. (**c**) shows how epistatic (solid line) and additive (dotted line) variances change with allele frequencies when $p_{A1} = p_{B1}$. Note that epistatic variance is at a maximum and additive variance at a minimum when the allele frequencies $p_{A1} = p_{B1} = 0.5$, which corresponds to the flat saddle region in Figure 1. As allele frequencies at loci A and B tend away from 0.5, the loci act more additively and epistatic variance is converted to additive variance. Additive variance for each locus is at a maximum when $p = 0.5$ at one locus and $p = 0$ or 1 at the alternate locus. That is, when there is no variance at one locus, the alternate locus acts completely additively (after Whitlock et al, 1995; Cheverud and Routman, 1996; Cheverud, 2000).

Is nonadditive variance important to adaptive evolution?
In order for the conversion of nonadditive to additive variance to be an important evolutionary process, a substantial amount of the genetic variance underlying fitness-related quantitative traits in natural populations must be nonadditive, that is, generated either by dominance or by epistasis (Goodnight, 1987, 1988; Cockerham and Tachida, 1988; Whitlock et al, 1993; Wang et al, 1998a). The relative amount of nonadditive variance is notoriously difficult to estimate (eg Frankel and Schork, 1996; Wade, 2002; Barton and Turelli, 2004), and the amount and evolutionary importance of non-additive variance has been a topic of considerable debate (eg Coyne et al, 1997; Wade and Goodnight, 1998). Theoretically, traits more closely associated with fitness are expected to have a relatively high proportion of nonadditive to additive variance because strong directional selection is expected to erode away additive variance, leaving nonadditive variance (eg Wright, 1977; Roff, 1997). These expectations are generally supported by the available data (Falconer, 1981; Merilä and Sheldon, 1999). Thus, it is possible that in natural populations there is little additive variance but substantial nonadditive variance for fitness traits. Conversion of nonadditive to additive variance could potentially release additive variance so that fitness traits could continue to respond to directional selection, whereas the evolution of fitness traits without conversion could be constrained (Goodnight, 1988).

Dominance versus epistatic variance: Although both dominant and epistatic gene actions are nonadditive, the evolutionary consequences of their conversion to additive genetic variance are likely to be quite different (Goodnight, 1987, 1988; Whitlock et al, 1993; Whitlock, 1995; Wade and Goodnight, 1998; Barton and Turelli, 2004). Theory has shown that the conversion of dominance to additive variance that occurs with inbreeding, population bottlenecks, and population subdivision can increase the additive variance, and thus heritability, above original levels (Robertson, 1952; Cockerham and Tachida, 1988; Willis and Orr, 1993; Wang et al, 1998a; López-Fanjul et al, 2000). However, most of the increase in additive variance will involve the expression of deleterious recessive alleles and is thus likely to lead to purging rather than to adaptive evolution (Willis and Orr, 1993; Wade et al, 1996). In contrast, if much of the nonadditive variance is epistatic, the fixation or near fixation of different epistatic partners will cause the remaining segregating epistatic partners to act more additively as long as there is an additive component to the basic gene action of the still-segregating locus(i). Selection may then act on these additively acting alleles. Thus, the fixation or near fixation of epistatic partners associated with inbreeding, population bottlenecks, and population subdivision can expose alleles otherwise hidden from selection in large, panmictic populations (Wright, 1977; Wade et al, 1996; Goodnight and Stevens, 1997; Meffert, 2000; Wade, 2000; Barton and Turelli, 2004).

Several authors maintain that the widespread nature of inbreeding depression and the ability of models including only dominance variance to explain most empirical examples of conversion of nonadditive to additive variance means that the relative contribution of dominance variance to conversion is high and thus that conversion of variance will not play a significant role in adaptive evolution (eg Barton and Turelli, 1989, 2004; Willis and Orr, 1993; Coyne et al, 1997; López-Fanjul et al, 2004). However, others contest these conclusions on the grounds that we still lack the theoretical, statistical, and empirical tools to accurately determine the nature of underlying gene action, particularly if epistasis is involved (eg Bryant and Meffert, 1996; Wade et al, 1996; Wang et al, 1998b; Meffert, 2000; Naciri-Graven and Goudet, 2003).

Potential of epistatic variance to contribute to the conversion process: Most evolutionary biologists from Fisher and Wright onward agree that physiological epistasis, defined as nonadditive interactions between genes, is ubiquitous. Indeed, this type of epistasis is integral to a wide range of evolutionary theories, from the maintenance of sex, recombination, and genetic variation, to speciation (reviewed in Wolf et al, 2000). However, there is much disagreement regarding whether epistatic genetic variance, or *statistical* epistasis, accounts for a significant proportion of the total phenotypic variance of natural populations (Cheverud and Routman, 1995). It is this question that is relevant to evaluating the potential evolutionary importance of the conversion of nonadditive to additive variance.

At equilibrium, large, panmictic populations are expected to be at or close to mutation-selection balance at all loci. Slightly deleterious mutant alleles may be segregating at two or more epistatically interacting loci, but because these alleles are held at low frequency by selection, most of this polymorphism will contribute to additive rather than to epistatic variance. Moreover, new mutations that are beneficial on average across the experienced environments and genetic backgrounds will quickly sweep to fixation. It is unlikely that these positively selected alleles will remain segregating long enough for another beneficial mutant to arise at an epistatically interacting locus. Thus, positively selected mutants will sequentially fix across a relatively uniform genetic background, and there will be very little epistatic variance (reviewed in Brodie, 2000).

Substantial conversion of additive-by-additive epistatic variance only occurs when the allelic frequencies of interacting loci are intermediate before the conversion process begins, meaning that there is substantial genetic variation at all interacting loci (López-Fanjul et al, 1999, 2000). Some believe that the maintenance of this type of genetic variation requires conditions not easily conceived in natural populations experiencing directional selection (eg López-Fanjul et al, 1999, 2000).

However, genotype–environment interaction as well as phenomena such as population structure and admixture, frequency-dependent selection, and balancing selection due to environmental heterogeneity or antagonistic pleiotropy are believed to be important in the maintenance of intermediate allele frequencies at single loci (eg Roff, 1997) and may also help maintain variation at multiple loci (eg Gillespie and Turelli, 1989; Wade and Goodnight, 1998; Peters and Lively, 1999). In addition, stabilizing selection may facilitate the maintenance of variation at interacting loci relative to directional selection because it operates on the properties of linkage groups rather than on the effects of individual alleles

(Lynch and Walsh, 1998). There is broad empirical support for the existence of many of these phenomena in natural populations (eg genotype–environment interaction: Sgro and Hoffman, 2004; Meffert and Hagenbuch, 2005; population structure: Hastings and Harrison, 1994; Wade and Goodnight, 1998; metapopulation structure: Hanski and Gaggioti, 2004; frequency-dependent selection: Kassen, 2002; Sinervo and Svensson, 2002).

Empirical evidence for epistatic variance: Despite the notorious difficulty of detecting epistatic variance (eg Cheverud and Routman, 1995; Goodnight, 1995; Whitlock, 1995; Frankel and Schork, 1996; Wade and Goodnight, 1998; Cheverud, 2000; Wade, 2001), epistatic variance can and does contribute to fitness-related traits (eg Bryant and Meffert, 1996; Long *et al*, 1996; Routman and Cheverud, 1997; Cheverud *et al*, 1999; Meffert, 2000; Kover and Caicedo, 2001; Bonhoeffer *et al*, 2004; Sanjuán *et al*, 2004). Recent QTL studies provide additional, more direct evidence that genes important to fitness do interact epistatically (Brockmann *et al*, 2000; Rüppell *et al*, 2004; reviewed in Cheverud, 2000). Moreover, there is a growing body of evidence supporting the possibility that substantial epistatic variance can exist within and between natural populations and subpopulations (Hard *et al*, 1992; Goodnight and Stevens, 1997; Lair *et al*, 1997; Cheverud, 2000; Fenster and Galloway, 2000; Templeton, 2000; Bradshaw *et al*, 2005).

Importantly, the specific types of epistatic interactions that are most likely to contribute to substantial conversion of variance and least likely to cause inbreeding depression often underlie traits important to fitness. For example, Routman and Cheverud (1997) found substantial evidence for epistatic interactions between QTL for juvenile body size in mice, including additive-by-additive epistasis. Interestingly, they determined that the types of epistasis that are predicted to make the largest contribution to the conversion of variance, additive-by-additive and dominance-by-additive epistasis, were twice as common and had more profound effects on additive variance than types of epistasis that do not make as substantive of a contribution to the conversion of variance. This is particularly impressive given that additive-by-additive epistasis is notably difficult to detect in genetic mapping studies (Routman and Cheverud, 1997). Many other recent QTL studies have detected additive-by-additive epistasis for fitness-related traits (reviewed in Cheverud, 2000), including litter size in mice (Peripato *et al*, 2004), flowering time in *Arabidopsis thaliana* (Juenger *et al*, 2005), and disease resistance in spring wheat (Yang *et al*, 2005).

Evidence for the conversion process

Conversion with restricted effective recombination
It is well-established that genetic diversity and heterozygosity decrease when a formerly outcrossing population undergoes inbreeding, population bottlenecks, or population subdivision (eg Wright, 1951; Robertson, 1952; Crow and Kimura, 1970; Lande, 1980; Whitlock and Fowler, 1999). However, the effect of these phenomena on additive genetic variance and thus on heritability and the ability of a population to respond to selection is more complex and less predictable (Wright and Cocker-

ham, 1985; Barton and Turelli, 2004). If most of the genetic variation underlying quantitative traits is additive, the amount of additive genetic variation within a population will decrease proportionately as F_{IS}, the inbreeding coefficient of the population, increases (Wright, 1951; Robertson, 1952; Lande, 1980).

These simple relationships between the inbreeding coefficient and additive genetic variance no longer hold if phenotypic trait values deviate from additivity (reviewed in Moreno, 1994). If much of the genetic variation for a trait is due to nonadditive variance within and/or between loci, the fixation or near fixation of allelic and epistatic partners that can result from inbreeding, population bottlenecks, or population subdivision may actually cause an increase in additive genetic variation (eg Goodnight, 1988; Whitlock *et al*, 1993; Wang *et al*, 1998a; Saccheri *et al*, 1999).

The first study to empirically demonstrate the release of additive genetic variance following a population bottleneck showed that additive genetic variation in housefly populations occasionally increased following a bottlenecking event (Bryant *et al*, 1986). In a later experiment, the lines were subjected to five additional founder-flush events and assayed for fitness (Bryant *et al*, 1990). The authors found that the lines had fully recovered from any inbreeding depression caused by bottlenecking and were able to quickly respond to selection to novel environments (Bryant *et al*, 1990; also reviewed in Meffert, 2000; Meffert and Hagenbuch, 2005). Similarly, additive genetic variance increased following a bottlenecking event in the Hawaiian fruit fly *Drosophila silvestris* (Carson and Wisotzkey, 1989) and a forced inbreeding event in *D. melanogaster* (López-Fanjul and Villaverde, 1989). In the latter study, the authors determined that the increase in additive variation for viability was best explained under a model that included the conversion of epistatic to additive variance.

More recently, Bryant and Meffert (1995) showed that the conversion of epistatic variance contributed to increased heritability for morphometric traits in bottlenecked relative to nonbottlenecked lines of houseflies (also see Meffert, 2000). Furthermore, Regan *et al* (2003) found that bottlenecked housefly lines had a more diverse set of responses to selection than nonbottlenecked lines. These results suggest that, contrary to the expectations of the additive model, bottlenecks may not always reduce evolutionary potential. Similar results were obtained by Wade *et al* (1996), and Pray and Goodnight (1997), who tracked the effect of inbreeding on phenotypic variance for traits important to fitness in *Triboleum castaneum*, and by Cheverud *et al* (1999), who studied the effects of inbreeding on additive variation in mice. Of particular note is a 1998 study of allozyme and quantitative genetic variation for fitness-related traits in North American populations of the pitcher-plant mosquito (*Wyeomyia smithii*) across a latitudinal gradient (Armbruster *et al*, 1998). The authors found that while allozyme heterozygosity declined precipitously with increasing latitude, additive genetic variance for preadult development time and critical photoperiod actually increased with latitude. Armbruster *et al* (1998) attributed this result to the conversion of nonadditive variance via the bottlenecking and population subdivision that accompanied *W. smithii*'s spread into northern regions following the retreat of glaciers at the conclusion of the

Pleistocene glaciation. This study was the first to document an evolutionary response linked to the conversion of nonadditive to additive variance in a natural system.

The maintenance and evolution of 'supergenes,' defined as closely linked loci that control phenotypic polymorphism (reviewed by Kelly, 2000), may also occur through a conversion of variance mechanism. Well-studied examples of supergenes include cases of color polymorphism in butterflies (eg Clarke and Sheppard, 1971; Naisbit et al, 2003) and land snails (Murray and Clarke, 1976), selfish genetic elements in mice (Silver, 1993), and self-incompatibility in flowering plants (reviewed in Castric and Vekemans, 2004). Supergenes are expected to evolve when balancing selection for the maintenance of certain gene combinations is strong relative to the recombination rate between the loci involved (Kelly, 2000). These conditions are facilitated when recombination between interacting loci is limited, when the effects of recombination are limited by high homozygosity, as with inbreeding (reviewed in Charlesworth, 2003), and when interacting loci are physically linked or occur within chromosomal inversions (reviewed in Wang et al, 2003). Supergenes thus evolve when interacting alleles can be co-inherited and act additively, perhaps via a conversion of variance process.

Conversion with physical limits on recombination

Chromosomal inversions: The idea that linked blocks of genes could play an important role in evolution largely stems from Dobzhansky's work on selectively maintained chromosomal inversions in natural populations of D. pseudoobscura (eg Dobzhansky, 1951, 1956; reviewed in Powell, 1997). Kimura (1956) further showed that if certain gene combinations increase fitness, an 'inversion or other cross-over reducing mechanism' (p 283) will be selectively favored and will often spread (also see Turner, 1967; Lande, 1984). This is because recombination between the genes in an inversion is often physically inhibited or even entirely blocked (Coyne et al, 1993; Navarro and Ruiz, 1997), which means that favorable gene combinations can be coinherited.

Allelic variation at genes spanned by a new favorable inversion will initially be mainly epistatic, because free recombination between the genes will still occur in most individuals. As the inversion spreads, this epistatic variance will be converted to additive variance between karyotypes. In this situation, there will essentially be two allelic types: (1) chromosomes carrying the inversion that have higher than the mean fitness of the ancestral population because they contain a combination of favorably interacting genes, and (2), chromosomes with free recombination that have the same mean fitness of the ancestral population. Effectively, individuals without the inversion are stuck in the flat saddle region of Figure 1, with a mean fitness of 0, because recombination breaks up any favorable (or unfavorable) gene combinations that may occur. In contrast, individuals with the inversion are at a fitness peak, with a fitness of $+1$. Additive variance will be at a maximum in this scenario when the inversion is at a frequency of 0.5.

Thus, in an analogous sense to the phenomena discussed above that cause reduced effective recombination, physically inhibited or blocked recombination caused by chromosomal inversions can enable evolutionary responses to selection via the conversion of epistatic to additive variance. As stated earlier, certain types of epistatic interactions, especially additive-by-additive epistasis, are most likely to contribute to the conversion of variance when the efficacy of recombination between interacting genes is reduced. However, when recombination is physically blocked between a whole set of genes, as in the case of genes spanned by inversions, the whole set of genes is inherited as a unit. This means that all types of epistatic interactions between these genes can contribute to the conversion of variance.

The question of whether chromosomal inversions can contribute to adaptation has received considerable empirical attention (reviewed in Powell, 1997). While a comprehensive review of this field is beyond the scope of this paper, we will provide a brief summary of the substantial body of research suggesting a link between inversions, recombination suppression, conversion of epistatic variance, and adaptation.

One important early study of ethological isolation from founder populations in chromosomally rearranged lineages of D. suboobscura found the most pronounced isolation for the only line homozygous for a chromosomal inversion, in which recombination is meaningless (Dodd and Powell, 1985). More recent work on D. suboobscura has indicated that the frequencies of certain inversions within both natural and laboratory populations are strongly correlated with different temperature regimes and seasons (Orengo and Prevosti, 1996; Kamping and Van Delden, 1999). Clines in inversion frequency related to variation in life history, morphological, and fitness-related traits and correlated to different climatic conditions have been characterized in D. suboobscura (Prevosti et al, 1988; Orengo and Prevosti, 1996; Schaeffer et al, 2003), other fruit fly species (Inoue et al, 1984; Rodriguez et al, 2000), and in mosquitoes (Coluzzi et al, 1979). Interestingly, Rodriguez et al (2000) found that only inversions associated with positive effects on trait values or fitness were involved in a latitudinal cline of D. buzzatti; inversions that were associated with neutral and negative effects on trait values or fitness did not show latitudinal patterns.

Some intriguing evidence linking chromosomal rearrangements and adaptive evolution comes from several recent studies of inversions in flies. Cáceres et al (1999) determined that common and/or fixed inversions tend to be long in both physical and map length (recombinational frequency) terms, and thus suppress recombination to a greater extent than rarer inversions (also see Cáceres et al, 1997). The authors interpreted this result to mean that longer inversions may have a greater chance of becoming common because the longer the inversion, the greater the chance that it includes interacting genes. Most recently, Schaeffer et al (2003) found that strong selection appeared to have acted on inversions in D. suboobscura, and argued that the inversions may have evolved as an adaptation to suppress recombination within coadapted gene complexes strongly linked to fitness.

The suppression of recombination linked to chromosomal inversions may also play a role in speciation. The common observation that closely related species are often fixed for different chromosomal inversions has led

researchers to consider the possibility of a link between inversions and speciation (eg White, 1978; Rieseberg *et al*, 1999; Noor *et al*, 2001; Rieseberg, 2001; Navarro and Barton, 2003a, b). Classical models for chromosomal speciation suggested that inversions facilitate speciation by acting as barriers to gene flow because inversion heterozygotes are often semisterile (reviewed by Rieseberg, 2001). More recent models assume that heterozygotes do not experience semisterility because recombination is suppressed in the region of inversion (see Coyne *et al*, 1993; Navarro and Ruiz, 1997) so that inversions are nearly neutral and can fix by drift (Noor *et al*, 2001; Rieseberg, 2001; Navarro and Barton, 2003a; Livingstone and Rieseberg, 2004). Subsequent to fixation by drift, inversions can act as a barrier to gene flow and populations can diverge at loci in the inverted region despite gene flow across the rest of the genome (reviewed in Livingstone and Rieseberg, 2004). Alternatively, as described above, inversions may be actively favored by selection if they suppress recombination between sets of favorably interacting alleles.

Recent studies provide further empirical evidence for a potential link between inversions and speciation. For example, many different inversions are fixed in humans and chimpanzees. A study of protein divergence between these two species found that the rate of divergence in inverted regions of the genome is more than double the rate of divergence in collinear regions (Navarro and Barton, 2003b; but see Bowers, 2003; Lu *et al*, 2003; Zhang *et al*, 2004). Furthermore, research on fruit flies has found that traits linked to reproductive divergence are often located in inverted regions (Noor *et al*, 2001; Machado *et al*, 2002). These studies suggest that evolutionary divergence during speciation may originate more commonly or be better-maintained in inverted regions. The conversion of variance process described above could be involved in the initial spread of these chromosomal inversions.

In general, there is a wide variety of support for the notion that the inhibition of recombination caused by chromosomal inversions may be selectively favored because beneficial gene combinations can be selected as an intact unit, though a definitive connection between inversions, increased access to additive variance, and a greater ability to respond to selection has yet to be shown. In our view, the conversion of epistatic to additive genetic variance that is likely to accompany the creation and fixation of chromosomal inversions may be an important factor in adaptive evolution and speciation.

Asexuality: As Sewall Wright (1977) first realized, the increased fidelity of genotypic transmission from generation to generation by asexual reproduction means that the response to selection might depart significantly from that predicted for a similarly diverse sexual population. More specifically, Wright suggested that mass selection upon a collection of genomes that are transmitted intact from generation to generation via asexual reproduction will act upon the composite properties of each genome as a whole (also see Lynch and Gabriel, 1983; Lynch, 1984a–c). This type of selection is potentially more efficient than selection upon sexual organisms, which, because genotypes are broken up each generation by genetic recombination, acts largely upon

the average additive effects of alleles rather than on groups of interacting loci. In turn, the faithful nature of asexual reproduction can constitute an advantage if the particular niche(s) to which a clone is well-adapted remains constant over time. In this situation, sexual reproduction will be at a disadvantage in terms of creating well-adapted offspring. This constitutes a cost of sex known as recombinational load, defined as the breakup of beneficial gene combinations by recombination (Maslin, 1968; White, 1973).

The creation of an apomictic (nonrecombinational) asexual lineage from an existing sexual population inherently involves a population bottleneck of one individual and immediate fixation of all allelic combinations within each new lineage. In fact, apomictic asexuality is the most effective way of converting nonadditive variance to additive variance because the entire genome is transmitted as a whole, thereby ensuring that even the most complex allelic/genic combinations remain intact (Lynch and Gabriel, 1983; Lynch, 1984b). All types of epistatic variance (including dominance components) are converted to among-lineage additive variance upon the creation of multiple asexual lineages from sexual progenitors. Thus, the expectation that asexual evolution is ineffectual relative to evolution in sexual competitors is only supported if most of the underlying genetic variance is truly additive (Lande, 1976; Lynch and Gabriel, 1983). Otherwise, the generation of multiple asexual lineages will result in the conversion of variance that is nonadditive for the sexual population to variance that is additive at the level of an assemblage of coexisting asexual lineages fixed for different combinations of genes (Wright, 1977; Lynch and Gabriel, 1983; Lynch, 1984b). The increased access to additive variance for an asexual assemblage is analogous to the conversion of epistatic to additive variance within a sexual population and could enable adaptive evolution for the asexual population in a direction that is unavailable to the sexual population (Lynch and Gabriel, 1983; Lynch, 1984b, c), though the ubiquity of sexual reproduction suggests that avoidance of recombinational load does not reliably counter the selective advantages of sex.

Nevertheless, a variety of studies have found evidence for evolution and adaptation occurring in a surprisingly effective manner in asexual populations (eg Parker, 1979a; Williamson, 1981; Glazier, 1992; Christensen *et al*, 1992; Toline and Lynch, 1994; Andrade and Roitberg, 1995; Sunnucks *et al*, 1998; Weeks and Hoffman, 1998; Wilson *et al*, 1999, 2003). These works cite such evidence as diverse and closely adapted clonal arrays (eg Parker, 1979a–c; Weeks and Hoffman, 1998; Wilson *et al*, 1999), natural clonal assemblages shown to have high (comparable to sexual) heritabilities for life history, morphological, and fitness-related traits (Stratton, 1991, 1992), and parthenogenetic genotypes that seem to outcompete sympatric sexual forms (eg Browne, 1992; Christensen *et al*, 1992; Weeks and Hoffman, 1998). Insight can also come from cyclical parthenogens, as demonstrated by Lynch (1984c). He determined that conversion of epistatic to additive variance occurred following episodes of sex in cyclically parthenogenetic *Daphnia*, and showed that this release of hidden genetic variance could lead to heritabilities higher than those achievable via obligate sexuality.

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One last example comes from the literature considering the evolutionary mechanisms underlying the repeated transition of a recombining sex chromosome to a largely nonrecombining sex chromosome (Fisher, 1931; Bull, 1983; Rice, 1987; Charlesworth, 1991; Ellegren and Carmichael, 2001; Nicolas *et al*, 2005). There is a general consensus that this transition occurs because selection will favor reduced recombination between the sex-determining locus and alleles that increase fitness in the heterogametic sex, but are detrimental to the opposite sex in the sex chromosome marking the heterogametic some sex.

In summary, there seems to be a wide range of evidence lending support to the possibility that the inheritance of intact genomes across generations plays a role in facilitating asexual adaptation. It is reasonable to conclude that the ecological success of some asexual populations, contrary to the intuitive expectations of a largely additive world, may be in part linked to the increased access to additive genetic variance of genetically diverse asexual assemblages.

Conclusions

There is a variety of evidence suggesting that limits on recombination may facilitate adaptive evolution and that a more extensive exploration of the genetic mechanisms underlying ecological and evolutionary success in situations where recombination is effectively or actually limited is warranted. In general, further study of adaptive evolution in recombinationally limited populations could provide insight into key issues, such as the evolutionary relevance of nonadditive genetic variance and the selective value of recombination. Following the lead of earlier work that emphasizes the potential importance of nonadditive variance (eg Lynch and Gabriel, 1983; Ritchie and Kyriacou, 1994), we stress that an understanding of the nature and prevalence of epistatic variance may often be a key step in elucidating the evolution and adaptation of populations and species.

Acknowledgements

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