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# GENETICS AND THE FITNESS OF HYBRIDS

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■ **Abstract** Over the years, the evolutionary importance of natural hybridization has been a contentious issue. At one extreme is the relatively common view of hybridization as an evolutionarily unimportant process. A less common perspective, but one that has gained support over the past decade, is that of hybridization as a relatively widespread and potentially creative evolutionary process. Indeed, studies documenting the production of hybrid genotypes exhibiting a wide range of fitnesses have become increasingly common. In this review, we examine the genetic basis of such variation in hybrid fitness. In particular, we assess the genetic architecture of hybrid inferiority (both sterility and inviability). We then extend our discussion to the genetic basis of increased fitness in certain hybrid genotypes. The available evidence argues that hybrid inferiority is the result of widespread negative epistasis in a hybrid genetic background. In contrast, increased hybrid fitness can be most readily explained through the segregation of additive genetic factors, with epistasis playing a more limited role.

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## INTRODUCTION

> The total weight of evidence contradicts the assumption that hybridization plays a major evolutionary role among higher animals. . . . Successful hybridization is indeed a rare phenomenon among animals.
>
> *Mayr (75, p. 133)*

> To be sure, the occasional production of an interspecific hybrid occurs frequently in plants. However, most of these hybrids seem to be sterile, or do not backcross with the parent species for other reasons.
>
> *Mayr (76, p. 233)*

The preceding quotes illustrate the historically common view of natural hybridization as an evolutionarily unimportant process. This view is largely based on the observation that crosses between divergent lineages often give rise to progeny with decreased levels of viability and/or fertility (e.g., 14, 75, 76, 105, 106). Despite the apparent rarity of "successful" hybrids in nature, a large body of literature on natural hybridization has accumulated over the years. The majority of this work has focused on either inferring evolutionary relationships based on the ability (or inability) to hybridize (e.g., 28, 51, 56, 69, 111), or deciphering the mechanisms that limit gene flow (e.g., 11, 12, 58, 59, 61, 67, 88, 96). When hybridization has been directly implicated in the evolutionary process, it has traditionally been for the role it may play in finalizing speciation (e.g., 40, 75; reviewed in 60). Hybrid zones, therefore, have generally been viewed as transient, with selection on mating preferences ultimately giving rise to "good" species or, if stable, as little more than an impediment to continuing divergence.

A less common viewpoint is that of hybridization as a relatively widespread and potentially creative evolutionary process (e.g., 3, 4, 44, 52, 70, 107). Indeed, introgression (the transfer of genetic material from one species into another via hybridization) has been documented in a wide variety of both plant and animal taxa (5, 93), and there is evidence that it may serve as a source of adaptive genetic variation (e.g., 52, 53, 70, 107). In addition, there are a number of well-documented cases of homoploid hybrid speciation, suggesting that natural hybridization may play an important role in evolutionary diversification (reviewed in 89).

The creative potential of natural hybridization depends critically on the production of recombinant genotypes that can outperform their parents in at least some habitats (6). Broadly speaking, hybrid fitness can be influenced by either endogenous or exogenous selection. Endogenous selection refers to that which acts against certain hybrid genotypes regardless of the environment in which they occur. This inherent loss of fitness is assumed to result from either meiotic irregularities or physiological/developmental abnormalities in individuals of mixed ancestry (hybrid incompatibility). Exogenous selection, on the other hand, refers to environment-specific fitness differences. According to this view, the distribution of genotypes across a hybrid zone is assumed to be governed by adaptation to different habitats. Consequently, although many hybrid genotypes will fail to

find suitable habitat, hybridization could lead to the production of recombinant genotypes that outperform their parents in certain habitats (2, 6, 78). Because the fitness of hybrids relative to their parents has been discussed extensively elsewhere (e.g., 6, 7, 13, 54, 101), we summarize it only briefly here. In general, the pattern that has emerged is one in which many, if not most, hybrids perform poorly as compared to their parents. Although hybrids tend to perform poorly on average, some fraction of hybrid genotypes are often found to outperform their parental counterparts under certain conditions (e.g., 18, 19, 47, 64, 91, 107). Indeed, recent theoretical work confirms that a small fraction of hybrid genotypes will likely outperform their parents, even in parental habitats (13). Therefore, we no longer need to ask whether or not hybrids will exhibit a wide range of fitnesses. They do. Of greater interest are the mechanisms underlying such fitness variation. As pointed out elsewhere, the outcome of hybridization depends not only on the distribution of hybrid fitness, but also on the underlying genetics (13).

In this review, we examine the genetic basis of hybrid fitness differences. Although chromosomal factors influence hybrid fitness, generally through their negative effects on hybrid fertility (e.g., 66, 99, 110), our focus is on the role of genic factors in determining the fitness of hybrids. As such, we begin with a summary of what is known about the genetic basis of hybrid inferiority. Although hybrids may suffer reduced fitness due to exogenous factors such as a lack of suitable habitat, the best genetic data on hybrid inferiority come from analyses of endogenous selection. We therefore focus on the genetics of hybrid incompatibility. We then review what is known about the genetic architecture of increased hybrid fitness. We are particularly interested in examining the extent to which loci governing hybrid fitness interact, both with other nuclear loci, as well as with some component of the cytoplasm. We close with a discussion of the likelihood that hybridization will lead to the establishment and spread of novel hybrid genotypes.

## HYBRID INFERIORITY

The role of epistasis in adaptive evolution has been a controversial issue ever since Sewall Wright and R.A. Fisher first formalized their views in the early 1930s. According to Wright (113, 114), natural selection retains favorably interacting gene combinations. Therefore, as a result of the highly integrated nature of the genome, selection may lead to the production of what Dobzhansky (43) has termed "coadapted" gene complexes. In contrast, Fisher (48) argued that natural selection acts primarily on single genes, rather than on gene complexes. In Fisher's view, therefore, selection favors alleles that elevate fitness, on average, across all possible genetic backgrounds within a lineage. Such alleles have been termed "good mixers" (75). Regardless of the role of epistasis within lineages, however, negative epistasis in a hybrid genetic background, or hybrid incompatibility, is fully consistent with both the Wrightian and Fisherian worldviews. This is because allelic fixation occurs in any one lineage without regard to the compatibility (or lack thereof) of new

alleles with those in any other lineage. Hybridization then produces a vast array of recombinant genotypes that have never before been subjected to selection. On average, these genotypes will be less well adapted than their parents, giving rise to some level of selection against hybrids.

Hybrid breakdown, or the reduction in fitness of segregating hybrid progeny that often results from intercrossing genetically divergent populations or taxa, has long been taken as evidence of unfavorable interactions between the genomes of the parental individuals (e.g., 39, 42, 43, 75, 80). The most widely accepted genetic model for the occurrence of such incompatibilities was first described by Bateson (15, as cited in 83), and later by Dobzhansky (39) and Muller (79, 80). In short, the Bateson-Dobzhansky-Muller (BDM) model assumes that an ancestral population consisting solely of individuals of the genotype *aa/bb* is broken into two parts that are temporarily isolated from each other. In one subpopulation, a new allele (*A*) is then assumed to arise at the first locus. Meanwhile, a new allele (*B*) is assumed to arise in the other subpopulation. Because individuals of the genotype *aa/bb*, *Aa/bb*, and *AA/bb* can interbreed freely, the *A* allele can then spread to fixation in the first subpopulation; likewise, individuals of the genotype *aa/bb*, *aa/Bb*, and *aa/BB* can interbreed freely, and the *B* allele spreads to fixation in the second subpopulation. However, although *A* is compatible with *b*, and *B* is compatible with *a*, the interaction of *A* with *B* is assumed to produce some sort of developmental or physiological breakdown, such that hybridization between the two subpopulations leads to the production of offspring with decreased levels of viability and/or fertility. Although this model focuses on negative interactions between differentiated regions of the nuclear genome, similar interactions between one or more regions of the nuclear genome and some component of the cytoplasm (e.g., the chloroplast or mitochondrial genome) could also play an important role in hybrid incompatibility. Unfortunately, the BDM model does not provide any mechanistic explanation as to how mutations that are neutral (or beneficial) within a given lineage will produce strongly disadvantageous incompatibilities when combined in a hybrid background.

More recently, Werth & Windham (109) proposed a model for the generation of incompatibilities at the polyploid level. This model states that allopatric populations of a single tetraploid species may experience silencing of the same gene, but in different parental genomes (reciprocal silencing; see Figure 1). Because every individual in this model carries two full genomic complements, these silencing events occur within either lineage with no detrimental effect on fitness. If these populations were to come back into reproductive contact, however, 25% of all gametes produced by first-generation hybrids would carry only nonfunctional copies of such a gene. If one or more of these genes were required for the function of gametes, there would be a marked decrease in hybrid fertility. Conversely, if there were no gametic problems, 6.25% of all $F_2$ hybrid individuals would carry no functional copies of such a gene. If one or more of these genes were required for survival, the $F_2$ generation would experience a reduction in viability. Lynch & Force (72) have since extended this model (and dubbed it duplication, degeneration, and complementation,

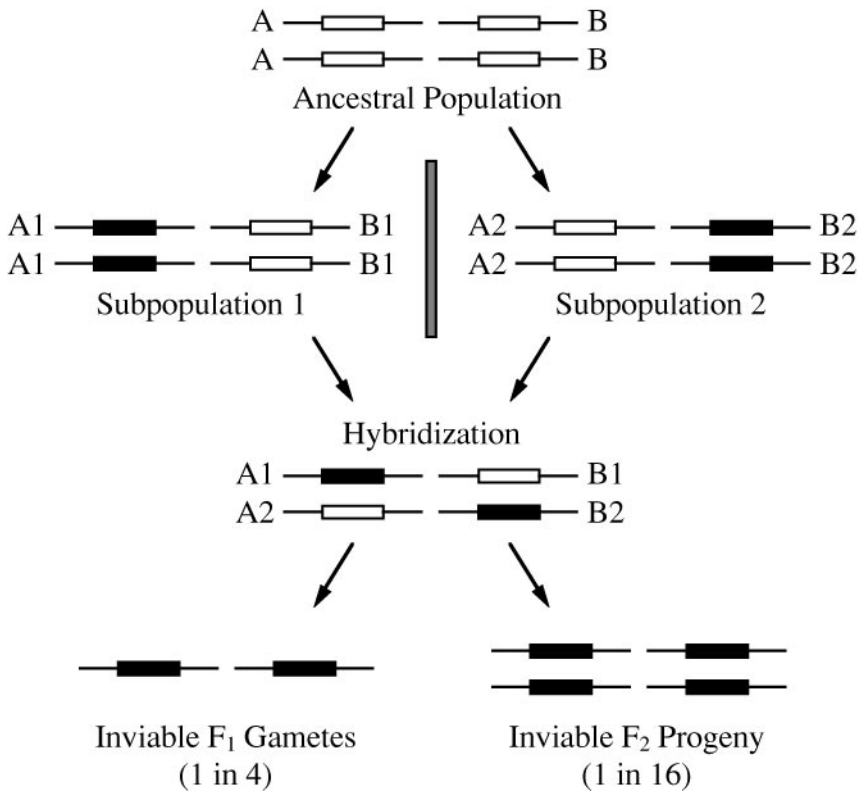


**Figure 1** Hypothetical example of reciprocal silencing of gene duplicates. Open boxes correspond to functional gene copies, whereas closed boxes denote silenced copies. Subpopulation 1 loses function at the A locus and retains it at the B locus, while the opposite occurs in subpopulation 2. One fourth of the $F_1$ gametes and one sixteenth of the $F_2$ zygotes resulting from crosses between subpopulations will carry only nonfunctional copies of the gene (Adapted from Figure 1 in Reference 72).

or DDC) to the silencing or functional divergence of any type of gene duplicate, not just those resulting from polyploidy. Unlike the BDM model, the DDC provides a simple mechanism by which hybrid-incompatibility can arise. Although this model is attractive in principle, data confirming or refuting it are lacking.

Despite our lack of insight into the genetic mechanisms underlying hybrid inferiority, a variety of empirical studies have confirmed the role of relatively widespread negative epistasis (reviewed in 116). What follows are recent examples from the animal and plant literature that have helped illuminate the nature of such genetic interactions. In some cases, these studies have also shed light on the within-lineage processes that may have given rise to the observed incompatibilities between lineages.

## *Drosophila simulans* and *D. mauritiana*

The best direct evidence on the role of gene interactions in hybrid sterility and inviability comes from *Drosophila* (see 29, 115, 116 for reviews). In particular, recent studies of hybrid incompatibility within the *D. simulans* clade have provided detailed insight into the complexity of such incompatibilities (25, 36, 57, 84–86, 104). In general terms, these studies have involved the introgression of small regions of *D. mauritiana* or *D. sechellia* chromosomes into the *D. simulans* genetic background. The results of this work indicate that hybrid sterility results from a large number of genetic interactions. Indeed, Palopoli & Wu (84) estimate that there are at least 40 loci that influence hybrid male sterility on the X chromosome alone, and Hollocher & Wu (57) found that the density of autosomal factors contributing to hybrid sterility is comparable to the density of X chromosome factors (but see 104). Moreover, many of these interactions involve more than two loci (25, 57, 86, 104). These sorts of higher-order interactions are, in fact, predicted by theory (82). Interestingly, the general pattern that has emerged is one in which conspecific genes often interact strongly (and negatively) when placed together in a hybrid genetic background (25, 57, 86). This body of work is also noteworthy in that it has led to the cloning and characterization of a major gene (*Odysseus*) involved in the production of male sterility in crosses between *D. simulans* and *D. mauritiana* (103). Although the function of this gene is still unknown, the authors found that it contains a homeobox with high sequence similarity to known genes from mice, rats, and nematodes. They also found that *Odysseus* has undergone extremely rapid sequence divergence over the past half million years, suggesting that positive selection has played a role in the evolution of hybrid incompatibility within the *D. simulans* clade.

## *Helianthus annuus* and *H. petiolaris*

Analyses of both synthetic hybrid lineages and natural hybrid zones between the annual sunflower species *Helianthus annuus* and *H. petiolaris* have provided some of the best evidence on the role of gene interactions in hybrid incompatibility between plant species (49, 91). In general, decreased hybrid fitness between these species results from reduced hybrid fertility. Although the genomes of these two species differ by three inversions and at least seven translocations (92), suggesting that hybrid sterility may result from chromosomal variation, genetic map-based analyses of experimental backcross hybrids indicate that most *H. petiolaris* markers in colinear (i.e., non-rearranged) genomic regions introgress into the *H. annuus* background at frequencies significantly lower than expected (91). This result suggests that loci in these regions of the *H. petiolaris* genome interact unfavorably with some component of the *H. annuus* genome. The majority of multilocus interactions (measured as linkage disequilibrium) were positive, indicating that *H. petiolaris* alleles interact favorably when placed together on the *H. annuus* genetic background. This finding is consistent with predictions of the

BDM model, in that selection should act in favor of those individuals that retain combinations of complementary genes from a given species (i.e., parental types). In addition, consistent with findings in *Drosophila* (see above), there were also a number of cases in which conspecific (i.e., *H. petiolaris*) genes interacted negatively when placed together in a hybrid background, suggesting the occurrence of deleterious higher-order interactions. In related work, Rieseberg and colleagues (49, 94) analyzed patterns of introgression in wild hybrid populations between these species. This work is especially noteworthy in that it represents the first application of a large number of mapped molecular markers to the analysis of natural hybrid zones. Overall, their findings mirrored the experimental hybrid lineages. Considering only the seven colinear linkage groups, there were at least eight (possibly ten) *H. petiolaris* chromosomal regions that introgressed at frequencies lower than expected (94). Analyses of hybrid fertility revealed a possible mechanism for this pattern: The majority of these underrepresented blocks were significantly associated with reduced pollen fertility. This result confirms fertility selection against certain hybrid genotypes as the most likely cause of reduced introgression.

## *Oryza sativa* ssp. *japonica* and *O. s.* ssp. *indica*

Both $F_1$ sterility and later-generation hybrid breakdown have been documented in intersubspecific crosses of rice (*Oryza sativa* L.; 81, 100). Interestingly, although $F_1$ sterility and hybrid breakdown often coincide in rice, hybrid breakdown sometimes occurs in the advanced-generation progeny of compatible (fully fertile) $F_1$ hybrids. In an attempt to elucidate the genetic basis of these phenomena, Li et al. (71) applied quantitative trait locus (QTL) mapping techniques to a cross between *O. s.* ssp. *japonica* and *O. s.* ssp. *indica*. In terms of $F_1$ sterility, the authors found evidence for the existence of "supergenes," or groups of tightly linked, favorably interacting genes within which recombination causes decreased fitness (35). Although the occurrence of cryptic structural rearrangements cannot be ruled out, $F_1$ hybrid sterility in rice is not generally associated with cytologically detectable abnormalities (27). This result suggests that $F_1$ sterility may, at least in part, be a genic phenomenon in rice. Regardless of the role of cryptic structural rearrangements, such incompatibilities arise as a result of recombination within differentiated regions. In order to account for the occasional occurrence of compatible $F_1$ hybrids, therefore, Li et al. (71) posited the existence of genes that influence recombination rates in rice. Indeed, Ikehashi & Araki (62) and Sano (95) both found evidence for genetic control of recombination rates in rice. These results suggest that hybrid fitness may be directly influenced by genes that regulate recombination. Interestingly, the phenotypic effect of the putative supergenes was strongly dependent on cytoplasmic background, providing evidence for the role of cytonuclear interactions in hybrid sterility. Consistent with theoretical predictions (82), Li et al. (71) also found evidence for widespread negative epistasis between the *indica* and *japonica* genomes. This result led the authors to conclude that "hybrid breakdown

may involve large numbers of genes and complex higher-order interactions, as reported in *Drosophila*" (p. 1146; see above).

## *Tigriopus californicus*

Hybrid breakdown in the marine copepod *Tigriopus californicus* has been the subject of numerous studies since the mid-1980s (20–24, 45). In short, Burton and colleagues have found that crosses between divergent, isolated populations of this species give rise to $F_1$ hybrids whose performance is virtually indistinguishable from their parents'. When these individuals are crossed to the $F_2$ generation, however, the resulting progeny often exhibit hybrid breakdown in terms of both development time and response to osmotic stress. Of particular interest is the observation that crosses between certain populations result in some sort of nearly lethal epistatic selection involving the region of the genome marked by the $Me^F$ allozyme (21). Indeed, $Me^F$ homozygotes are extremely rare in the $F_2$ generation, with an estimated viability of less than 8% of the interpopulational heterozygote. This result is reminiscent of the "synthetic lethal" systems discussed by Dobzhansky (41), in that otherwise harmless loci seem to interact to produce a lethal (or nearly so, in this case) phenotype. Another intriguing finding of this work is the observation of decreasing levels of cytochrome *c* oxidase (COX) activity as the mitochondrial genome of one population is introgressed into the nuclear background of another (45). Because COX is composed of subunits encoded by both nuclear and mitochondrial genes, its activity may reflect the coordinated function of the two genomes. Although their results varied among crosses, Edmands & Burton (45) found strong support for the hypothesis of deleterious nuclear-mitochondrial interactions in certain crosses. In view of the critical role of COX in the electron transport chain (it catalyzes the final step), cytonuclear coadaptation of this enzyme provides a plausible mechanism by which some degree of hybrid incompatibility may arise.

## *Iris fulva* and *I. brevicaulis*

Work on natural and experimental Louisiana iris hybrid populations indicates that both nuclear and cytonuclear interactions influence hybrid viability (19, 33, 34). In their analysis of the genetic structure of a natural hybrid zone between *Iris fulva* and *I. brevicaulis*, Cruzan & Arnold (33) documented the occurrence of differential seed abortion among hybrid genotypes. More specifically, intermediate hybrid seeds experienced markedly higher rates of abortion relative to parental-like seeds. This result suggests that intermediate hybrid genotypes are selected against owing to incompatibilities between the *I. fulva* and *I. brevicaulis* genomes. In a related study, Burke et al. (19) investigated the role of both nuclear and cytonuclear interactions in determining the frequencies of $F_2$ genotypes produced in crosses between the same two species. Consistent with the findings of Cruzan & Arnold (33), there was an overall deficit of intermediate hybrid genotypes in the $F_2$ generation (Figure 2). Analyses of single and multilocus segregation patterns also revealed a variety of nuclear and cytonuclear interactions. Of particular interest was the complete absence of individuals homozygous for the *I. brevicaulis* allele

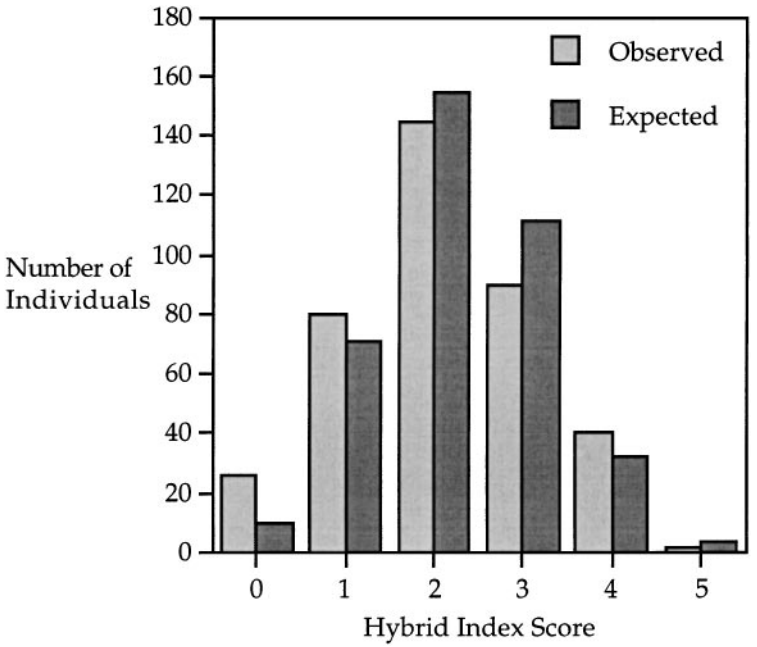


**Figure 2** Observed and expected genotypic distributions of $F_2$ seedlings resulting from a cross between *Iris fulva* and *I. brevicaulis*. Hybrid index scores are based on genotypes at a series of species-specific nuclear markers. The observed distribution is significantly different from the expected distribution ($\chi^2 = 31.75$, df $= 4$, $P < 0.001$; Redrawn from Figure 1*C* in Reference 19).

at a marker known as L180. As in the case of *Tigriopus* (see above), this result suggests that the region of the *I. brevicaulis* genome marked by L180 interacts with one or more different regions of the *I. fulva* genome to produce synthetic lethality (41). The potential negative effect of cytonuclear interactions on hybrid viability was illustrated by a significant excess of *I. fulva* alleles (and a deficit of *I. brevicaulis* alleles) in one particular region of the genome on the *I. fulva* cytoplasmic background, but not on the *I. brevicaulis* cytoplasmic background. The nonreciprocal nature of this deviation suggests that hybridization has disrupted favorable interactions between this region of the *I. fulva* nuclear genome and some component of the *I. fulva* cytoplasm, leading to selection against the *I. brevicaulis* genotype in this region. Once again, this result indicates the possibility of hybrid incompatibility due to cytonuclear coadaptation.

## *Gossypium hirsutum* and *G. barbadense*

Jiang et al. (64) investigated the role of multilocus interactions in restricting introgression between two polyploid species of cotton, *Gossypium hirsutum* and *G. barbadense*. After three generations of backcrossing with *G. hirsutum*, the authors

found large and widespread deficiencies of *G. barbadense* chromatin. In fact, there were no *G. barbadense* alleles at nearly 30% of the loci under study, and seven independent *G. barbadense* chromosomal regions were entirely absent. Because the genomes of these two species appear to be colinear, this result led the authors to conclude that unfavorable genic interactions in certain hybrid genotypes protect these regions of the *G. hirsutum* genome from introgression. However, the observed absence of certain *G. barbadense* chromosomal blocks could also be explained in completely nonepistatic terms. In other words, *G. hirsutum* may simply harbor better alleles in these regions, leading to the selective loss of *G. barbadense* alleles, regardless of genetic background. This being said, it seems unlikely that *G. hirsutum* alleles would outperform *G. barbadense* alleles in all seven regions, making epistasis the most plausible explanation. In addition to these seven "protected" chromosomal regions, the authors detected significantly more interactions among unlinked pairs of loci than expected by chance. Because the occurrence and/or magnitude of these interactions varied across backcross families, there may have been additional, higher-order interactions that went undetected. In view of this widespread epistasis, it is especially interesting to note that a disproportionate number of the negative interactions detected by Jiang et al. (64) occurred between subgenomes. Although this result is superficially consistent with the DDC, there is no evidence to suggest that these negative interactions tend to occur between homoeologous loci (P. Chee & A.H. Paterson, personal communication).

## HYBRID SUPERIORITY

In general, natural hybridization can contribute to adaptation and/or speciation in one of two ways. First, introgression may lead to the transfer of adaptations from one taxon into another, perhaps allowing for range expansion of the introgressed form (70; but see 16, 50). Alternatively, hybridization may lead to the founding of new evolutionary lineages (see 6, 89 for references). As alluded to above, the creative potential of natural hybridization depends not only on the production of relatively fit hybrid genotypes, but also on the genetic architecture of such hybrid superiority. The importance of genetic architecture lies in the likelihood of establishment and spread of favorable hybrid genotypes. Indeed, as Barton (13) has pointed out, natural selection can pick out rare, relatively fit hybrid individuals, but only if their offspring are also fit.

At a genetic level, increased hybrid fitness can arise in several ways. First-generation hybrids often exhibit heterosis, or hybrid vigor, especially if their parents are inbred. Depending on the genetic basis of such heterosis, however, the increase in fitness may be short-lived, breaking down with the passing of generations. In later generations, relatively fit hybrids may result from either the production of novel, favorably interacting (epistatic) gene combinations, or through the combining of advantageous alleles across noninteracting (additive) loci. In any case, exogenous selection is believed to play a central role in the establishment of relatively fit hybrids. The main reason for this is that, in the absence of niche

differentiation, new hybrid genotypes are likely to be overwhelmed by competition and/or gene flow from the parental populations (17, 90).

Unfortunately, although a number of studies have documented the production of relatively fit hybrids (see 6, 8 for examples), there are few data on the genetic basis of increased hybrid fitness. There are two reasons for this. First, as pointed out previously, the initial production of relatively fit hybrid individuals is expected to be a rare occurrence. Similar to the study of beneficial mutations, which are also exceedingly rare, the genetic analysis of increased hybrid fitness has therefore been difficult. Second, many of the studies dealing with hybrid fitness have relied on statistical comparisons of performance across classes (e.g., parental, $F_1$, $F_2$, backcross, etc.) rather than on detailed analyses of specific hybrid genotypes (7, but see HYBRID INFERIORITY above). Recently, however, experimental crosses as well as analyses of natural hybrid zones have begun to provide data on the genetic architecture of increased hybrid fitness.

Evidence for the role of epistasis in the production of relatively fit hybrids, although limited, comes from several sources. As was the case for hybrid incompatibility, the best data on the genetics of increased hybrid fitness in plants come from the work of Rieseberg and colleagues on the annual sunflower species *H. annuus* and *H. petiolaris* (49, 91). In addition to providing evidence for the role of epistasis in hybrid sterility, genetic map-based analyses of synthetic hybrid lineages between these species have revealed favorable heterospecific gene interactions (91). This result led the authors to conclude that "a small percentage of alien genes do appear to interact favorably in hybrids" (p. 744). Consistent with this finding, analyses of natural hybrid zones between these species also uncovered evidence of favorable heterospecific gene interactions in the form of significant, negative disequilibrium between certain pairs and triplets of unlinked markers (49). In addition, Burke et al. (19) documented the occurrence of favorable heterospecific cytonuclear interactions in crosses between *Iris fulva* and *I. brevicaulis*. This work suggests that increased hybrid fitness can arise not only as a result of interactions among nuclear loci, as in the case of sunflower, but also as a result of interactions between the nuclear genome and some component of the cytoplasm. Finally, in addition to the restricted introgression described above (see HYBRID INFERIORITY), Jiang et al. (64) detected several instances of higher than expected rates of introgression when *Gossypium barbadense* is backcrossed against *G. hirsutum*. This discovery led the authors to conclude that "genomic interactions do not always favor host chromatin" (p. 798). Rather, it appears that favorable heterospecific interactions may encourage the introgression of certain chromosomal blocks from one taxon into another. However, introgression analyses such as this should generally be interpreted with caution. In the absence of detectable associations between the chromosomal region of interest and one or more regions of the recipient genome, nonepistatic explanations are fully consistent with the data.

Because of the emphasis placed on niche divergence by many students of hybridization, the potential for the production of relatively fit hybrids is often tied to the production of novel or extreme hybrid phenotypes (e.g., 17, 55, 70, 102). As

**TABLE 1** Hypothetical example of transgressive segregation due to the complementary action of genes with additive effects (from Reference 90)

| | Phenotypic values | | | |
|---|---|---|---|---|
| **QTL** | **Species A** | **Species B** | **Transgressive $F_2$** | **Transgressive $F_2$** |
| 1 | +1 | −1 | +1 (A) | −1 (B) |
| 2 | +1 | −1 | +1 (A) | −1 (B) |
| 3 | +1 | −1 | +1 (A) | −1 (B) |
| 4 | −1 | +1 | +1 (B) | −1 (A) |
| 5 | −1 | +1 | +1 (B) | −1 (A) |
| Total | +1 | −1 | +5 | −5 |

it turns out, such transgressive segregation appears to occur frequently in crosses between divergent lineages in both plants and animals (reviewed in 90). Moreover, QTL mapping studies have consistently implicated the additive effects of complementary genes, rather than epistasis, as the mechanism by which transgressive phenotypes arise (see Table 1) (e.g., 38, 65, 74, 108). In fact, QTL alleles often have effects that are opposite in direction to that expected on the basis of overall trait values (90). In other words, alleles reducing a trait are sometimes found in species with a high trait value, whereas alleles increasing a trait are sometimes found in species with low trait values. Unfortunately, most studies to date have gone only as far as documenting the production of extreme phenotypic variants. Therefore, the connection between transgressive segregation and the production of relatively fit hybrid genotypes remains tenuous. A number of studies have documented transgressive segregation for traits such as fecundity, as well as tolerance to various biotic and abiotic stresses (see 90 for references). Given the right environmental conditions, these sorts of traits clearly have adaptive significance. It therefore seems likely that transgressive segregation, presumably due to the additive effects of alleles across loci, has the potential to contribute to the success of certain hybrid lineages.

Although exogenous selection is generally assumed to play a crucial role in the production and establishment of relatively fit hybrid genotypes, it is also possible that hybridization could give rise to genotypes that are intrinsically more fit than their parents. One mechanism by which this may occur is through the purging of mutational load (46). Due to the constraints of finite population size, mildly deleterious alleles can become fixed within lineages, leading to the gradual erosion of fitness (inbreeding depression; e.g., 68, 77). Hybridization between lineages could, therefore, lead to the production of heterotic $F_1$ hybrids due to the masking of deleterious recessive alleles. In later generations, one possible outcome of such heterosis would be the introgression of favorable alleles from one parental population into the other (63). Alternatively, if the hybrid offspring

are isolated in some way from their parents, the joint effects of recombination and natural selection may decrease the frequency of deleterious alleles, ultimately giving rise to a true-breeding hybrid lineage with increased fitness relative to its parents. Although the so-called "dominance hypothesis" of inbreeding depression has received considerable support (e.g., 26, 31, 32, 68), the application of this idea to the potential adaptive consequences of natural hybridization has received little attention. Such purging of mutational load via hybridization has, however, been suggested to play a role in the evolution of invasiveness in plants (46). Furthermore, common garden experiments in *Helianthus* have documented hybrid lineages that exhibit higher fecundity than their parents (LH Rieseberg, unpublished data).

## EVOLUTIONARY IMPLICATIONS

The main conclusion that can be drawn from genetic analyses of hybrid incompatibility is that postzygotic reproductive isolation generally results from widespread, negative epistasis in a hybrid genetic background. Such analyses cannot, however, distinguish between interactions that were initially involved in reproductive isolation and those that arose later. The main reason for this is that hybrid sterility and inviability are predicted to evolve nonlinearly (i.e., faster) with respect to time (82). This "snowballing" effect could, therefore, lead to an overestimate of the number of genes required for speciation. What we do know is that the complex and widespread nature of these incompatibilities makes them relatively effective barriers to genetic exchange between taxa. Indeed, as the number of loci that contribute to reduced hybrid fitness increases, the likelihood of producing relatively fit hybrid genotypes decreases, and the proportion of the genome protected from gene flow increases. However, the efficacy of low hybrid fitness as a barrier to gene flow varies across the genome, and even strong postzygotic barriers can fail to preclude successful hybridization. For example, in spite of the extremely strong sterility barriers between members of the *Drosophila simulans* clade (see HYBRID INFERIORITY above), a phylogenetic analysis of mtDNA sequences placed certain interspecific mtDNA types together (Figure 3) (98). One clade in this phylogeny contained mitochondrial haplotypes of all three species, whereas the other clade contained haplotypes of both *D. simulans* and *D. mauritiana*. This result led the authors to conclude that introgressive hybridization had occurred between these well-isolated species, a finding that was later supported by the results of experimental crosses (9).

When considering the evolutionary importance of natural hybridization, we are thus faced with an odd dichotomy of data. On the one hand, there is a substantial body of evidence documenting that, in the majority of cases, hybrid matings give rise to progeny with decreased levels of fertility and/or viability (e.g., 14, 40, 75, 105, 106, 112). In fact, along with various prezygotic barriers to hybridization, this sort of reproductive isolation is the very reason why we have distinct species. On

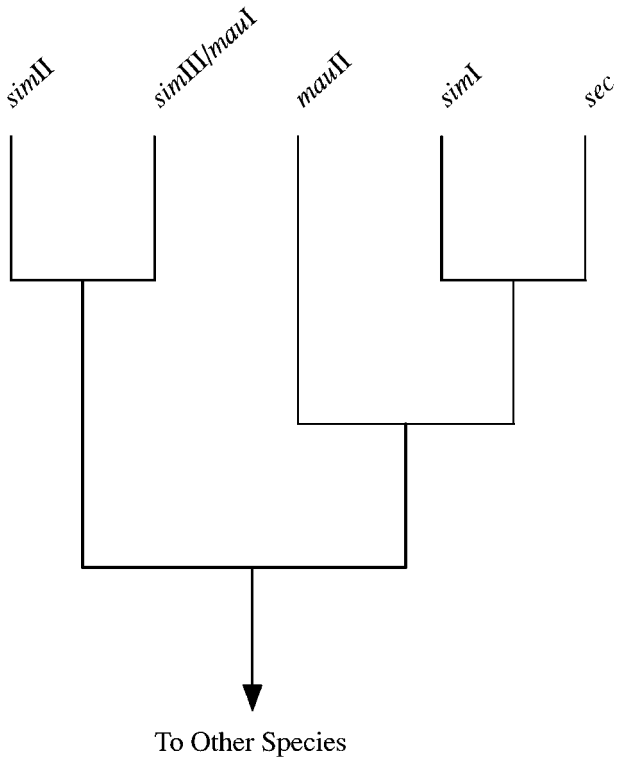


**Figure 3** Mitochondrial DNA phylogeny of *Drosophila simulans* (*sim*I, *sim*II, *sim*III ), *D. mauritiana* (*mau*I, *mau*II ), and *D. sechellia* (*sec*) (Redrawn from Figure 2*B* in Reference 98).

the other hand, there are numerous examples of potentially adaptive introgression (5, 93), as well as the production of new hybrid species (reviewed in 89). This dichotomy underscores a fundamental aspect of the evolutionary process, namely the overwhelming importance of rare events. Indeed, it is widely recognized that evolution proceeds as a direct consequence of extremely rare events—the occurrence of beneficial mutations, long-distance migration, founder events, etc.,—yet, with reference to the production of relatively fit hybrid genotypes, it has been argued that the rarity of such individuals precludes an important role for hybridization in evolution (75, 76). Barton (13) has gone on to argue that, in abundant species, mutation is not limiting and favored variants are therefore more likely to arise via mutation than hybridization. What this view neglects to recognize is that such mutations may arise anywhere within the range of a species, but may only be favored in certain locales. Although the same might be said of novel variants resulting from hybridization, hybrid matings often occur near the edge of a species range or in marginal habitats—just the sort of places where new variants may be most

likely to survive and thrive (2, 4, 78). In contrast to mutation, which will generally occur at the same low rate across the range of a species, hybridization thus provides a mechanism by which genetic variation can be generated in areas where the resulting variants are most likely to invade and utilize novel habitats.

But what about the likelihood that favored hybrid variants will persist and spread? As pointed out previously, this depends on the underlying genetic basis of increased hybrid fitness, as well as the circumstances under which these rare individuals occur (13). In contrast to hybrid incompatibility, where widespread epistasis seems to be the rule, the genetic basis of increased hybrid fitness is less clear. Although there is evidence that favorable epistatic interactions may be involved in the production of relatively fit hybrids, explaining the persistence and spread of these genotypes is somewhat problematic. Indeed, when considering the impact of epistatic factors on the creative potential of natural hybridization, the argument closely mirrors the Wright/Fisher debate over the importance of epistasis in adaptation (48, 113, 114). Alleles at unlinked loci will be rapidly dissociated by recombination. Thus, in the absence of an extremely strong selective advantage, epistatic selection will be effective only during the first few generations following the onset of hybridization (97). In short, favorably interacting gene complexes resulting from hybridization will face the same difficulties that adaptive gene combinations face in Wright's shifting balance theory of evolution (30). The spread of novel epistatic gene combinations out of a hybrid zone should, therefore, occur only under extremely rare circumstances. Before rejecting the importance of favorably interacting gene complexes in influencing the outcome of hybridization, however, it is important to consider the possibility that the conditions appropriate for the establishment and/or spread of favorably interacting hybrid gene combinations can (and do) occur, albeit rarely. For example, hybrid founder events may play a critical role in the establishment of new hybrid lineages, and episodes of high migration or strong selection could aid in the spread of favorable gene combinations from one population to another. These rare instances may have a tremendous impact on the trajectory of existing or new evolutionary lineages.

The evolutionary importance of nonepistatic factors, on the other hand, is less difficult to explain. Alleles that are favored regardless of genetic background will readily introgress across hybrid zones, even if they are initially associated with loci involved in decreased hybrid fitness (87). Because such alleles can rapidly spread to fixation, at least in certain habitats, adaptive trait introgression may be difficult to detect. Therefore, the numerous examples of introgression documented in the hybridization literature may be just the tip of the iceberg. Perhaps more important, however, is the role that additive factors may play in niche divergence. Indeed, the most likely way in which hybrids will initially become established and achieve isolation from their parents is via adaptation to a novel habitat. In fact, most stabilized introgressants and hybrid species are ecologically isolated from their parents (1, 6, 89). Moreover, these lineages often occur in habitats that are extreme, rather than intermediate, with respect to the requirements of their parents. So how does

this niche divergence arise? Most evidence suggests that the production of extreme (transgressive) phenotypes occurs through the additive effects of alleles segregating at complementary genes (see HYBRID SUPERIORITY above). Adaptation of hybrids to a novel habitat may, therefore, simply result from: (*a*) the generation of adaptive (and additive) genetic variation via hybridization, and (*b*) selection favoring extreme phenotypes following hybridization. Alternatively, hybridization could lead to the production of individuals with unique character combinations (55). Some fraction of these recombinant types may be especially well suited to an available, unique habitat and will therefore be able to increase numerically, at least locally. Because these ecologically isolated recombinants will be more or less released from the competitive and swamping effects of close contact with their parents, they will be free to evolve independently and, perhaps, develop some degree of reproductive isolation.

## CONCLUSIONS AND FUTURE DIRECTIONS

The prominent role of epistasis in postzygotic reproductive isolation was first proposed well over half a century ago (15, 39, 79, 80). Since that time, numerous investigators have confirmed that negative epistasis in a hybrid genetic background is, indeed, largely responsible for the common observation of hybrid inferiority. Unfortunately, although these studies have provided insight into the widespread nature and complexity of such genetic interactions, the underlying mechanisms are still largely unknown. To more fully understand the nature of these barriers, we must move beyond the abstract notion of locus A interacting negatively with locus B (see HYBRID INFERIORITY above). One promising area of inquiry would be to investigate the role of gene duplicates in producing hybrid incompatibility. Perhaps the easiest approach would be to map hybrid sterility in a cross between polyploid species. If complementary sterility loci map to the same position on homoeologous chromosomes, the results would provide evidence that the silencing or functional divergence of gene duplicates (in this case derived through polyploidy) plays a role in the evolution of species incompatibilities.

Another promising line of research is the identification of the loci that interact to produce incompatibilities. Great progress has been made on this front by Wu and colleagues, who have identified and characterized a locus involved in hybrid male sterility (*Odysseus*) in *Drosophila* (85, 86, 103). This is, however, but a single example. Before any generalizations can be made about the types of loci likely to be involved in hybrid incompatibility, we need additional examples from a variety of study systems. Moreover, although the introgression approach utilized in the identification of *Odysseus* has proven to be a powerful technique, interacting loci derived from the other species cannot be identified. The logical next step in such studies, therefore, might be to use introgressed individuals carrying a heterospecific incompatibility factor as a tool to identify other genomic regions that interact with the factor of interest. In the case of hybrid male sterility, introgressed females

of species B carrying a male sterility factor from species A could be crossed against a panel of advanced-generation (and fertile) male hybrids segregating for the species A genome on a species B background. By scoring male fertility in the resulting progeny, it may be possible to localize interacting factors. These candidate regions could then be targeted for introgression analyses in much the same way that *Odysseus* was identified in *Drosophila*.

In terms of the genetic basis of increased hybrid fitness, much of the evidence (empirical as well as theoretical) points to the importance of additive factors in the establishment and spread of favorable hybrid genotypes. However, the QTL mapping approaches generally employed in studies that have documented transgressive segregation have low power for detecting epistasis (73). Thus, epistasis may play a larger role in transgressive segregation than previously believed, but may have gone largely undetected. In order to investigate this possibility more rigorously, modified mapping approaches may be necessary. Perhaps the most useful approach would be to use recombinant inbred lines (RILs; 10) or recombinant congenic (RC) strains (37), which control for the effects of genetic background. These strategies, therefore, enhance the ability to identify interactions between a given marker and the background on which it occurs. Whatever the cause of transgressive segregation, the connection between phenotype and fitness needs to be made before we can be certain that this phenomenon plays an important role in the production of relatively fit hybrid lineages. One approach might be to compare QTL combinations found in naturally occurring hybrid lineages with those required for the production of the most extreme phenotypes (90). Correspondence would provide convincing, albeit indirect, evidence that transgressive segregation played a primary role in the evolution of such lineages. Alternatively, transplant experiments could be used to test the fitness effects of various phenotypes (or QTL combinations) in the wild. This approach would provide direct evidence on the potential fitness effects of transgressive segregation.

We have now entered a new phase of research on natural hybridization. Instead of focusing on this process as an impediment to "normal" divergence, or as an evolutionary epiphenomenon, numerous investigators are approaching their studies assuming that natural hybridization can be evolutionarily important in its own right. Indeed, the future is bright for studies of natural hybridization. The tools required for detailed genetic analyses are widely available, and there is now a freedom to investigate previously discounted questions and hypotheses.

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