MINI REVIEW

A gene's eye view of epistasis, selection and speciation

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Abstract

In this mini-review, I discuss the effects of gene interaction or epistasis from a 'gene's eye view.' By a 'gene's eye view' of epistasis, I mean that I will consider a single, bi-allelic locus, A, whose effects on fitness result only from its interactions with alleles of another, unknown locus, X. I will show how changes in the frequencies of alleles at the background locus affect the relationship of alleles at the A-locus to fitness. Changing the genetic background changes the fundamental characteristics of the A-locus, such as the magnitude and sign of allelic effects on fitness, and, consequently, it changes the strength and pattern of selection. I consider each of the four kinds of pair–wise interactions between two loci and show that some kinds of epistasis are more sensitive than others to population genetic subdivision. Lastly, I show that some kinds of epistasis are more likely than others to affect the process of speciation and contribute to or be responsible for general genetic features of interspecific hybrids, such as Haldane's rule.

Introduction

The genetic architecture of a phenotype consists of the genes, the interactions among them (epistasis), and the interactions among genes and environments (G × E) that affect the phenotype's expression (Wade *et al.*, 2001). For a phenotype with a 'complex' genetic architecture, epistasis and G × E play significant roles as opposed to a phenotype with a 'simple' architecture, in which interactions of any sort are relatively unimportant. Epistasis contributes to inbreeding depression, developmental homeostasis, plasticity, evolution of sex and recombination, mating system evolution, speciation and interdemic selection, because all of these topics involve phenotypes with a complex genetic architecture. For example, in speciation, epistasis contributes to reproductive isolation because genes that function well in the genetic background of conspecifics function poorly in the genetic background of interspecific hybrids. Such a change in the sign of a gene's effect from positive to negative can only

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be achieved by interactions (Wade, 1992; Johnson & Wade, 1996). In the same way, gene interactions are essential to understanding developmental homeostasis (or canalization), in which alleles at one locus reciprocally diminish allelic effects at other loci (Wagner *et al.*, 1998).

Wright (1931, 1969) considered epistasis to be 'ubiquitous' and stated that 'The inadequacy of any evolutionary theory that treats genes as if they had constant effects, favourable or unfavourable, irrespective of the rest of the genome, seems clear' (Wright, 1969, p. 88). He emphasized that the '…existence [of epistasis] must be taken as a major premise in any serious discussion of population genetics and evolution' (Wright, 1969, p. 105). Wright (1931) developed his 'adaptive landscape' as a way of illustrating nonlinearities in the map between two-locus gene combinations and fitness, although he found it inadequate for representing gene interactions of higher dimensionality. Nevertheless, Wright's heuristic and the genetic ideas on which it is based have been criticized (Coyne *et al.*, 1997, 2000; Phillips, 1998). The role of epistasis in microevolutionary processes within a single population often can be minimized by assumption or by transformation (Brodie, 2000). Speciation theory is

a good example of how the epistasis can be minimized in microevolution and yet be essential to macroevolution. Genetic epistasis causes a reduction in fitness of inter-population hybrids (macroevolution), yet it plays no role at all in the microevolution within populations preceding the speciation event (microevolution) (Charlesworth *et al.*, 1987; Coyne *et al.*, 2000; cf. review by Johnson, 2000). The 'meaningful' simplicity of 'beanbag genetics' suffices for within-population theory (see recent defence by Crow, 2001), but the beans become magic, enchanted with epistasis, when it comes to explaining the origin of species. Why so?

In multilocus population genetic theory, the relationship between epistasis for fitness and polymorphism has been investigated with a number of different models (cf. Christiansen, 2000). In general, there have been two findings: (1) the number of possible polymorphic equilibria increases with the number of interacting loci, and (2) there are many circumstances under which the effects of interaction are weak relative to main effects. Despite the ubiquity of gene interactions in physiological genetics, in large populations with random mating and weak selection, recombination results in a sufficient mixing among genetic backgrounds that the effects of specific alleles on the phenotype are constant or nearly so (Turelli & Barton, 1994). In this circumstance, epistasis has minimal effects on microevolutionary processes. However, in small populations, with nonrandom mating, reduced recombination, and stronger selection, epistasis causes the allelic effects at single loci to change with genetic background; they are not constant (Wade & Goodnight, 1998; Goodnight & Wade, 2000; cf. Wolf *et al.*, 2000 for a recent overview). In this circumstance, epistasis can have important effects on microevolutionary processes (Wade, 2000). Because there is a continuum between small and large population size, between weak and strong selection, and between free and no recombination, present population genetic theory does not present us with a clear understanding of how or when epistasis invalidates the assumption of the near statistical constancy of allelic values. As Christiansen (2000, p. 161) puts it, 'The level of generality in the description of the dynamical effects of selection decreases quite rapidly when the genetic assumptions of these simple models are relaxed, and much of the knowledge of more complicated models is based upon extrapolations from analyses of highly simplified models of selection and from numerical analyses of the model dynamics. Rather few general properties of multilocus models are known…'

That microevolutionary theory without epistasis appears to 'explain' so many patterns may be a tribute more to the power (and bias) of additive models than it is to capturing the genetic essence of nature (Wade, 1992; Cheverud & Routman, 1996; Templeton, 2000). Observations are necessarily theory laden and, hence, the absence of epistasis in the theory affects and reinforces

how nature is perceived and interpreted. Overall, it is clear that, in much of evolutionary theory, adaptation is interpreted from a 'gene's eye view' with little discussion of gene interactions or genetic background (Dawkins, 1989; Coyne *et al.*, 1997, 2000; Crow, 2001; Wade, 2001).

In this review, I will illustrate the effects of epistasis from a 'gene's eye view', rather than repeat arguments about its relevance to current evolutionary research or review experimental designs for its measurement as is performed at length in papers in Wolf *et al.* (2000). By a 'gene's eye view' of epistasis, I mean that I will imagine a single, known bi-allelic locus, A, whose effects on fitness derive solely from its epistatic interactions with alleles of another, unknown locus, X. In experimental genetics, it is common to identify segregating alleles at a locus (or segregating molecular marker) associated with detectable phenotypic effects, to map the locus, and then to begin studies to assign it adaptive function and selective value. At the beginning of such studies, only the existence of segregating variation at the focal locus is known. Whether alleles at this locus function alone or in combination with some other segregating locus (or loci) is not known. Indeed, current methods of genetic analysis may be biased *against* finding the epistatic partners of the known locus when they exist (e.g. Cheverud & Routman, 1996).

Here, I investigate how epistasis with an unknown partner affects the assignment of adaptive function and selective value to a gene already in hand. I will show how gene frequency variation at the unknown locus determines not only the kind of selection (directional, disruptive, or balancing) at the focal locus but also whether or not segregating alleles are of major or minor effect. For some kinds of epistatic interaction, the focal locus will appear to experience balancing selection, as is consistent with the proliferation of interior equilibria in general multilocus models (see above). With epistasis and population subdivision, an allele may have only a minor phenotypic effect on a genetic background common in some demes. At the same time, in other demes where other backgrounds are common, the same allele could have a major effect. The role of genes of major vs. minor effect in adaptive evolution is a frequently debated topic. However, coherent discussion is impossible when the effect of a gene changes either (1) temporally, as the genetic background in which it is expressed changes, or (2) spatially, so that the same gene simultaneously has a minor effect in some demes but a major effect in others. The actual situation is even more difficult because, with epistasis, not only can the magnitude of an allelic effect depend upon genetic background, but also its sign (Wade, 2001).

In the sections to follow, I will examine first, how different kinds of epistasis influence the estimated 'additive' selective value of two segregating alleles, A_1 and A_2, at the A-locus within populations. Secondly, I will consider how population genetic subdivision at an unknown background locus, X, measured by Wright's F-statistic, creates variation among demes in the observed

effects of alleles at the **A**-locus. I will also show that, because population subdivision has different effects on the different kinds of epistasis, the among-deme variance in the magnitude and sign of allelic effects at the **A**-locus differs for the different kinds of epistasis. Differently put, with some kinds of epistasis, the **A**-locus is much more sensitive to population genetic structure than it is with other kinds of epistasis. These changes in allelic effect at the **A**-locus with epistasis and population genetic subdivision mean that the 'gene's eye view' of **A**-locus adaptation may vary during the evolutionary lifetime of an allele. Alleles cannot be said to be uniformly good or bad, or major or minor, because, with epistasis, these genic attributes are unstable and change with changes in genetic background, such as those caused by random genetic drift or selection at other loci.

Lastly, I will relate the effects of epistasis within subdivided populations to the Dobzhansky–Muller model of speciation, where epistatic interactions among loci play a prominent role in reproductive isolation via their deleterious effects on hybrid fitness. I show that the kinds of epistasis most sensitive to population genetic subdivision should also play a greater role in speciation than types of epistasis less sensitive to subdivision. To illustrate this point, I will show how the sex differences in hybrid fitness known as Haldane's rule can be explained by the kinds of epistasis most sensitive to population genetic subdivision. My approach to Haldane's rule, based upon epistatic variation *segregating within populations*, is somewhat different from that of Turelli & Orr (1995, 2000). They 'assume that each species is fixed at all loci' (Turelli & Orr 2000, p. 1664), so that their analysis begins much later in the evolutionary process than the one presented here.

The basic model: the kinds of epistasis

Consider a diploid organism with two alleles at locus **A**, A_1 and A_2, where A_1 is associated with lower performance and A_2 with higher performance. Similarly, consider two alleles, X_1 and X_2 in frequencies p and q, respectively, at the unknown locus, **X**. With the standard quantitative genetic decomposition (Crow & Kimura, 1970), allelic interactions at these loci can be partitioned into additive-by-dominance (K_{XAa} and L_{AXx}), dominance-by-dominance (J_{AaXx}), and additive-by-additive (I_{AX})

epistatic effects to obtain Table 1. The subscripts denote the known and unknown loci, **A** and **X**, respectively. Any kind of allelic interaction between two bi-allelic loci can be partitioned completely into these four orthogonal components of epistasis (Crow & Kimura, 1970).

The marginal selective values of the **A**-locus genotypes (row five of Table 1) are obtained by averaging over the three **X**-locus genotypes, assuming multilocus Hardy–Weinberg proportions for simplicity. For example, the marginal value of the A_1A_1 genotype is calculated as the average of the values of the $A_1A_1X_1X_1$, the $A_1A_1X_1X_2$ and the $A_1A_1X_2X_2$ genotypes. The average value equals $[(p^2)(-a - x + I_{AX}) + (2pq)(-a + D_X - L_{AXx}) + (q^2)(-a + x - I_{AX})]$. This expression can be reduced to $[-a - (p - q)(x - I_{AX}) + 2pq(D_X - L_{AXx})]$ as given in Table 1, column 2, row 5. Note that interactions between the two loci (I_{AX}, L_{AXx} and K_{XAa}, J_{AaXx}) as well as the main (x) and dominance (D_X) effects of the **X**-locus are components of the marginal phenotypic values of the **A**-locus genotypes. However, because the terms in x and D_X are common to all three **A**-locus genotypes, they do not contribute to the phenotypic *differences* among them.

It is standard practice to assign effects, $-a'$ and $+a'$, respectively, to the A_1 and A_2 alleles by taking the difference in phenotypic value of the two homozygotes, A_1A_1 and A_2A_2, and dividing it by 2. This gives an expression for a' equal to $[a - (p - q)I_{AX} + 2pqL_{AXx}]$, which is clearly a function of the additive-by-additive (I_{AX}) and additive-by-dominance (L_{AXx}) epistasis. Indeed, even if the A_2 allele had no main effect at all ($a = 0$), the marginal phenotypes would still appear to have 'main' effects resulting from these epistatic interactions with the unknown locus, **X**. As noted by Falconer & Mackay (1996), 'The concept of additive genetic variance does not carry with it the assumption of additive gene action; and the existence of additive variance is not an indication that any of the genes act additively (i.e. show neither dominance nor epistasis).' This principle can be extended to the concept of allelic main effects: *the existence of a statistical main effect is not an indication that a gene has any effect independent of its genetic background*. Note also, that in calculating a', alleles at the **A** and **X** loci were assumed to be in Hardy–Weinberg equilibrium, i.e. there was no linkage disequilibrium between them. Hence, alleles at the **A**-locus do not have to be associated in any way with those at the **X**-locus for this principle to be true. Epistasis

Table 1 The standard decomposition of phenotypic value into additive (a, x), dominance (D_A, D_X), and epistatic (I_{AX}, K_{XAa}, L_{AXx}, J_{AaXx}) components. The frequency of the X_1 allele is p and that of X_2 is q.

Genotypes	A_1A_1	A_1A_2	A_2A_2
X_1X_1	$-a - x + I_{XA}$	$-x + D_A - K_{XAa}$	$+a - x - I_{XA}$
X_1X_2	$-a + D_X - L_{AXx}$	$+D_A + D_X + J_{AaXx}$	$+a + D_X + L_{AXx}$
X_2X_2	$-a + x - I_{XA}$	$+x + D_A + K_{XAa}$	$+a + x + I_{XA}$
A-locus genotypes	$-a - (p - q)(x - I_{XA})$	$+D_A - (p - q)(x - K_{XAa})$	$+a - (p - q)(x + I_{XA})$
Marginal fitness	$+2pq(D_X - L_{AXx})$	$+2pq(D_X + J_{AaXx})$	$+2pq(D_X + L_{AXx})$
Marginal allelic values	$-a'$	D_A'	$+a'$

$a' = a - (p - q)I_{XA} + 2pqL_{AXx}$ and $D_A' = D_A + (p - q)K_{XAa} + 2pqJ_{AaXx}$.

influences the estimate of main effects at any participating locus, whether that locus is randomly associated with alleles at other loci or not.

The effect of different kinds of epistasis on the selective value of alleles at the *A*-locus

In this section, I will set main and dominance effects (a, x, D_A and D_X) equal to zero, in order to focus exclusively on gene interactions. I will consider each kind of epistasis separately, by setting its effect equal to s and the other three kinds of epistasis to zero, in order to show how different kinds of gene interaction affect the estimate of selection at the focal locus.

Additive-by-dominance epistasis ($L_{AXx} = s$; $K_{XAa} = J_{AaXx} = I_{AX} = 0$)

Epistasis of this type results from interactions between homozygosity at the *A*-locus and heterozygosity at the *X*-locus that affect fitness (Fig. 1a; Table 2, row 3). From the 'gene's eye view' of the *A*-locus, this type of epistasis

**Table 2** Additive-by-dominance epistasis alone ($L_{AXx} = s$; $K_{xaa} = J_{AaXx} = I_{AX} = 0$).

Genotypes	A_1A_1	A_1A_2	A_2A_2
X_1X_1	1	1	1
X_1X_2	$1 - s$	1	$1 + s$
X_2X_2	1	1	1
Directional selection on A	$1 - 2pqs$	1	$1 + 2pqs$

appears as directional selection favouring allele A_2 when s is positive but favouring A_1 when s is negative. Because heterozygosity ($2pq$) at the unknown locus, X, is a multiplier of s, it affects the strength of the selection at the *A*-locus (Table 2, row 5). Thus, the strength of selection at the *A*-locus is sensitive to processes that affect *X*-locus heterozygosity, such as gene flow, inbreeding, random genetic drift, or selection at loci linked to the *X*-locus. Note that, although loci *A* and *X* may be unlinked, selection on other loci near *X* will nevertheless affect the apparent selective value of *A*-locus alleles. Clearly, any change in allele frequencies at the *X*-locus, changes the relative fitness of *A*-locus genotypes (Fig. 1a;
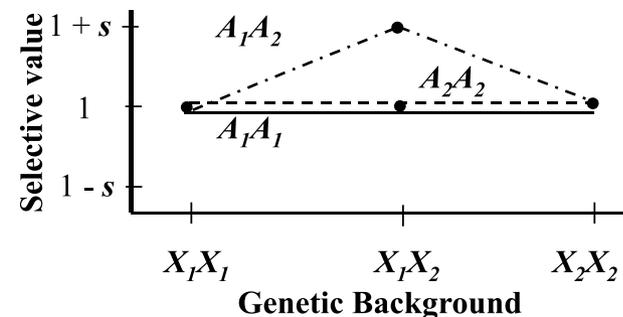

A) Additive-by-dominance interaction (L_{AXx})
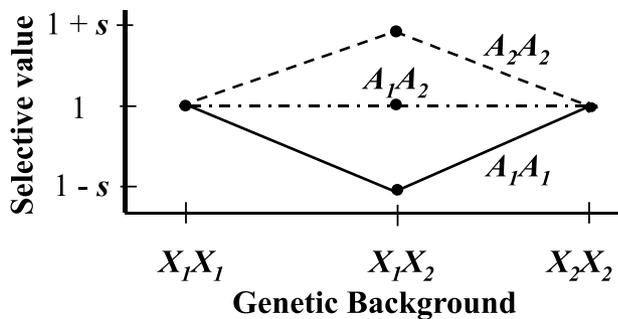
B) Dominance-by-additive interaction (K_{XAa})
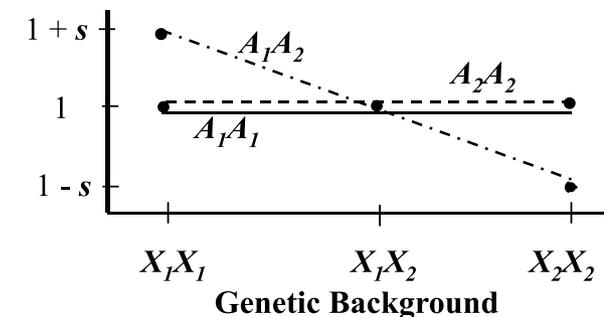
C) Dominance-by-dominance interaction (J_{AaXx})

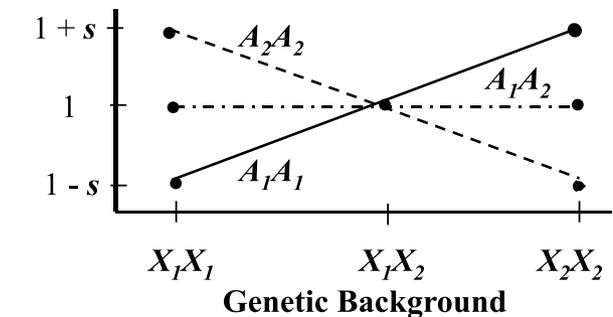**D)** Additive-by-additive interaction (I_{AX})

Fig. 1 A graphical representation of the effects of different kinds of epistatic interactions on the marginal fitnesses of *A*-locus genotypes.

Table 2, row 5). It is in this way that different samples from the same population or different studies of the *A*-locus in different populations could give rise to different estimates of the magnitude of effect of *A*-locus alleles.

Dominance-by-additive epistasis ($K_{XAa} = s$; $L_{AXx} = J_{AaXx} = I_{AX} = 0$)

Epistasis of this type occurs when interactions between homozygosity at the *X*-locus and heterozygosity at the *A*-locus affect fitness (Fig. 1b; Table 3, column 3). It appears as balancing selection at the *A*-locus, when the X_1 allele is rare [i.e. when $-s(p - q) > 0$], but disruptive selection when the alternative allele, X_2, is rare [i.e. when $-s(p - q) < 0$]. When the frequencies of the alleles at the *X*-locus are nearly equal, then the *A*-locus appears to be neutral because $[-s(p - q)]$ equals zero when p equals q. Again, it is clear that change in the frequency of alleles at the background locus *X* changes selection at the *A*-locus (Fig. 1b). Both the strength and direction of selection on A_1A_2 heterozygotes (over-dominance, under-dominance or neutrality) depend upon *X*-locus allele frequencies (Table 3, row 5).

Dominance-by-dominance epistasis ($J_{AaXx} = s$; $K_{XAa} = L_{AXx} = I_{AX} = 0$)

This type of epistasis results from interactions between heterozygotes at both loci (Fig. 1c; Table 4, column 3). Like dominance-by-additive epistasis (K_{XAa}), depending upon the sign of the effect (s), dominance-by-dominance epistasis (J_{AaXx}) can result in over-dominance ($J_{AaXx} = s > 0$), under-dominance ($J_{AaXx} = s < 0$), or neutrality ($s = 0$) at the *A*-locus. The strength of selection at the *A*-locus (Table 4, row 5) is proportional to

heterozygosity at the *X*-locus ($2pq$) as was seen for directional selection with additive-by-dominance epistasis (L_{AXx}). If an allele at *X* became fixed, then the *A*-locus would become neutral.

The functional redundancy of many homologous gene pairs during early development and the regulatory interactions among them (e.g. Hoxa-10 and Hoxa-11, Branford *et al.*, 2000) are suggestive of this kind of epistasis, because individuals doubly heterozygous may display mutant or abnormal phenotypes. However, few studies create and measure phenotypes for the full combinatorial set of genotypes (as in Table 1). Thus, it is difficult to partition out the different kinds of epistasis. At first glance, it might appear that dominance-by-dominance epistasis plays an important role in determining the mutant phenotypes produced by double heterozygotes. However, a loss of 25% function for the double heterozygotes, with zero fitness whenever a major gene is homozygous, decomposes into all of the other kinds of additive, dominance and epistatic effects but *no* dominance-by-dominance interactions (i.e. $a = x = D_A = D_X = K_{XAa} = L_{AXx} = I_{AX} = 0.25$, $J_{AaXx} = 0$). The existence at one locus of heterozygous modifiers of dominance at another and the manifestation of new phenotypes in double heterozygotes tend to generate some, nonzero amount of epistasis.

Dominance-by-additive and dominance-by-dominance epistasis both can give rise to marginal fitness values at the *A*-locus consistent with balancing selection. For this reason, epistasis for fitness contributes to the increase in the number of polymorphic equilibria in multilocus theory.

Additive-by-additive epistasis ($I_{AX} = s$; $L_{AXx} = J_{AaXx} = K_{XAa} = 0$)

This type of epistasis results from interactions between homozygotes at both loci (Fig. 1d; Table 5, rows 2 and 4) and can manifest itself as directional selection at the *A*-locus. The direction of selection depends upon the product of the sign of the additive-by-additive effect (s) and the allele frequency difference at the *X*-locus $[(p - q)]$. Goodnight & Wade (2000) identified this type of gene interaction as one of the most important because, in subdivided populations, the relationship between the A_1 allele and fitness is expected to change from deme to deme (see below). Cheverud & Routman (1996) also

Table 3 Dominance-by-additive epistasis alone ($K_{XAa} = s$; $L_{AXx} = J_{AaXx} = I_{AX} = 0$).

Genotypes	A_1A_1	A_1A_2	A_2A_2
X_1X_1	1	$1 - s$	1
X_1X_2	1	1	1
X_2X_2	1	$1 + s$	1
Balancing or disruptive selection on A	1	$1 - s(p - q)$	1

Table 4 Dominance-by-dominance epistasis alone ($J_{AaXx} = s$; $K_{XAa} = L_{AXx} = I_{AX} = 0$).

Genotypes	A_1A_1	A_1A_2	A_2A_2
X_1X_1	1	1	1
X_1X_2	1	$1 + s$	1
X_2X_2	1	1	1
Balancing or disruptive selection on A	1	$1 + 2pqs$	1

Table 5 Additive-by-additive epistasis alone ($I_{AX} = s$; $K_{XAa} = L_{AXx} = J_{AaXx} = 0$).

Genotypes	A_1A_1	A_1A_2	A_2A_2
X_1X_1	$1 + s$	1	$1 - s$
X_1X_2	1	1	1
X_2X_2	$1 - s$	1	$1 + s$
Directional selection on A	$1 + s(p - q)$	1	$1 - s(p - q)$

identified it as one of the 'most important' kinds of epistasis because it contributes most heavily to the generation of new additive variance within demes by random genetic drift (Goodnight, 1987, 1995). Many examples of this type of epistasis are available from quantitative trait loci (QTL) studies. For example, in the mouse, additive-by-additive epistasis has been shown to characterize genes affecting susceptibility to colon tumours (Groot *et al.*, 1992), lung tumours (Fijneman *et al.*, 1996), skin tumours (Nagase *et al.*, 2001), *Leishmania* (Lipoldova *et al.*, 2000), diabesity (Reifsnyder *et al.*, 2000), and resistance to *Mycobacterium tuberculosis* (Kramnik *et al.*, 2000).

Population genetic subdivision causes among-deme variation in selection at the *A*-locus

When a population is subdivided into local demes, they become genetically different from one another at a rate and to a degree determined by a variety of factors, including the effective size of local demes, N_e, the amount and pattern of migration among them, m, and the metapopulation processes of extinction and recolonization (Wade & McCauley, 1988; Whitlock & McCauley, 1990; Whitlock *et al.*, 1993). The *F*-statistics of Wright (1969) describe this process of genetic differentiation of local populations for single genes, but Wright (1969) considered this single-gene framework 'wholly inadequate' for characterizing the differences among demes caused by multiple interacting gene systems. Wright's *F*-statistics have been extended to two loci in the form of two-locus descent measures developed by Cockerham & Weir (1973). These two-locus measures have been used to investigate how epistasis changes the genetic differentiation of mean deme phenotypes and how it can cause an increase in genetic variance with inbreeding (Goodnight, 1987, 1995, 2000; Whitlock *et al.*, 1993). The derivation and biological interpretation is somewhat involved and cannot be adequately addressed in the context of this review. Instead of considering the simultaneous effects of random drift on two linked loci, in this review, I will illustrate the effects of epistasis and population subdivision as seen through the 'gene's eye view' of the *A*-locus. In this view, I will consider the frequency of alleles at the *A*-locus as fixed and unchanging and examine how their estimated effects on the phenotype vary because of the effects of population subdivision on the *X*-locus. This situation is like that of an experimental geneticist, who crosses alleles at the

A-locus, holding them at a fixed frequency by design, into a set of different genetic backgrounds, such as those generated by random drift (see, for example, experiments of Wade, 1985, 2000). In the sections that follow, I will examine the two ways in which selection at the *A*-locus is changed by population genetic subdivision: (1) average selection within demes; and (2) selection among demes.

Additive-by-dominance epistasis (L_{AXx} = s) *or* dominance-by-dominance epistasis (J_{AaXx} = s)

Selection at the *A*-locus is influenced by heterozygosity at the *X*-locus when either of these kinds of gene interactions is present (Table 6, rows 2 and 4). Because random genetic drift reduces average heterozygosity at the *X*-locus within demes from $2pq$ to $2pq(1 - F)$, for both kinds of epistasis, population subdivision can be viewed as reducing the average strength of selection within demes from s to $s(1 - F)$. With additive-by-dominance epistasis, directional selection at the *A*-locus, averaged across demes, will be *weaker* in a subdivided population, where F is greater than zero than it is in a nonsubdivided population. In this sense, epistasis represents a genetic constraint by reducing the rate of gene frequency change by selection (Whitlock *et al.*, 1993). In a similar manner, in a subdivided population with dominance-by-dominance epistasis, on average, balancing ($s > 0$) or disruptive ($s < 0$) selection at the *A*-locus is also lessened by population subdivision. In demes fixed for either allele at the *X*-locus, the *A*-locus will appear neutral with no selective value associated with either the A_1 or A_2 alleles.

Dominance-by-additive epistasis (K_{XAa} = s) or additive-by-additive epistasis (I_{AX} = s)

Average within-deme selection at the *A*-locus is not influenced by population subdivision with either of these kinds of gene interaction (Table 6, rows 3 and 5). Because random genetic drift does not change average allele frequencies across a metapopulation, selection on average remains the same with population subdivision as without it. However, the variance among demes in genotypic fitness equals $\{4s^2F_{ST}pq\}$ and it could be sufficient to reverse the direction of selection in some demes for either kind of epistasis. In the limit, consider a fraction of demes, p, fixed for the X_1 allele and a complementary fraction, q, fixed for the X_2 allele. With additive-by-additive epistasis (Table 5, row 5), A_1 would

Type of epistasis	A_1A_1	A_1A_2	A_2A_2
Additive-by-dominance	$1 - 2pqs(1 - F)$	1	$1 + 2pqs(1 - F)$
Dominance-by-additive	1	$1 - s(p - q)$	1
Dominance-by-dominance	1	$1 + 2pqs(1 - F)$	1
Additive-by-additive	$1 + s(p - q)$	1	$1 - s(p - q)$

Table 6 Population subdivision and average within-deme selection.

be selected against in p of the demes, whereas, in q of the demes, it would be favoured. With dominance-by-additive epistasis (Table 3, row 5), balancing selection would maintain polymorphism at the A-locus in a fraction of demes p, whereas disruptive selection, with fixation of either A_1 or A_2 would occur in the remaining fraction of demes.

The role of epistasis in speciation

The Dobzhansky–Muller model of speciation is schematically illustrated in Table 7 for females homogametic at the X-locus and males heterogametic. Deleterious gene combinations occur only in hybrids between populations but not during evolution within any population under this theory. The ancestral species has the genotype, $A_0A_0X_0X_0$ in females and $A_0A_0X_0$ in males. Under the Dobzhansky–Muller model, populations in allopatry diverge by the combined forces of mutation and natural selection. Thus, in allopatry, daughter species 1 acquires allele A_1 by mutation and it later becomes fixed by natural selection. Similarly, daughter species 2 acquires and fixes the X_1 allele. Although the A_1 and X_1 alleles are incompatible, they do not co-occur in either the ancestral population or the daughter populations (Charlesworth *et al.*, 1987; Turelli & Orr, 1995, 2000; Coyne *et al.*, 2000). However, when the two evolved daughter species are crossed in sympatry, the interspecific hybrids are distinguished from the ancestor and from both daughter species by the expression of dominance-by-dominance epistasis (J_{AaXx}) in females and by dominance-by-additive epistasis (K_{XAa}) in males (Turelli & Orr, 1995, 2000). If there is a sex difference in the phenotype of F1 hybrids, then the values in Table 7 indicate that it could result from differences in the sign of these two epistatic effects: (1) the dominance-by-dominance (J_{AaXx}) epistatic effects experienced by the homogametic sex; and (2) the dominance-by-additive (K_{XAa}) epistatic effects

experienced by the heterogametic sex. Importantly, *both of these kinds of epistasis permit fitnesses of **A**-locus genotypes to change from balancing selection to disruptive selection with change in background at the interacting X-linked locus.*

Haldane's rule (Coyne, 1992; Wade *et al.*, 1997), under which the heterogametic sex but not the homogametic sex is rare, sterile, or absent in interspecific hybrids is the best known generality about sex differences in the phenotypes of F1 hybrids. Under Haldane's rule, the fitness of the heterogametic F1 hybrids, here the males, is lower than that of the homogametic hybrids (the females). From Table 7, it is evident that this pattern could result from a relatively greater deleterious effect of dominance-by-additive epistasis (K_{XAa}) on male hybrids relative to the effects of dominance-by-dominance epistasis (J_{AaXx}) on female hybrids. Because of the role that X-linked background alleles play in changing the relationship between autosomal alleles and fitness, these two kinds of epistasis would be expected to contribute to the 'large X effect' in introgression studies (e.g. Coyne, 1992; Turelli & Orr, 2000). That is, introgression of an X-allele from one daughter species into the background of another should lead to the expression of dominance-by-additive epistasis (K_{XAa}) in the heterogametic male hybrids and dominance-by-dominance epistasis (J_{AaXx}) in the homogametic female hybrids.

The scenario presented here differs from the theory of Turelli & Orr (1995, 2000), which explains Haldane's rule in terms of epistasis between genes *fixed* between daughter populations descended from a common ancestor. It also differs from the Dobzhansky–Muller model, which assumes that 'postzygotic isolation in interspecific hybrids results from deleterious interactions between alleles that have never been ''tested'' together in a common genome' (Coyne *et al.*, 2000). I am arguing here about segregating and interacting genes in an ancestral population. Specifically, from a gene's eye view, there are types of epistasis that can convert over-dominance to

Table 7 The Dobzhansky–Muller model of speciation where females are homogametic and males are heterogametic. The ancestral form is of genotype, $A_0A_0X_0X_0$ in females and $A_0A_0X_0$ in males. In allopatry, daughter species 1 acquires the A_1 allele by mutation and it becomes fixed by natural selection. Similarly, daughter species 2 acquires and fixes the X_1 allele. When crossed in sympatry, the interspecific hybrids are distinguished from the ancestor and from both daughter species by the expression of dominance-by-dominance epistasis (J_{AaXx}) in females and by dominance-by-additive epistasis (K_{XAa}) in males. In backcrosses to either daughter species, additive-by-dominance (L_{AXx}) and dominance-by-additive epistasis (K_{XAa}) are also expressed.

	A_0A_0	A_0A_1	A_1A_1
Females			
X_0X_0	$-a - x + I_{XA}$ Ancestral species	$-x + D_A - K_{XAa}$ Mutation and natural selection	$+a - x - I_{XA}$ Daughter species 1
X_0X_1	$-a + D_X - L_{AXx}$ Mutation and natural selection	$+D_A + D_X + J_{AaXx}$ Interspecific hybrids	$+a + D_X + L_{AXx}$ Backcross to daughter species 1
X_1X_1	$-a + x - I_{XA}$ Daughter species 2	$+x + D_A + K_{XAa}$ Backcross to daughter species 2	$+a + x + I_{XA}$
Males			
X_0	$-a - x + (I_{XA})/2$ Ancestral species	$-x + D_A - (K_{XAa})/2$ Mutation and Natural selection	$+a - x - (I_{XA})/2$ Daughter species 1
X_1	$-a + x - (I_{XA})/2$	$+x + D_A + (K_{XAa})/2$ Daughter species 2	$+a + x + (I_{XA})/2$ Interspecific hybrids

under-dominance or balancing selection to disruptive selection. Disruptive selection can drive the genetic differentiation of daughter populations descended from a common ancestor. Not only are these types of epistasis particularly sensitive to population genetic subdivision but they are also the same types of epistasis invoked in explanations of Haldane's rule (Turelli & Orr, 1995, 2000). Thus, my theory addresses how epistasis, segregating in an ancestral population, might contribute to the origin of those fixed genetic differences between daughter populations that cause reproductive isolation and Haldane's rule. This viewpoint is somewhat controversial in that Coyne *et al.* (2000, p. 311) state '…we disagree sharply with their (Wade & Goodnight, 1999) suggestion that we should try to understand the causes of Haldane's rule by studying intraspecific variation.'

In summary, epistatic interactions between *X*-linked and autosomal genes have several features that make them uniquely relevant to speciation: (1) they are unusually sensitive to population subdivision; (2) change in background at X-linked loci can convert balancing selection to disruptive selection at interacting autosomal loci; and (3) there can be a difference in the kinds of X-autosome epistatic effects expressed by the heterogametic and homogametic hybrids.

Discussion

In this paper, I have used the statistical framework for characterizing two-locus interactions from quantitative genetics to illustrate how epistasis can affect the assignment of function to alleles at a focal locus. Although it is common in evolutionary genetic textbooks to discuss how and why narrow sense heritability estimates are conditional on gene frequency and environment, the effects of epistasis on heritability are rarely mentioned. It is clear, nevertheless, that the estimated additive effect of a gene and, hence, its contribution to the additive variance changes with the frequencies of its epistatic partners (Wade, 1992; Cheverud & Routman, 1995a,b; Falconer & MacKay, 1996; Goodnight, 1987, 1995, 2000). With epistasis, the effect of an allele in one deme can be different in magnitude or sign from its effects in another because of variation from deme to deme in genetic background. For example, with additive-by-additive epistasis (Table 5, row 5), the magnitude and sign of the effect of the A_1 allele are expected to vary across demes in a metapopulation. Whereas the A_1 allele is a 'good gene', advantageous in a locality where the X_1 allele is common, it is not advantageous everywhere. It is a 'bad gene', selected against wherever the X_1 allele is rare. Thus, the 'gene's eye view' of the A_1 allele as a favourable or deleterious gene is too simplistic. The sign of a gene's effect on fitness is sensitive to variations in genetic background caused by random genetic drift, mutation, and selection whenever there is epistasis. Out-breeding depression and speciation theory both depend upon the effect of an allele being positive in the genetic background of its own population but negative in the genetic background of some other population. In the absence of genotype-by-environment interaction, this type of negative correlation of within-population and between-population allelic effects requires epistatic gene action (Wade, 1992; Johnson & Wade, 1996). Additive-by-additive interactions always provide this kind of variation in allelic effect between differentiated backgrounds.

These same concerns apply to discussions of the role of genes of major and minor effect in evolution. The size of an allele's effect changes with genetic background. For example, the level of heterozygosity at the *X*-locus determines the magnitude of the effect of the A_1 allele with additive-by-dominance epistasis (see Table 2, row 5). When heterozygosity at the *X*-locus is high, the A_1 allele has a major effect on fitness. However, when heterozygosity at the *X*-locus is low, the A_1 allele is a minor fitness allele. It is even more problematic in subdivided populations, where the A_1 allele can be a gene of major effect in one deme but a minor effect gene in another. With epistasis, the magnitude of a gene's effect on fitness changes because of variations in genetic background caused by random genetic drift, mutation and selection.

Whereas the process of adaptation can be explained without gene interactions (Coyne *et al.*, 1997; Crow, 2001), speciation and reproductive isolation cannot. The fitness of interspecific hybrids in the Dobzhansky–Muller model is lowered because genes that function well in conspecific backgrounds, function poorly in the heterospecific background. For reasons discussed above, some kinds of epistasis should play a larger role than others in speciation. However, in the model, the negative epistasis (Johnson, 2000), which is expressed in the hybrid background, does not exist within the ancestral population or in either of its descendant daughter species. It is not a component of within-population adaptation. Nevertheless, there are many examples of genes segregating within populations, which not only exhibit epistasis, but also exhibit the kinds of epistasis most likely to be associated with speciation. Indeed, the near neutrality or very low rate of nonsynonymous gene substitution typically observed in studies of molecular evolution (cf. Table 14.1 in Li, 1997) is consistent with a world in which gene interactions are ubiquitous, population subdivision is common, and alleles frequently change their temporal and spatial relationship to fitness. Interactions among genes are particularly important in understanding the origin and evolution of complex phenotypes. Although the human genome may contain only 30–40 000 genes, this number of genes permits more than 5.0×10^8 interactions between gene pairs. Understanding epistasis is the key to developing efficient and repeatable experimental methods for dissecting complex phenotypes into their component loci,

understanding their interactions, and explaining individual variations in phenotype (Wade, 2001).

Acknowledgments

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