Epistasis and its consequences for the evolution of natural populations

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Throughout the neodarwinian synthesis, theorists have debated the role of gene interactions, or epistasis, in the evolutionary process. Unfortunately, empirical measurement of the role of epistasis in the evolution of natural populations has, until now, been difficult. Two developments in empirical approaches have occurred: (1) application of quantitative genetic theory to the evolution of natural populations, and (2) the concurrent development of molecular marker-assisted techniques to understand the architecture of quantitative genetic variation. Thus, exciting developments in both theory and empirical data collection provide the stimulus needed for documenting the role of epistasis in the evolutionary process.

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The neodarwinian synthesis defined the conceptual framework of present evolutionary studies. Yet two of the most important contributors to the synthesis, Fisher and Wright, had dramatically contrasting views of the processes responsible for the evolution of natural populations. Their differences emphasize the relative importance of additive gene effects versus non-additive interactions among genes (Box 1) in the evolutionary process.

The premise of Fisher's theory is that evolution is primarily due to selection acting on the effects of individual loci, independent of variation at other loci[1]. He believed that additive or main effects of genes determined their evolutionary fate and that non-additive components of genetic variation had as little evolutionary importance as non-heritable factors[2]. In part, this was because of Fisher's belief that species were essentially panmictic. Panmixis, according to Fisher, allows genes to be tested in all genetic backgrounds; thus, additive effects determine their evolutionary fate.

In contrast, the notion that selection acts to form coadapted or interacting gene complexes is central to Wright's shifting balance theory (SBT) of evolution[3,4]. Wright's vision of the adaptive landscape with fitness peaks and valley(s) relies on epistatic gene action (the converse, that the presence of epistasis indicates peaks and valleys, is not necessarily true). Wright believed genes to be commonly found in a limited number of genetic backgrounds owing to population structure resulting from limited gene flow. Consequently, the evolution of relationships among genes is more likely. If epistasis does not contribute to genetic variation for fitness then there is no valley(s) between the peaks and thus little need to invoke his SBT. If an allelic substitution contributes to the fitness of an organism independent of the genetic background then 'simple' fisherian selection is all that is required to move a population to a higher adaptive peak.

Much empirical work over the past 30 years has demonstrated that species exhibit significant population genetic structure and are therefore far from panmictic[5]. Furthermore, any factor that causes departures from panmixia (e.g. asexuality, selfing and geographic isolation) limits the recombination pool and facilitates the development and maintenance of coadapted gene complexes. However, we still have too little information on the role of epistasis in the evolutionary process to resolve the fundamental conflict between Fisher and Wright. Furthermore, even if Wright's SBT is not shown to be relevant to the evolutionary process, epistasis may influence evolutionary models.

The question of paramount importance is: how common is epistasis? If epistasis potentially plays a central role in evolutionary process, why has empirical work quantifying its importance lagged so far behind theory? A partial explanation is the lack of use of an evolutionary relevant definition and the difficulty of quantifying epistasis (Box 1). For epistasis to contribute to the evolutionary process, it must underlie phenotypic variation. Traditionally, epistasis has been associated with the action of genes that affect mendelian traits. In this context, epistasis refers to the expression of a phenotype and not to how it contributes to phenotypic variation in natural populations[2] (Box 1). However, the relationship between epistatic gene action and epistatic variance is dependent on allele frequencies[6]. Thus if allele frequencies have changed, the absence of contemporary levels of population epistatic genetic variation may not reflect the fundamental role of gene interaction in the past evolution of populations.

A second reason for the lack of empirical work is the difficulty in quantifying epistasis. We are interested in how epistasis contributes to standing variation of fitness-related traits either at the within or between population level. If fitness is a polygenic 'trait', then we need quantitative genetic approaches to quantify the effects of epistatic interactions. Drawing inspiration from the fundamental work of Pearson, Wright and Fisher and taking

Box 1. Epistasis and coadapted gene complexes defined

Physiological epistasis: Here, epistasis is a ubiquitous phenomenon, related to the instance where specific gene products in a metabolic pathway determine the formation of other products downstream in the pathway. However, laboratory examples of epistasis of this type do not demonstrate the role of epistasis to the contribution of standing genetic variation (see text). In this context, epistasis has historically been used to describe the situation in which one gene masks the expression of another, for instance the recovery of 9:7 ratios, instead of the expected 9:3:3:1 ratios in the F_2 of dihybrid crosses.

Statistical epistasis: The quantitative genetic definition of epistasis refers to the degree to which phenotypic variation is determined by interactions among genes. If epistasis is important, then, in a statistical sense interactions, rather than main effects, are the fundamental properties of genes responsible for evolution. Genes selected for their joint effects on fitness form coadapted gene complexes. In current usage, epistasis also refers to interactive effects among nucleotides within a locus, or within gene epistasis. In contrast, the additive effects of genes refers to their overall main effects across different genetic backgrounds. Note that the variation may be quantified within populations or may contribute to differentiation among populations.

Selection: Epistasis for fitness can also result when variation for a trait is additive, but selection is either stabilizing or disruptive. In this case, the fitness effects of a gene depends on which alleles are present at other loci. This non-linear mapping of gene effects onto fitness does not support the contrasting models of evolution proposed by Fisher and Wright but does contribute to the maintenance of genetic variation.

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advantage of the enormous theoretical and applied development of quantitative genetics associated with animal and crop improvement, evolutionary biologists in the early 1980s demonstrated the utility of applying quantitative genetic approaches to understanding fundamental problems in evolutionary biology[7,8]. Almost concurrently, powerful and accessible molecular techniques have been developed that allow us to map loci affecting the expression of quantitative traits (QTL), hence permitting more-detailed examination of the genetic architecture of fitness in natural populations[9]. Thus, evolutionary biologists are at a unique juncture. Whereas theory has far outpaced empirical determination of the importance of epistasis, now, with the advent of molecular techniques and the application of quantitative genetic approaches to natural populations, empiricists have much more powerful tools to examine the relevance of epistasis to the evolutionary process.

Measuring epistasis and evaluation of the methods

Many approaches have been used to quantify the role of inter-locus interactions in the evolution of natural populations. On the organismal level, Simpson[10] interpreted Wright's notion of adaptive topography in terms of coadaptation for phenotypic features. At the genetic level, evidence for epistasis has come from a number of different approaches (see Box 2 and Table 1 for description and evaluation of methods):

(1) multilocus associations including supergenes, tightly linked genes affecting both morphological[11] and molecular characters[12];
(2) hybrid breakdown as a result of mixing differentiated gene pools[13,14];
(3) evaluation of interactions among chromosome segments through QTL mapping[15];
(4) the contribution of non-additive variation to quantitative traits, especially fitness[16];
(5) the formation of linkage disequilibrium under selection[17,18];
(6) analysis of the response to selection in subdivided populations[19].

Of these genetic methods, (1) to (3) measure the *present* contribution of epistasis to differentiation. Since additive processes of allele substitution may result in epistatic differentiation among populations and/or species[13,20], genetic structure measured by these methods may not necessarily reflect the contribution of selection for coadapted genes. However, the epistasis measured by these methods may influence the potential of a species or a population for future evolutionary change, and may contribute to the initial stages of post-zygotic reproductive isolation[6]. The contribution of epistasis to the *ongoing evolutionary process* can only be evaluated using methods (4) to (6).

Box 2. Methods of evaluating epistasis

I. Contribution of epistasis to differentiation

- *Phenotypic associations (adaptive syndrome):* Measures contribution of non-additive interactions among phenotypic characters by demonstrating that specific combinations of traits confer high fitness.
- *Multi-locus associations:* Linkage disequilibrium, nonrandom associations between groups of nucleotides or alleles may indicate epistatic relationships.
- *Hybrid breakdown:* Quantifies epistasis by breaking up coadapted gene complexes. Reduced fitness of recombinant hybrids of crosses between lines, populations or species in comparison with the mid-parent, and the F_1 hybrid generation, indicates epistasis. Genetic mapping techniques in which crosses are conducted between individuals that have fixed differences for known markers and that differ in performance can provide greater resolution of epistatic interactions. Fitness of hybrids 'mapped' onto the linkage map reveals the effects of flanking marker regions and their interactions on fitness.

II. Contribution of epistasis to the evolutionary process

- *Variance partitioning:* Resemblance among relatives is used to quantify the contribution of additive and non-additive effects among loci to within population phenotypic variation.
- *Selection analysis:* The development of multilocus associations and their fitness consequences is quantified across generations in populations under constant selection.
- *Selection in subdivided populations:* Conditions for the establishment of epistatic gene complexes are created experimentally. These complexes are then tested for their development using line-cross methodology.

Of the methods that quantify the contribution of epistasis to present differentiation, hybrid breakdown is perhaps most powerful for two reasons. First, one has more power to detect epistasis by comparing the behavior of the means of the different generations (Parental, F_1, F_2, and so on) versus the interaction represented in variance components (Table 1). Second, this approach tests the effect of the physical disruption of putative coadaptive gene complexes through recombination. As such, it is a direct estimate of the contribution of epistasis to differentiation. This differentiation can be either environmentally based or driven by the fixation of complementary lethal or semi-lethal gene systems[21,22]. It is also independent of the constraints of allele frequencies. Genic combinations that are rare in populations (thus contributing little epistatic variance as demonstrated by variance component analysis) are resurrected to high frequencies in the hybrid and segregating populations.

The model of gene effects describing the behavior of F_2 or other segregational generation hybrids in relation to their parents and F_1 is well understood and is sometimes referred to as line-cross methodology[23,24]. Marker-assisted techniques (QTL mapping) complement the biometrical approach by allowing one to determine the presence of genic interactions over finer scales, that is, between intervals flanked by markers, and have been particularly useful in determining more precisely the genetic basis of reproductive isolation among species of *Drosophila*[22]. However, there are substantial statistical problems that need to be overcome before inferences of epistasis based on the molecular marker based approaches can be made, especially for outbred populations[25]. The major problems include (1) limited sample sizes of closely linked recombinant markers, and (2) Type I errors that are associated with the likelihood of detecting significant interactions given the potentially large number of tests [$N!/2(N-2)!$], where N is the significant QTL affecting the trait. Potential solutions include examination of later segregating generations to increase the likelihood of recombination and sequential experiments where QTL's are identified and specific gene combinations are constructed and tested for their effects on fitness. Development of theory that allows map construction with the simultaneous action of selection acting on epistatic interactions is also needed.

In contrast to inferring past selection, the contribution of selection on multilocus associations to ongoing adaptation can most clearly be evaluated by following the transmission of genetic markers across generations. In one of the most elegant demonstrations, Clegg, Kahler and Allard[18] tested the adaptive significance of particular allelic combinations by following the evolution of multilocus associations across generations in experimental crosses of cultivated barley. By measuring viability and fertility components of selection associated with linkage blocks marked by four isozymes, they were able to demonstrate large fitness differences among distinct three-locus combinations, implying that selection on epistatic complexes was operating within the experimental population. The advent of QTL mapping may allow us to measure these associations over varying segments of the genome and determine their effects on fitness in much greater detail.

Significance of epistasis to evolutionary studies: examples

In addition to differentiating Fisher's and Wright's models of evolution, current

Table 1. An evaluation of the methods to measure epistasis

Method	Advantages	Disadvantages
I. Procedures that identify contribution of epistasis to current differentiation		
Phenotypic associations (adaptive syndromes)	Trait interactions demonstrated in ecological context	Relationship among genes not necessarily epistatic (except, for example, heterostyly)
Multilocus associations	Relatively easy to document	Linkage disequilibrium does not necessarily reveal epistasis Portion of genome evaluated for fitness limited to flanking regions of markers
Hybrid breakdown	Direct measure of contribution of epistasis to fitness Detects fixed epistatic interactions Genome-wide measure of epistasis Comparisons of means is statistically powerful Can be used in association with QTL mapping techniques	Can only be measured on differentiated groups (although hybrid breakdown in asexual and highly selfing organisms may be observed within populations)
II. Procedures that evaluate contribution of epistasis to the evolutionary process		
Variance partitioning	Well-developed theory Provides information on other aspects of genetic profile	Epistasis measured as an interaction in ANOVA: this requires very large experiments to ensure statistical accuracy Epistatic interactions should become rapidly fixed within populations, obscuring their detection
Selection analysis	Direct measure of selection for epistatic interactions	Limited by marker availability and numerical constraints of genotyping many individuals
Subdivided populations	Direct test of the shifting balance theory of evolution	Infers epistasis from patterns of evolutionary change

theoretical findings indicate that the presence or absence of epistasis is relevant to many major evolutionary phenomena such as the evolutionary definition of the gene, maintenance of sex, the evolution of selfing, phenotypic plasticity, developmental homeostasis, and founder effect genetic revolutions. The presence of epistasis also has implications for conservation and restoration of endangered organisms and the maintenance of genetic resources. Given the relevance of epistasis to these major areas of current research in evolutionary biology, it is fundamental to determine whether epistasis is pervasive, and if so, how it influences the evolutionary process.

The following sections serve to bring attention to the role of gene interaction in diverse and important evolutionary phenomena. It must be emphasized that there are different forms of epistasis[26] (Box 3) and that these forms might have different consequences for each of the phenomena in terms of the evolutionary outcomes.

What is a gene?

A gene is traditionally defined as a region coding for a single polypeptide or some functional complementarity (a cistron). While these definitions have suited most usage in evolutionary biology, functional analysis at the level of fitness can lead to alternative definitions. Because recombination breaks apart the genome of sexual organisms, the functional unit must be something smaller than the genome. In this context, Turner[27] asked why does the genome not congeal? His own answer was that recombination prevents the genome from evolving as a coadapted complex. Dawkins[28] suggested that this smaller functional unit should be evolutionary biology's definition of 'gene' and it should be operationally identified by the existence of competing units (alleles).

When genetic variation for fitness is entirely additive in a sexual population, the long-term persistence (and possible fixation) of a single nucleotide is dependent mainly on the relative fitness of other nucleotides at that same position in the genome. With recombination, nucleotides at other positions are of little long-term consequence. Thus, every nucleotide is an allele and the gene is the nucleotide. However, if epistatic variation exists, the fate of a single nucleotide depends on its interaction with nucleotides at other positions in the genome. Whether different groups of interacting nucleotides persist depends then on whether the relative strengths of selection and recombination allow the groups to congeal and effectively to become different alleles. Recent results suggest that substantial linkage disequilibrium resulting from interactions between loci can be generated with epistatic selection so long as recombination (r) is not much greater than the intensity of epistatic selection (s) (Ref. 29). Thus, from the viewpoint of function at the level of fitness, a gene can be as small as a single nucleotide or as large as a chromosomal region bounded by nucleotides for which the ratio $s:r$ is approximately ≥ 1.

Evolution of natural populations

As already discussed, much of the controversy concerning the role of epistasis in evolution is associated with the contrasting views of Wright and Fisher. To evaluate the relevance of Wright's adaptive topography, we must know the density of coadapted peaks or the scale at which epistasis for fitness contributes to selective differentiation[6]. Is epistatic selection a constant feature of the differentiation of populations, acting at all levels of genetic divergence, or does adaptive evolution require only the occasional incorporation of novel gene complexes[30], perhaps only those associated with speciation?

The answer to these questions will have important consequences for how we study the evolutionary process. Epistasis which results in reversals of fitness and consequently a rough fitness topography of peaks and valleys is essential to Wright's SBT. However, even if populations are not required to evolve lower fitness (that is, no valleys separate the peaks), or to evolve lower fitness to change adaptive states, epistasis for fitness suggests that evolution will be more complex than simple fisherian models. For example, Lande and Arnold[7] view evolution as a linear process (e.g. fisherian); knowledge of selection intensities, heritabilities and genetic and phenotypic covariances allow us to estimate the trajectory of trait evolution. If, instead, epistasis is important, then trait evolution may follow a non-linear trajectory, as is indeed observed in certain long-term selection experiments[16] (alternative explanations include erosion of genetic variance and conflicts between artificial and natural selection[19]). The response to selection of allele frequencies may not be predictable as changes in combinations of genes will affect the selective regime experienced by each locus[31]. In turn, the selection gradient may fluctuate as different combinations of characters result in changing optima. Consequently, 'context and interaction are of the essence'[32].

In addition, epistasis may, under some conditions, contribute to the fisherian model of mass selection. Both theoretical[33,34] and empirical[19,35] work demonstrates that epistatic genetic variation can be converted to additive genetic variation via drift, facilitating a response to selection. Thus the loss of additive genetic variation through drift may be counteracted by the conversion of non-additive to additive genetic variation.

Founder-effect speciation

Several theories of founder-effect genetic revolution[36] leading to speciation are derivative versions of SBT. In these, reproductive isolation is associated with a 'genetic reorganization' reflecting substitution of one epistatically coadapted gene complex for another during population bottlenecks and consequent relaxed selection associated with colonization of new sites. They essentially differ from SBT in not requiring the export of novel and more favorable gene combinations, because the colonizing population cannot experience gene flow with ancestral populations owing to spatial or ecological isolation. The likelihood of founder effect speciation depends on the genetic assumptions but appears to increase if there are series of transitions across shallow valleys[37] or if intermediate ridges connect the peaks[38]. In the latter case, the environment in which the populations evolved may have favored intermediate allele frequencies, or alleles that were present in the evolution of the populations (but that were no longer present) conferred intermediate fitness between two peaks, thus connecting the peaks along a ridge. Consequently, crosses between the populations result in progeny of low fitness. Population differentiation that is epistatically based will increase polymorphic variation for epistatic gene complexes, facilitating speciation via founder effects[38].

Evolution of mating systems

The origin and maintenance of sexual reproduction is a fundamental paradox in evolutionary biology because asexual reproduction has an intrinsic twofold advantage over sexual reproduction[39]. One theory that has generated a great deal of recent interest finds sexual populations to have an advantage over asexual populations if mutations act epistatically for fitness[40,41]. If there is synergistic reinforcing epistasis such that each additional deleterious mutation leads to a larger decrease in fitness, then the mean fitness of sexual populations will exceed that of asexual populations. This difference arises from selection removing a larger fraction of the deleterious mutations in sexual populations that regenerate variation through both segregation and recombination. With reinforcing epistasis, sexual populations have lower mutational loads and therefore higher mean fitness than asexual populations. If this theory is verified, it implies that epistatic interactions for fitness are pervasive across a wide variety of organisms.

Current models of the evolution of selfing focus on the parallel evolution of inbreeding depression with mating system[42]. Inbreeding depression, probably resulting from the expression of deleterious recessive alleles[43], is considered to be the primary factor preventing the evolution of selfing in outcrossing organisms. How quickly these recessive deleterious alleles can be purged from the population, and hence how likely selfing will evolve, is in part determined by whether or not there are interactions among the deleterious alleles. Similar to the evolution of sex, synergistic reinforcing epistasis among deleterious alleles will lead to a more-rapid rate of purging of these alleles from the population and facilitate the evolution of selfing.

The experimental evidence concerning modes of gene action among mutations is limited and inconclusive (see Ref. 44 and citations within). The accumulation of non-lethal mutations over time in *Drosophila* stocks results in an accelerated decline in vigor; there is also evidence that increasing inbreeding results in a greater rate of decrease in fitness for dairy cattle, poultry, mice and guinea pigs. However, there is little evidence for an accelerated decline in fitness associated with increased inbreeding in maize or inbred lines of wild species.

Note that both discussions of the role of epistatic interactions among mutations are not related to the issue of the relevancy of SBT. Mating system evolution addresses the question of how epistatic interactions among deleterious mutations influence the rate and dynamics of their elimination, whereas SBT is concerned with the spread of favorable genetic variation.

Developmental homeostasis and plasticity

The ability of organisms to withstand genetic and environmental disturbances encountered during development and to produce predictable phenotypes is known as developmental homeostasis[45]. Two contrasting, but not mutually exclusive, hypotheses have been put forward to explain the genetic basis of developmental homeostasis: heterozygosity[46] and coadapted gene complexes[13]. The controversy may be interpreted as one of scale, with the proponents of the alternative hypotheses, Lerner and Dobzhansky, believing in the importance of stabilizing selection in producing an optimal phenotype. However, Lerner stressed the role of the buffering capacity of heterozygotes at the *intra*genic level, while Dobzhansky focused on the integrative properties of coadapted gene complexes at the *inter*genic level. Limited evidence supports both models[47]. Distinguishing between the two hypotheses of developmental homeostasis will impact our understanding of the importance of heterozygosity, as well as the role of selection acting on groups of interacting coadapted genes.

To discriminate between the hypotheses an approach is required whereby both heterozygosity and coadaptation can be examined factorially in the same system. One such approach is to use hybridization or line-cross methodology to determine simultaneously what role heterozygosity and coadaptation play in developmental homeostasis. The difference in performance of the F_1 and F_2 (or later segregational generations) can be used to determine separately the role of coadaptation and heterozygosity. This approach, in conjunction with QTL mapping would provide more-detailed understanding of the genetic basis of homeostasis.

Conservation genetics

Epistasis also has important implications for the conservation of genetic resources, that is, genes found in wild relatives of domestic plants and animals. The

Box 3. Types of gene interaction

For simple digenic interactions, one can consider the progeny of the F_2 of a dihybrid cross (AABB × aabb). In the absence of epistasis, the effect of A or a at the A locus, or B or b at the B locus, is independent of the genotype of the second locus. However, with epistasis there are non-additive effects between loci and these non-additive effects can be manifested among the homozygote class (AABB vs aaBB, and so on), which describes the effect of the A locus on the additive effect of substituting B for b at the B locus and vice versa, the combined homozygote and heterozygote class (AABb vs aaBb, and so on), which describes the effect of the A locus on the dominance of B at the B locus, and between the double heterozygote (AaBb), which describes the effect of dominance of A at the A locus on the dominance of B at the B locus.

When discussing the effects of mutant, recessive alleles, one can describe the effect of making a genotype increasingly homozygote for the recessive alleles. Diminishing epistasis covers the cases where increasing the homozygosity of an individual across loci for the recessive alleles reduces fitness by less than the sum of the individual effects at each locus. Conversely, reinforcing or synergistic epistasis is exhibited if the fitness of an individual made increasingly homozygous decreases by more than the sum of the individual effects.

success of introgression of adaptively significant gene blocks from wild relatives or land races into cultivar genomes will depend on the degree of genic coadaptation in the progenitor species, as well as the behavior of these gene blocks in a new genetic background.

Furthermore, the role of coadaptation among genes will help to determine strategies for successful management of rare and endangered species[48]. With increasing fragmentation of populations of wild plants and animals and consequent inbreeding, do we dare mix gene pools to restore heterozygosity? The success of genetic manipulation to restore a population's vigor will depend on the genetic basis of adaptation[49]. If epistatic interactions are prevalent, mixing of gene pools could lead to hybrid breakdown, necessitating a rethinking of management strategies in conservation and restoration.

Future directions

Contrasting views of the genetic architecture underlying fitness-related traits have polarized evolutionists since Darwin's time[50]. The embodiment of darwinism with mendelian principles of genetic transmission led to the widespread acceptance of natural selection acting on continuous variation. However, a fuller description of the nature of gene action, that is, whether it is largely additive or epistatic, is necessary for a precise understanding of evolutionary modes. The theoretical framework and molecular techniques now exist to partition additive from epistatic gene action on fitness-related traits. Thus, the next few years promise to yield exciting data that will allow us to come to a fuller understanding of the processes responsible for the evolution of natural populations.

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