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THE LIMITS TO KNOWLEDGE IN QUANTITATIVE GENETICS

Michael Lynch

Department of Biology

University of Oregon

Eugene, Oregon 97403

Phone: 541-346-5579

FAX: 541-346-2364

Email: mlynch@oregon.uoregon.edu

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The limitations to our understanding of evolutionary genetic phenomena lie primarily in the empirical domain, as mathematicians have repeatedly shown that they are up to the challenges of modeling essentially any population-genetic phenomenon that can be envisioned. Until recently, one of the major constraints in our attempts to understand the mechanisms by which populations evolve has been the inaccessibility of the gene. Advances in molecular technology now enable us to routinely survey populations for variation at the molecular level, although almost all such surveys involving functional genes are focused on coding regions as opposed to the frequently much more complex (and potentially more significant) regulatory regions. The latter shortcoming will certainly be surmounted in the near future, and it is fair to say that there are really no longer any fundamental limitations (other than financial ones) to our ability to monitor the dynamics of individual alleles in natural or artificial populations. Nevertheless, despite the major advances in mathematical theory and in molecular technology, one might argue that we are not much closer to a mechanistic understanding of the evolution of complex phenotypes than we were in 1920. One of the major challenges confronting evolutionary geneticists is still the development of a general and biologically based synthesis that will facilitate such understanding.

I have chosen to restrict my discussion on the limits to knowledge in evolutionary biology to issues in quantitative genetics, the subdiscipline that deals with the inheritance and evolution of multilocus traits. It was interest in phenotypic diversity that drove the development of the so-called modern synthesis in the first half of this century, and the primary research of many evolutionary geneticists is still focused on the mechanisms responsible for morphological, physiological, and/or behavioral diversification within and among species. The vast majority of characters falling into these categories are quantitative, encoded by a large number (dozens to perhaps hundreds) of loci. What follows is a brief exposition on some of the major unresolved issues in quantitative genetics, their significance, and an attempt to address the degree to which they will ever be resolvable. History has shown that scientists have regularly surpassed barriers that were previously perceived as insurmountable, so one might argue that any attempt to identify the limits to scientific knowledge is a futile exercise. On the other hand, uncritical acceptance of dominant paradigms can impede scientific inquiry and progress. A close look at our *perceived* limits of knowledge and their relative significance may provide a useful perspective on the most useful directions of future research.

Phenotypes versus Genetic Values

A serious limitation of the classical theory of quantitative genetics is its phenomenological nature. Due to the multilocus nature and environmental dependence of the expression of most quantitative traits, it is usually impossible to use phenotypic information to make precise statements about the underlying genotypes of individuals. As a consequence, most studies in quantitative genetics concentrate on variation at the population level and the partitioning of such variation into causal components (associated, for example, with additive effects, maternal effects, developmental noise, etc.) Sophisticated statistical methods (for example, BLUP or best linear unbiased prediction) do provide a basis for estimating the breeding values of individuals when phenotypic measures are available from multiple relatives, and these methods are employed extensively in animal breeding to identify elite individuals for selective breeding. In addition, for crop plants that can be propagated clonally or as inbred lines, general combining abilities can be estimated for individual lines and specific combining abilities for pairs of lines. However, all of these concepts are statistical, not biological, in nature. For example, a breeding value is simply an estimate of the expected phenotype of an offspring when the focal parent is randomly mated. As an estimate, a breeding value is never known with absolute certainty, but more significantly, such a composite measure tells us nothing about the actual allelic states of the loci involved in the expression of the phenotype or about modes of gene action.

Similar criticisms can be levied against the concept of variance-component partitioning. For example, the additive genetic variance, which is the goal in attempts to estimate heritabilities of quantitative traits, is formally related to the variance of breeding values. Here, the word additive can be quite misinformative, as it refers to the behavior of phenotype distributions in a statistical sense and need not convey any information on the physiological mode of gene action (Cheverud and Routman, 1995). Situations exist in which there can be substantial nonadditive interactions among segregating genes and yet very little nonadditive genetic variance; the outcome depends on the average effects of alleles in all genetic backgrounds. As a consequence of the hierarchical way in which genetic components of variance are defined in a statistical sense, higher-order components involving nonadditive interactions are virtually always smaller in magnitude than the first-order (additive) component, and this appears to have led to widespread misconception that dominance and epistasis are of minor importance in the expression of quantitative traits.

Despite these limitations, quantitative-genetics theory has been a fundamental source of many of the methods of applied statistics, and has played an instrumental role in applications of selective breeding and in the development of management strategies in conservation biology. One of the great contributions of quantitative genetics is its ability to reveal the extent to which standing variation for complex traits is due to genes versus environment, but one of its greatest weaknesses is its failure to yield much insight into the biological nature of quantitative variation. There is now great hope that QTL analysis (the localization and characterization of quantitative-trait loci by use of molecular markers) will remove this shortcoming, an issue that I will address below.

The Nature of Quantitative Variation

QTL analysis involves the search for associations between molecular markers and the expression of quantitative traits. The degree of such associations depends on the magnitude of linkage disequilibrium between the marker locus and the QTL, on the rate of recombination between the two, and on the magnitude of the QTL effect. The very nature of the enterprise is biased in that loci with very small effects are generally undetectable and in that the estimated effects associated with detectable loci tend to be inflated (i.e., there is a statistical bias towards false positives). Moreover, there is generally a very large gap between the crude localization of a QTL with a marker and its subsequent identification and characterization.

An alternative entree into the genetic basis of quantitative variation is the candidate-locus approach. Here the idea is to exploit the rich array of studies in molecular/developmental biology that have revealed the functions of various protein-coding loci through the phenotypic effects of null mutations. Loci that are functionally connected to the trait of interest can then be surveyed for segregating variation involving more minor mutations in natural populations. This approach was successfully used to show that some of the variation for bristle numbers in natural populations of *Drosophila melanogaster* is associated with the *achaete-scute* region (Mackay and Langley, 1990) and the *scabrous* locus (Lai et al., 1994). In addition, life-history variation in *D. melanogaster* has been found to be associated with variation in copy number of the 28S ribosomal RNA gene (Templeton et al., 1989; Hollocher et al., 1992). These kinds of results raise the possibility that the loci whose major effects have been identified by knock-out mutations in laboratory species may be the same loci that are responsible for smaller-scale variation in natural populations. If this is found to be the case, the field of inquiry in quantitative genetics will be dramatically expanded and facilitated.

We are still a very long way from a complete elucidation of the molecular basis of any quantitative trait, although the efforts now being expended in agricultural companies and in medical genetics suggest that major advances will be made soon. For example, substantial progress has been made recently in identifying the loci that are responsible for the major morphological differences between domesticated maize and its wild progenitor teosinte (Doebley and Stec, 1993). Thus, in principle, with enough effort, QTL analysis can reveal the full array of loci, alleles, and the interactions that determine the range of variation for specific quantitative traits in specific model systems. What then?

Although this line of endeavor has by no means reached the point at which we can clearly delineate the limits to what we can accomplish, the issues can certainly be addressed. It should be clear that QTL analysis at best reveals the loci that are currently expressing variation in a population. While such information may provide insight into future potential directions of evolution in a focal population, it does not necessarily tell us anything about the pathway by which the current population mean phenotype was acquired. The loci that were most involved in past evolution could very well be the ones lacking in observable standing variation. Moreover, it is by no means clear that the loci observed as significant in any one species have the same significance in other species.

One of the more remarkable generalities that has emerged from molecular studies of development is the degree to which homologous genes have been recruited for different functions in different species and the extent to which similar morphological structures in different species can be products of very different genetic pathways. Most of this work has involved comparisons of model species from different phyla (Gerhart and Kirchner, 1997), but recent work with nematodes has revealed how remarkably different developmental mechanisms can yield nearly identical morphological structures in species from different families (Eizinger and Sommer, 1997), and work with members of different orders of echinoderms has revealed similar complexities (Lowe and Wray, 1997). If these types of results turn out to be general, then the specific genes that are involved in morphological development in any one species may be fairly restricted in their phylogenetic relevance.

At issue here is the fundamental question of the extent to which information on microevolutionary processes yields any insight into macroevolutionary patterns. Arguments have been made that microevolutionary theory can adequately explain virtually all macroevolutionary phenomena (Charlesworth et al., 1992), but it is not immediately apparent how the recent revelations in developmental biology can be accomodated by the existing theory. Certainly, it is fair to say that there is a very large gap between our understanding of how bristle numbers evolve in natural populations of flies and of how the extraordinary degree of morphological differentiation arose among the animal phyla.

The Meaning of Quantitative Variation

I now turn to the more fundamental issue of genetic variation itself and its relevance to studies in evolutionary genetics. One of the central parameters of quantitative genetics is the so-called narrow-sense heritability, which is the fraction of phenotypic variation that is additive genetic in basis. Practical interest in this parameter arises from the fact that the response to directional selection is expected to equal the product of the selection differential (the difference between mean phenotypes before and after selection, but prior to reproduction) and the heritability. This "breeders' equation" is the closest thing that we have to a predictive theory of evolution --- if we know the heritability of a character, then we should be able to predict the response to a specific amount of selection. (Things get more complicated when multiple characters are simultaneously exposed to selection, but these complications can be accomodated by a multivariate form of the theory; Hazel, 1943; Lande, 1988). One difficulty with the heritability concept is that methods for estimating it often only give crude approximations, as these are generally contaminated by nonadditive or nongenetic sources of variance. A more fundamental problem concerns the nature of standing genetic variation for quantitative traits.

A recent survey for a diversity of traits in a variety of plant and animal species suggests that the average persistence time of a new mutation for a quantitative trait is on the order of a hundred generations (Houle et al., 1996). Since the reciprocal of the persistence time is approximately equal to the average selection coefficient against a mutant allele (Crow, 1992), this suggests that the average mutant allele for a quantitative trait has a deleterious fitness effect of about 1%. This level of selection intensity is qualitatively in accord with results that have been obtained in laboratory mutation-accumulation experiments, raising the hypothesis that most of the standing genetic variation for quantitative traits is a simple consequence of a balance between the input of mildly deleterious alleles by mutation and their elimination by weak selection. If this is the case, then a substantial fraction of the standing genetic variation that we quantify as heritability may be of little relevance to long-term adaptive evolution. If the subset of alleles that are of relevance to adaptive evolution are essentially “rubies in the rubbish,” then our usual surrogate measure of evolvability (the total standing amount of additive genetic variance) is misguided. Discriminating between genes that are rubies and those that are rubbish will not be a simple matter, particularly since the fitness effects of most alleles are very likely contextually dependent, i.e., neither unconditionally beneficial nor unconditionally deleterious.

A second issue of concern with respect to the practical meaning of measures of genetic variation for quantitative traits involves the degree to which gametic-phase disequilibria exist among quantitative-trait loci. Consider the extreme situation in which the effects of all genes can be characterized as + and -, and imagine the case in which all chromosomes have four genes in either the series + - + - or -+ - +. This is a case of complete repulsion disequilibrium, in that every - gene is paired with a + gene. In such a population, every diploid individual would have exactly four + and four - genes, and there would be no expressed genetic variation for the trait, despite the presence of substantial variation within each locus. The expected existence of such repulsion disequilibrium was first suggested by Mather (1952) in his polygenic balance model for characters under stabilizing selection, and has been formally verified in a number of theoretical studies (e.g., Bulmer, 1971; Gavrilets and Hastings, 1995). The alternative extreme is the situation in which all chromosomes are of state + + + + or - - - -. In this case, disequilibrium is of the coupling (or reinforcing) type, and the level of expressed genetic variance for the trait will be exaggerated with respect to the equilibrium situation in which + and - genes are distributed randomly. The point of this example is that measurable (expressed) genetic variance for quantitative traits can deviate substantially from the potential level that would be observed in the absence of disequilibria. If significant repulsion disequilibrium exists for quantitative traits under stabilizing selection, then a pool of hidden genetic variance will exist that can subsequently be released through recombination. Unless linkage is extraordinarily strong, such a reserve of genetic variation may be made available to a population exposed to directional selection much more rapidly than new variation can be created by mutation.

Only a few attempts have been made to evaluate whether substantial disequilibria exist for quantitative traits. Studies with *Daphnia* have yielded evidence of both coupling and repulsion disequilibria for life-history traits (Lynch, 1984; Lynch and Deng, 1994). A series of comparisons of intact chromosomes extracted from wild populations of *Drosophila* with recombinants between them have also suggested the existence of coadapted groups of linked alleles (reviewed in Lynch and Walsh, 1998). Future studies that simply removed populations from the field and subjected them to several rounds of recombination with a minimum of selection could provide substantial insight into this issue. If significant repulsion disequilibria exist, then the level of expressed genetic variance for a quantitative trait should increase following a few rounds of random mating.

All of these examples serve to illustrate that although we are reasonably good at quantifying standing levels of genetic variance for quantitative characters, we are still far from the point of being able to make unequivocal statements about the relevance of such variation for evolution, other than the fact that (on average) characters with higher levels of additive genetic variance will probably respond more strongly to short-term evolutionary pressures. We are still unable to make any general statements as to how rapidly organisms can evolve in response to long-term selective pressures. This question is of substantial importance to breeders of economically important species (Hill, 1982). It is also of central importance in conservation biology, especially with respect to issues such as global warming. In principle, populations can cope with environmental change by simply evolving *in situ*, but there is a cost to natural selection in the form of reduced survival and/or fecundity. Thus, there must be a critical rate of environmental change beyond which the cost of natural selection is so great that populations cannot maintain themselves demographically. By definition, this point is equivalent to the maximum sustainable rate of evolution, and any long-term ecological changes that exceed this rate must spell ecological catastrophe for the species in question. Understanding the limits to the rate of evolution is a substantial challenge for applied evolutionary biology. Recent theory has provided some qualitative insight into the issue (Lynch and Lande, 1993; Burger and Lynch, 1994), but convincing quantitative answers will require empirical work.

Population Genetics and Population Dynamics

One of the most glaring gaps in the broad field of population biology is the lack of integration between its two subdisciplines, population genetics and population ecology. Historically, population geneticists have assumed populations of either infinite size or of constant finite size, while population ecologists have usually ignored genetics entirely. As a consequence, we know very little, from either the theoretical or the empirical perspective, of the relationship between population genetics and population dynamics/population size. In principle, one might expect that populations that evolve adaptively would also expand numerically, and that populations that find themselves in situations where deleterious genes have accumulated would decline numerically. However, the exact nature of such relationships presumably also depends on the extent to which interacting species (competitors, predators, parasites, and prey) are undergoing evolutionary adaptation versus deterioration. Moreover, important synergisms between population size and evolutionary dynamics may be mediated by random genetic drift, in that small populations are more vulnerable to accumulation of deleterious mutations and less likely to fix beneficial mutations than are large populations.

Theoretical work in this area has largely been confined to a single issue of interest to conservation biologists --- the critical effective size below which a population is evolutionarily compromised (reviewed in Lande, 1995; Lynch, 1996; Burger and Lynch, 1997). It is generally believed that a population will progressively accumulate a deleterious mutation load by random genetic drift if its effective size remains much smaller than the reciprocal of the average deleterious effect of a new mutation. Eventually, this load may become so great that the population cannot maintain itself, at which point a mutational meltdown rapidly leads to population size reduction, an enhanced rate of accumulation of deleterious mutations by random drift, and finally to population extinction. On the other hand, there must be an approximate upper bound to the effective size of a population beyond which the population behaves adaptationally as though it were effectively infinite. Quantitative values for these critical effective population sizes are highly dependent on the distribution of mutational effects for quantitative characters, an issue that is currently the subject of substantial debate (Keightley, 1994; Crow, 1997; Garcia-Dorado, 1997). The best we can say at this point is that populations with long-term effective sizes smaller than 100 individuals are likely to be doomed evolutionarily, whereas populations with long-term effective sizes in excess of 1,000 or so individuals are unlikely to be greatly compromised evolutionarily.

Issues Concerning Outbreeding Depression and Species Incompatibilities

A fundamental issue in evolutionary genetics with broad implications is the extent to which genomes from distantly related populations are mutually compatible. For example, in conservation biology, there is considerable concern about the consequences of hybridization between introduced and native populations (e.g., the stocking of salmonid hatcheries with members of foreign drainage basins). In addition, attempts to understand the mechanisms of speciation can hardly proceed without giving attention to the issue of genomic incompatibility.

What have we learned over the past few decades about outbreeding depression? First, a number of well-established examples demonstrate that crosses between closely related populations can give rise to depressed fitness in the F_1 progeny (Templeton et al., 1976; Burton, 1990; Waser and Price, 1994). Second, the few cases that have attempted to laboriously dissect the genetic basis of species differentiation (all with *Drosophila*) have shown that a very large number of factors are involved, even when very closely related taxa are considered (Wu and Palopoli, 1994). In both types of studies, it is clear that negative epistatic interactions between foreign gene pools are involved.

What has not emerged is any general understanding of the genes (or even gene families) that are involved in hybrid breakdown, and it is perhaps unreasonable to expect that any general statements will ever be possible in this area. Isolated populations will diverge over time as they randomly go to fixation for mutations arising at different loci. Some aspects of divergence are certainly due to adaptation to local environmental differences, while others very likely arise as a consequence of intrinsic adaptation (as new mutant alleles are selected for or against on the basis of the genetic background in which they arise). With polygenic systems, there can be innumerable solutions to the same evolutionary problem. Thus, because of the stochastic nature of the mutation and fixation processes, it seems very likely that the genes that underlie the reproductive barriers between any particular pair of species will be largely unique to that species pair and of little general relevance.

A more general concern is the relevance of genes that can be shown to be involved in reproductive incompatibilities to the process of speciation even in particular pairs of species. The issue here is that a large fraction of the genetic differences between even the most closely related species will generally have arisen subsequent to the time at which reproductive incompatibility was first established. Like the issue of genetic variance, the problem here is that the genes of greatest relevance to the process of speciation may be "rubies in the rubbish."

In principle, this type of problem can be minimized by restricting studies of speciation to extremely closely related taxa (or perhaps more suitably, to distantly related populations of the same species), but even this does not eliminate the issue of the specificity of genetic differentiation. This is not to say that no general statements about the mechanisms of reproductive isolation will ever be possible. One such generalization has long been established for species with sex chromosomes --- the observation, known as Haldane's rule, that when only one sex resulting from a hybridization event exhibits reduced survivorship and/or fertility, it is invariably the heterogametic sex (Laurie, 1997; Orr, 1997).

Summary

This year marks the 80^{th} anniversary of Fisher's (1918) insightful paper, a compelling mathematical unification of various observations on quantitative characters, statistics, and basic Mendelian mechanisms of inheritance. Despite the major mathematical advances that have been made since then, quantitative-genetic theory is still framed largely in statistical/phenomenological terms rather than in terms that describe the mode of gene action. Part of the reason for this state of affairs is our extremely shallow understanding of the genetic basis of quantitative-trait variation and of the mechanisms by which complex characters evolve. Although a vast number of empirical studies of quantitative characters have been performed with laboratory populations, with species of agronomic importance, and with humans, most of these have been focused on population-level properties, such as means and variances. New molecular techniques promise to yield important insights into the genetic basis of variation for specific traits in a few model species in the very near future, but the extent to which molecular dissection will provide a complete resolution to our understanding of the evolutionary process remains to be seen. This will depend largely on the degree to which quantitative-trait variation is defined by a large number of genes of very small effects, an issue for which there is a fair amount of circumstantial evidence in a number of cases. Although recent work suggests that a few genes of moderate effect can often explain a substantial fraction of the standing variation for quantitative traits, it remains to be seen whether this fraction is of much relevance to the process of adaptive evolution. If a large fraction of the variation that contributes to adaptive divergence is attributable to genes of very small effects, then molecular analysis of QTLs may be of limited value to our understanding of the evolution of natural populations (although it will certainly still play a major role in artificial selection programs).

The ability to evolve is just as much a defining attribute of life as the ability to replicate. Thus, it is remarkable that while ecologists have contributed greatly to our understanding of the chemical, physical, and biological limits that constrain the spatial and temporal distributions of organisms, evolutionary biologists have given almost no attention to the evolutionary limits of species, i.e., to the abilities of species to adapt evolutionarily to selective challenges as opposed to going extinct. If we agree that the global environment is changing at an unprecedented rate, then it should be clear why the development of a deep understanding of this issue should be one of the central challenges of evolutionary biology. For the past three decades, ecologists have pursued a large number of large-scale and long-term programs of ecosystem research. Because of the stochastic and very long-term nature of evolutionary processes, it is hard to see how a mechanistic understanding of evolution can be achieved without an empirical agenda that embraces highly replicated, multi-generational studies.

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