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Possible consequences of genes of major effect: transient changes in the G-matrix

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Abstract

Understanding the process of evolutionary divergence requires knowledge of the strength, form, and targets of selection, as well as the genetic architecture of the divergent traits. Quantitative genetic approaches to understanding multivariate selection and genetic response to selection have proven to be powerful tools in this endeavor, particularly with respect to short-term evolution. However, the application of quantitative genetic theory over periods of substantial phenotypic change is controversial because it requires that the requisite genetic parameters remain constant over the period of time in question. We show herein how attempts to determine the stability of key genetic parameters may be misled by the 'many genes of small effect' type of genetic architecture generally assumed in quantitative genetics. The presence of genes of major effect (GOMEs) can alter the genetic variance-covariance matrix dramatically for brief periods of time, significantly alter the rate and trajectory of multivariate evolution, and thereby mislead attempts to reconstruct or predict long term evolution.

Introduction

Biological diversity results, in part, from the processes that generate phenotypic divergence among populations. The primary mission of evolutionary biology always has been to understand these processes. While it is generally agreed that selection plays a key role in producing phenotypic diversity, the details remain unclear. The strength, form and consistency of diversifying selection, as well as the specific target traits, remain unknown for most taxa (Endler, 1986; Kingsolver et al., 2001). Attempts to better understand the nuances of selection are complicated by the interaction between genetics and selection that produces adaptive evolutionary change.

The appreciation that organisms are truly collections of traits and cannot be reduced to a single 'key' characteristic further muddles attempts to elucidate past selection. Descriptions of the process of multivariate evolution have led to the recognition that phenotypic evolution results from a combination of both direct selection on a trait and indirect selection on correlated traits (i.e., correlated response to selection) (Lande, 1979; Arnold, 1994). Divergence in any trait among populations or species may therefore result from direct selection on that trait or from selection on other correlated characters.

The dissection of multivariate evolution has been significantly advanced by the application of quantitative genetics, which provides a framework for understanding and investigating the patterns of variation within and covariation among characters. This approach has been successfully applied to aspects of phenotypic evolution such as measuring multivariate inheritance (Lynch & Walsh, 1998), quantifying selection in the wild (e.g., Reznick et al., 1997), and distinguishing the role of selection and drift (Lande, 1976; Lofsvold, 1988). The cornerstone of quantitative genetics is the genetic variance-covariance, or '**G**-', matrix, which describes the patterns of additive genetic variation and covariation between traits and determines the response to selection across gen-

erations. By considering the **G**-matrix for a group of traits, it is possible to predict how selection on one trait or group of traits will cause evolutionary response in others (Lande, 1979; Lande & Arnold, 1983; Grant & Grant, 1995). The major axes of the **G**-matrix describe the dimension of evolutionary 'least resistance', or the direction in which the most variation is available for response to selection (Schluter, 1996). Populations with different **G**-matrices will evolve along different multivariate trajectories even if they experience identical selection. If the fitness surface is sufficiently rugged, then different **G**-matrices can produce divergent outcomes to long-term evolution (Price et al., 1993; but see Zeng, 1988).

The utility of quantitative genetics as a tool for understanding long-term evolutionary dynamics depends on the stability of the **G**-matrix. Whether or not (and under what conditions) **G** remains constant is a contentious issue, and one that must ultimately be solved empirically (Turelli, 1988). The usual approach to this problem is to compare **G**-matrices among related populations or species, and interpret a lack of difference between **G**-matrices as an indication of constancy during divergence. Although few general conclusions can be drawn from the range of taxa studied (reviewed in Phillips & Arnold, 1999), these studies do indicate that the assumption of similar **G**-matrix structure is at least plausible. Currently, there are few examples of **G**-matrices that differ greatly in shape between closely related populations or species (Roff, 2000). While this approach contributes to our understanding of **G**-matrix stability, it provides only snapshots in time represented by the populations (and generations) examined. **G**-matrices that are presently similar are generally assumed to have never changed.

The validity of this interpretation depends on the genetic architecture underlying phenotypic divergence. Classical quantitative genetic theory is based on the assumption that traits are controlled by many genes each of small effect. In this case, changes in the frequency of any one allele would have a negligible effect on the overall pattern of genetic variance and covariance and mutation balances the loss of variance due to selection (Lande, 1980). However, the validity of this genetic architecture has been challenged recently on both theoretical and empirical fronts. Building from Fisher's geometric model (1930), Orr (1998) showed that genes of major effect (GOMEs) are expected to be involved in adaptive evolution. While the frequency of GOMEs fixed during adaptation is expected to be rare relative to genes with small effect, GOMEs are expected to account for a considerable fraction of the adaptive divergence between populations. Moreover, GOMEs are expected to often have large pleiotropic effects (Fisher, 1930; Orr, 1998). A growing body of empirical literature also indicates that GOMEs are commonly involved in adaptive evolution (e.g., Orr & Coyne, 1992; Bradshaw et al., 1998).

Well-developed theoretical treatments have found that predictions based on Gaussian infinitesmal genetic architecture do not differ substantially from those based on genes-of-major effect when selection is weak and optimizing (Turelli, 1990; Barton & Turelli, 1991; Turelli & Barton, 1994). In contrast, we consider the effect of GOMEs on the **G**-matrix during periods of phenotypic divergence, when a GOME increases in frequency to fixation. GOMEs can alter the **G**-matrix dramatically, if only for brief periods of time (Carriére & Roff, 1995). **G**-matrices that are presently identical may have diverged dramatically in the past while GOMEs are segregating. We show how transient changes can significantly alter the rate and trajectory of multivariate evolution and also how such changes may mislead attempts to reconstruct or predict long-term evolution. Finally, we suggest an empirical program to study the genetic architecture of evolutionary divergence and the constancy of the **G**-matrix.

The model

We assume that at some initial time, t_0, the GOME that will eventually fix does not yet exist or is at some negligible frequency. For simplicity, we assume there are only two traits of interest, z_1 and z_2. The pattern of genetic variance and covariance is given by:

$$\mathbf{G}(t_0) = \begin{bmatrix} G_{11}(t_0) & G_{12}(t_0) \\ G_{12}(t_0) & G_{22}(t_0) \end{bmatrix}, \tag{1}$$

where $G_{ii}(t_0)$ is genetic variance of z_i at t_0 and $G_{ij}(t_0)$ is the genetic covariance between z_i and z_j at t_0. Following standard quantitative genetics theory, this (co)variance is assumed to result from many genes of small effect.

Defining $h_i^2(t_0)$ as the heritability of z_i at t_0, $P_{ii}(t_0)$ as the phenotypic variance of z_i at t_0 and $\rho_{ij}(t_0)$ as genetic correlation between z_i and z_j at t_0, we can write the elements of $\mathbf{G}(t_0)$ as

$$G_{11}(t_0) = h_1^2(t_0)P_{11}(t_0), \tag{2}$$

$$G_{22}(t_0) = h_2^2(t_0)P_{22}(t_0), \tag{3}$$

and

$$G_{12}(t_0) = \rho_{12}(t_0)\sqrt{h_1^2(t_0)h_2^2(t_0)P_{11}(t_0)P_{22}(t_0)}. \quad (4)$$

At time t, a GOME arises through mutation. Throughout this paper, we use the term GOME to describe an allele that causes large changes in the phenotype relative to the ancestral allele (i.e., GOMEs only exist when there are two alternative alleles at a locus and the difference in phenotype produced by these two alleles is large). For simplicity, we assume that the GOME has only additive effects. The relative phenotypes of the two traits for each of the three GOME genotypes are shown in Table 1. The magnitude of the effect of the GOME is described by the parameter γ_i that measures the phenotypic effect on trait z_i relative to the phenotypic standard deviation of the population at time t_0 (i.e., γ measures the effect in units of phenotypic standard deviations). Carriére and Roff (1995) similarly modeled the importance of GOMEs including dominance effects to heritabilities and genetic correlations. Our model is mathematically equivalent but presented from the perspective of the **G**-matrix. We use our model primarily to evaluate the importance of GOMEs in determining the rate and direction of evolutionary response to selection.

Table 1. Relative phenotypes produced by the three GOME genotypes

Trait	GOME Genotype		
	A_1A_1	A_1A_2	A_2A_2
z_1	$-\gamma_1\sqrt{P_{11}(t_0)}$	0	$+\gamma_1\sqrt{P_{11}(t_0)}$
z_2	$-\gamma_2\sqrt{P_{22}(t_0)}$	0	$+\gamma_2\sqrt{P_{22}(t_0)}$

Following the approach of Lande (1983) for modeling the evolution of a trait jointly influenced by a GOME and by multiple loci of small effect, we assume that the variation produced by loci of small effect remains constant through mutation and recombination. We also assume that the GOME remains in linkage equilibrium with the quantitative genetic background (Lande, 1983). Defining the frequency of the new GOME allele, A_2, at time t as p_t, we can describe the elements of **G** at any time as function of both the quantitative genetic background variation and the GOME:

$$G_{11}(t) = P_{11}(t_0)(h_1^2(t_0) + 2p_t(1-p_t)\gamma_1^2), \quad (5)$$

$$G_{22}(t) = P_{22}(t_0)(h_2^2(t_0) + 2p_t(1-p_t)\gamma_2^2), \quad (6)$$

and

$$G_{12}(t) = \sqrt{P_{11}(t_0)P_{22}(t_0)} \times \times\left(\rho_{12}(t_0)\sqrt{h_1^2(t_0)h_2^2(t_0)} + + 2p_t(1-p_t)\gamma_1\gamma_2\right). \quad (7)$$

Equations 5–7 illustrate that the elements of **G** depend on p, the frequency of the GOME. The extent to which any given element of **G** is altered by the GOME depends, of course, on the magnitude of effect of the GOME on the relevant trait or traits (i.e., γ_i). When $p_t = 0$ or $p_t = 1$, the GOME does not contribute to the genetic variance and $\mathbf{G}(t) = \mathbf{G}(t_0)$. Thus, the effect of the GOME on **G** is transitory, changing **G** while $0 < p < 1$, and returning **G** back to its original state upon fixation. A similar result has been previously demonstrated and graphically presented for heritabilities and genetic correlations (Carriére & Roff, 1995). Our model assumes that the quantitative genetic background remains constant. The **G**-matrix changes only because the frequency of the GOME changes. It is possible that the quantitative genetic background does not remain constant but rather changes in such a way that it compensates for the changes caused by the GOME, allowing the **G**-matrix to remain constant even while the frequency of the GOME changes, however, we find this scenario unlikely.

The importance of transitory changes in the **G**-matrix for understanding the dynamics of long term evolution depends on both the magnitude of effect of GOMEs as well as their frequency of occurrence. GOMEs with large, and especially large pleiotropic, effects cause more extreme departures from $\mathbf{G}(t_0)$. Let $\boldsymbol{\delta}$ be a vector describing the deviation of the population mean caused by the GOME from the prediction based on $\mathbf{G}(t_0)$ alone. With a linear fitness function (constant selection, e.g., Figure 1), $\boldsymbol{\delta}$ will simply be a vector describing the GOME's magnitude of effect on each trait, $\boldsymbol{\delta} = \boldsymbol{\gamma}$, where

$$\boldsymbol{\gamma} = 2\begin{bmatrix} \gamma_1\sqrt{P_{11}(t_0)} \\ \gamma_2\sqrt{P_{22}(t_0)} \end{bmatrix}. \quad (8)$$

With respect to divergence, the deviation caused by a GOME relative to the total change in a trait during divergence is of more interest, and depends on the magnitude of effect of the GOME, the amount of quantitative genetic background variance, and the period of time. Assuming the individual fitness function (selection surface) is linear, the total change in

mean phenotype, after the GOME has gone to fixation, will be

$$\begin{aligned}\Delta\bar{z}_T(t) &= \bar{z}(t) - \bar{z}(t_0), \\ &= t(\mathbf{G}(t_0)\boldsymbol{\beta}) + \delta, \end{aligned} \quad (9)$$

where $\boldsymbol{\beta}$ is the vector of directional selection gradients (Lande & Arnold, 1983). The first term describes the change in the mean phenotype due to the quantitative genetic background variance while $\boldsymbol{\delta}$ describes the change due to the GOME. As t becomes large, the fraction of the total phenotypic change attributable to the GOME decreases. Thus, if GOMEs occur very rarely with respect to t, then the total change in mean phenotype will be reasonably well predicted using only $\mathbf{G}(t_0)$. In this case, the GOME's contribution to evolutionary divergence is small relative to the cumulative effect of many generations of selection on the quantitative genetic background variation.

For a GOME to impact long term evolutionary dynamics, it must affect at least one trait targeted by selection. A GOME is more likely to substantially alter the rate and trajectory of evolution if, while polymorphic, it causes patterns of covariance that are different from those produced by the quantitative genetic background (e.g., Carriére & Roff, 1995). For example, the GOME might strongly affect two traits in the same way (i.e., positive pleiotropy, γ_1 and $\gamma_2 \gg 0$, or γ_1 and $\gamma_2 \ll 0$), but the quantitative genetic covariance between these two traits is zero or negative ($\rho_{12}(t_0) \leqslant 0$). In this case, the GOME generates a positive covariance between the two traits while it is segregating. Alternatively, the GOME might affect only a single trait ($|\gamma_1| \gg 0$ and $\gamma_2 = 0$), but the quantitative genetic background variance of the two traits is strongly correlated ($|\rho_{12}(t_0)| \gg 0$). In this case, the GOME temporarily increases the genetic variance of only trait z_1 (see Eqs. 5–6), so that the relative importance of indirect selection in determining multivariate response is reduced while the GOME segregates.

Discussion

To many biologists, the notion of a constant **G**-matrix may seem unlikely given that genetic variation is known to be a consequence of segregating alleles and that changes in the frequencies of these alleles will change the amount and pattern of genetic (co)variation. When traits have an oligogenetic basis rather than matching the theoretical construct of the Gaussian infinitesimal model, changes in the **G**-matrix are expected during evolution (Barton & Turelli, 1987; Turelli, 1988; Barton & Turelli, 1989). Yet these 'expected' changes in the **G**-matrix have not been readily observed among different populations or closely related species (reviewed in Phillips & Arnold, 1999; Roff, 2000). These data make it difficult to completely dismiss the 'many genes of small effect' type of genetic architecture assumed in classical quantitative genetics. However, an emerging body of theoretical and empirical research indicates that GOMEs may frequently contribute to adaptation (e.g., Orr & Coyne, 1992; Bradshaw et al., 1998; Orr, 1998) – an observation that appears at first glance to be at odds with reports of a fairly stable **G**-matrix. This paradox can be resolved by considering the role of GOMEs that arise occasionally on top of classical quantitative genetic background variation. A GOME can dramatically alter the **G**-matrix produced by classical quantitative genetic background variation; however, these changes will be transitory and the **G**-matrix will return to its original form leaving no signature of its transient change in the existing pattern of genetic variation and covariation.

Our model predicts that the importance of GOMEs depends on four features: (1) the magnitude of effect of the GOMEs relative to background variation, (2) the pleiotropic nature of GOMEs relative to the patterns of covariance in the background variation, (3) the frequency with which adaptive mutations of large effect occur, and (4) the shape of the individual selection surface. The first three factors influence how much GOMEs alter the **G**-matrix relative to the existing genetic effects of classical quantitative genetic background variation, while the fourth factor determines how these effects are translated into evolutionary change. GOMEs have two consequences for a population – a direct effect on the phenotypic distribution and an indirect effect of changing the way selection acts on the quantitative genetic background variation when the selection surface is non-linear. Under some conditions, GOMEs may do little more than affect the rate of approach to an evolutionary optimum, whereas in other situations they may alter the long-term direction of evolution.

To understand this spectrum of effects, we need only consider multivariate evolution on a phenotypic selection surface given the background **G**-matrix, and then examine the changes expected when a GOME arises. A phenotypic selection surface describes the fitness of an individual as a function of its phenotype (Phillips & Arnold, 1989), and a population can be

thought of as a cloud of points on this surface. The amount of evolutionary change in a generation due to the background quantitative genetic variation depends on the strength of directional selection (i.e., the average slope of the selection surface Lande, 1979). GOMEs change phenotypes rapidly in evolutionary time, moving the cloud of points from one place on the selection surface to another.

If the selection surface is linear then the slope experienced by a population will be the same regardless of where that population is located on the surface (i.e., the amount and direction of evolutionary change due to classical quantitative genetic background variation will be the same each generation as in Eq. 9). In this case, the effect of a GOME is to move the population towards a region of higher fitness in a relatively big step. GOMEs will always move the population in an uphill direction because only GOMEs with adaptive phenotypic effects will increase in frequency. A population that experiences GOMEs will diverge further in phenotypic space from the ancestral population than a comparable population whose **G**-matrix is entirely due to classical quantitative genetic background variation. Recall that $\boldsymbol{\delta}$ is defined as the deviation of the population mean phenotype away from the location predicted assuming the **G**-matrix is constant (i.e., $\mathbf{G}(t) = \mathbf{G}(t_0)$ for all t). When the selection surface is linear, $\boldsymbol{\delta}$ is equal to the phenotypic effect of the GOME (Figure 1, 2(a)).

In contrast, when the selection surface is non-linear $\boldsymbol{\delta}$ can be less than, much greater than, or generally different than, the simple phenotypic effect of the GOME. If the selection surface is non-linear, then the local slope experienced by a population will depend on the region of the surface occupied. Non-linearity can have opposing effects depending on the shape of the surface. For surfaces that plateau, as is the case when a population moves toward an optimum, a GOME may move a population onto a flatter region of the selection surface. In this case, the amount of phenotypic change due to classical quantitative genetic background variation in each generation will be less than before the GOME arose, because the selection experienced by the population is weaker (i.e., $\boldsymbol{\delta}$ will be less than the phenotypic effect of the GOME, Figure 2(b)). Conversely, a GOME may move a population across a relatively flat region of the selective surface and onto the slope of a peak. In this case the population experiences stronger selection than before the GOME arose, and the amount of change due to classical quantitative genetic background variation in each generation increases (i.e., $\boldsymbol{\delta}$ will be greater than the phenotypic effect of the GOME, Figure 2(c)). With some forms of non-linear selection, GOMEs can also change the direction of selection acting on classical quantitative genetic background variation. If the selection surface is sufficiently rugged, a single GOME could move the population into the zone of attraction of a different peak on the adaptive landscape (Price, Turelli & Slatkin, 1993; Whitlock et al., 1995). Such an effect would lead to fundamentally different phenotypic optima (Figure 3(a)).

For a GOME to fix in a large population, its net effect on fitness must be positive. However, this does not mean the GOME will be 'ideal'. Unlike genes with small effects, fixation of a GOME could cause a population to overshoot its phenotypic optimum (Fisher, 1930; Lande, 1983; Orr, 1998). A pleiotropic GOME may cause important adaptive changes in some key traits but cause non-adaptive or maladaptive changes in other traits (so long as the net fitness effect of the GOME is positive; e.g., Carriére et al., 1994). When a GOME causes a population to overshoot its optimum or causes maladaptive changes in some traits, subsequent selection is expected to act on genes with small effects to correct these problems (Figure 3(b)). For example, if a GOME at one locus causes a trait to be larger than the optimum, subsequent selection at other loci will fix alleles that decrease the size of the trait. Such alleles of opposing effects are commonly observed (e.g., Tanksley, 1993), illustrating that divergence caused by GOMEs can be subsequently masked by genes with small effects. It is, of course, possible that balancing selection prevents eventual fixation of the GOME and instead results in polymorphism (though this may require extreme conditions; Lande, 1983). In this case, the effects of the GOME will be incorporated into the current **G**-matrix because the segregating GOME will contribute to the genetic (co)variance in the population.

If the pleiotropic effects of a GOME are large but selectively neutral, the GOME can cause some traits to diverge in non-adaptive ways. If no genetic correlation exists between two traits in the quantitative genetic background variation (i.e., $\rho_{12} = 0$), then selection to increase the first trait would not cause any change in the second selectively neutral trait. If a GOME arises that has large positive effects on both traits, then fixation of this GOME will cause both traits to increase (as in Figure 1). Retrospective selection analysis based only on the endpoints of selection and the **G**-matrix at this time would not only overestimate the strength of

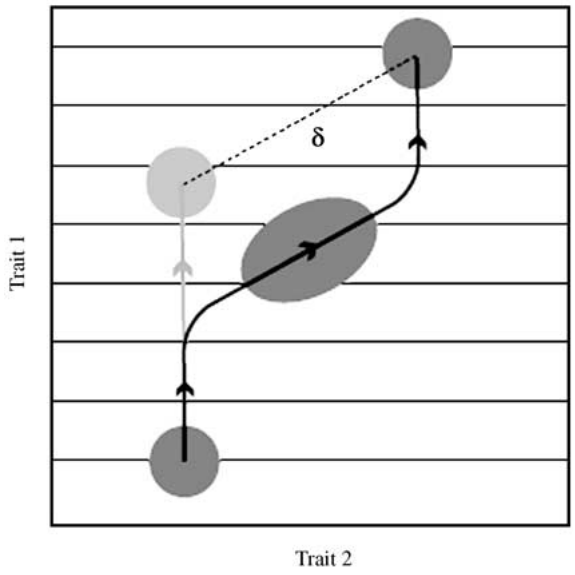

Figure 1. Evolution with a GOME. The figure depicts a population evolving on a linear fitness surface (an inclined plane; lines bars represent contours of equal fitness), where selection favors increased values of Trait 1 and Trait 2 is neutral. The lower dark shaded circle represents the phenotypic distribution of the population at time t_0. Note there is no correlation between the two traits. The dark curve depicts the change of the population mean phenotype over generations. After some time, a GOME arises, temporarily changing the pattern of variance-covariance (large darkly shaded oval). While the GOME segregates, a positive genetic correlation exists between the two traits, so that the existing force of selection drives the population in a new direction. After the GOME has reached fixation, the phenotypic distribution returns to its initial state (upper darkly shaded circle). The lightly shaded curve and circle show the predicted evolution of population in the absence of the GOME. The dashed line labeled **δ** describes the difference between the result of evolution with versus without the GOME. The dimensions of **δ** depend on the magnitude of effects of the GOME on the two traits.

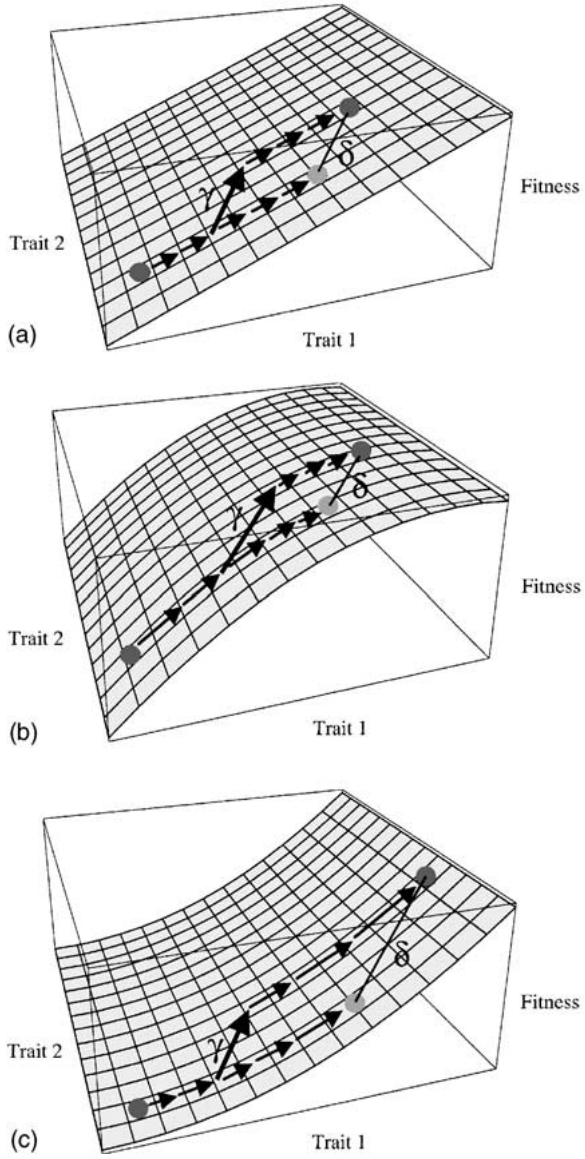

Figure 2.

selection on the first trait but would wrongly conclude that there was directional selection on the second trait (i.e., it would wrongly conclude that the divergence in the second trait was adaptive).

Assuming that alternative GOME alleles fix in different populations, the GOME can make a substantial and permanent contribution to the difference in phenotypic means between the populations (see Figure 1). However, because the effect of the GOME on the **G**-matrix is transient, it may be missed by comparing **G**-matrices between populations. The duration of the influence of the GOME on evolutionary dynamics depends on how long it segregates, which is in turn a function of the strength of selection on the allele.

Our treatment of the effect of GOMEs on genetic architecture is clearly oversimplified. In particular, we assume that GOMEs do not associate with GNOMEs (genes not of major effect). If GOMEs and GNOMEs do not remain in linkage equilibrium, which is likely under strong selection and/or physical linkage, a variety of effects on the variance/covariance structure can occur. Some of these are transient and will disappear after GOMEs fix, but will nonetheless alter the dynamics beyond the scenario presented here. Other effects, including the correlated evolution of linked loci, may permanently alter the structure of the **G**-matrix. Nonetheless, even our simplistic treatment shows that currently similar **G**-matrices may have differed during the process of divergence, and attempts to use

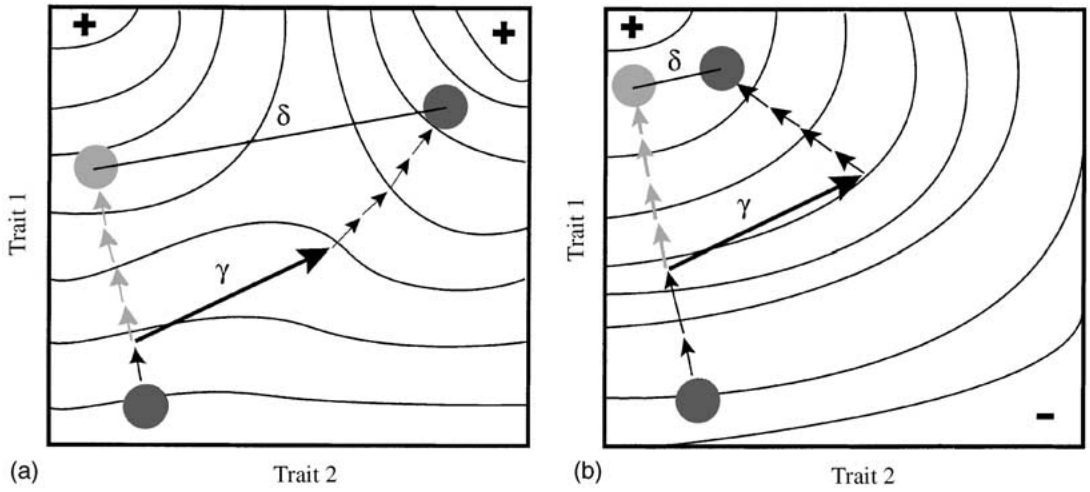

Figure 3. Evolution on complex selection surfaces where both traits experience selection. Surface are shown as contour plots with curved lines indicating contours of equal fitness (other symbols as in Figure 2). (a) On a surface with multiple peaks, the GOME can move the population into the domain of attraction of an alternative peak. The outcome of long-term evolution is very different with the GOME than it would be without it ($\boldsymbol{\delta} \gg \boldsymbol{\gamma}$). (b) On a surface with only a single adaptive peak, temporary maladaptive evolution may occur in one trait. A GOME arises that is favorable for Trait 1 but has maladaptive pleiotropic effects on Trait 2. The overall effect of the GOME on fitness is positive so the GOME fixes, but the phenotypic value of Trait 2 is further from its univariate optimum than before the GOME arose. Much of the subsequent evolution compensates for these maladaptive pleiotropic effects via fixation of GNOMEs with opposing effects. The phenotypic outcome of long-term evolution is rather similar with the GOME as without it, although the genetic basis of these changes is quite different.

these parameters to make prospective or retrospective predictions about long-term evolution may mislead.

Empirical detection of GOMEs

The importance of GOMEs during divergence and their relative impact on quantitative genetic applications requires empirical evidence of the frequency, relative magnitude and degree of pleiotropy of GOMEs from natural populations. Marker-assisted quantitative trait locus (QTL) analysis provides a means for detetecting and measuring GOMEs that contribute to phenotypic differences between divergent populations, but these studies are rarely conducted or reported in such a way that results can be integrated with other quantitative genetic information. In general, there are at least two criteria that might be used to identify QTLs of major effect: (1) the effect of the QTL is large relative to the difference between divergent groups, or (2) the QTL has a large effect relative to the standing genetic variance within one of the groups. When the difference between divergent groups is large relative to the genetic variation within groups, these two criteria will be essentially the same. Usually the first criterion is adopted (e.g., Tanksley, 1993; True et al., 1997; Bradshaw et al., 1998) and QTLs are recognized as being of major effect when they explain some large fraction of the variation within the QTL mapping population. A few examples of GOMEs and their pleiotropic effects are shown in Table 2. From the perspective of understanding how variation within

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Figure 2. Evolutionary consequences of GOMEs. The figure depicts a population evolving on each of three different types of selection surfaces. In all cases, selection acts only to increase Trait 1. (a) When the population evolves on a linear fitness surface, the deviation, $\boldsymbol{\delta}$, is equal to the direct effect of the GOME (i.e., $\boldsymbol{\delta} = \boldsymbol{\gamma}$). (b) When the population approaches a peak with decreasing strength of selection, the indirect effect of the GOME (moving the population to an area of weaker selection) dampens the direct effect of the GOME so that the resulting deviation is less than the phenotypic effect ($|\boldsymbol{\delta}| < |\boldsymbol{\gamma}|$). (c) When the selection surface is convex, the GOME rapidly moves the population up the surface onto a steeper region of the surface. Subsequent selection is stronger so that the rate of evolution after the GOME has fixed is faster than the rate that occurred prior to its existence. In this case, the indirect effect of the GOME serves to exaggerate the GOME's direct phenotypic effect ($|\boldsymbol{\delta}| > |\boldsymbol{\gamma}|$). Circles represent the position of the population at different times during evolution. Small arrows indicate evolutionary response due to the quantitative genetic background variation over some constant unit of time (length of arrow indicates relative magnitude of response; larger responses occur in steeper regions of the surface where selection is stronger). The lightly shaded arrows indicate the predicted evolution of the population in the absence of the GOME. The large bold arrow, $\boldsymbol{\gamma}$, is the phenotypic effect of the GOME and indicates the rapid movement of the population across the selection surface caused by the fixation of the GOME not long after it arises. Note that there is initially no genetic correlation between the two traits but the GOME has pleiotropic effects on both traits. The deviation, $\boldsymbol{\delta}$, indicates the difference in evolutionary divergence with versus without the GOME.

Table 2. Percent variance explained (PVE) and pleiotropy of potential GOMEs detected in QTL studies

Parent 1	Parent 2	QTL	Trait	PVE (F_2 mapping population) %	Reference
Mimulus lewisii	M. cardinalis		Lateral petal reflex	68.8	Bradshaw et al. (1998)
		A_L	Upper petal reflex	51.4	
			Corolla width	31.5	
Mimulus lewisii	M. cardinalis		Petal carotenoids	83.0	Bradshaw et al. (1998)
		D_C	Lateral petal reflex	16.2	
			Upper petal reflex	7.1	
			Petal width	5.4	
			Pistal length	33.1	
Zea mays mays	Zea mays parviglumis		No. cupules in single rank	20.3	Doebley and Stec (1993)
			Average length of vegetative internodes	24.6	
		UMC107 (tb1)	No. branches in primary lateral infloresence	24.3	
			Percentage cupules lacking pedicellate spikelet	12.9	
Zea mays mays	Zea mays parviglumis		No. cupules in single rank	24.6	Doebley and Stec (1993)
			Tendency of ear to shatter	41.7	
			Hardness of outer glume	17.5	
		UMC60	Average length of vegetative internodes	45.3	
			Percentage cupules lacking pedicellate spikelet	19.3	
			No. ears on lateral branch	15.5	
			Percentage male spikelets in primary lateral infloresence	9.6	

populations contributes to differences between populations it is more useful to use the second criterion above and report the size of effects relative to the amount of genetic variation existing within one of the parental populations.

Note that the variation in a QTL mapping population (e.g., F_2 population) can greatly exceed the variation within either of the parental populations, especially when the parental populations are highly divergent (de Vicente & Tanksley, 1993; Bradshaw et al., 1998; Lynch & Walsh, 1998). Even factors that explain only a moderate fraction of the variation in a QTL mapping population may be quite large relative to the standing quantitative genetic variation in one of the parental populations. We are aware of no QTL studies of long-term divergence that report estimates of the **G**-matrix for either of the parental populations (but see work on artificial selection on *Drosophila* bristle number (reviewed in Mackay, 1995, 1996)). Thus, it is currently impossible to assess how QTLs

generally relate to patterns of genetic variance and covariance within populations. Some recent studies have moved towards this approach by reporting magnitudes relative to the environmental variance within an inbred parental line (e.g., True et al., 1997; Zeng et al., 2000).

To appropriately interpret QTL analyses for identifying GOMEs, there are at least three important caveats. Effects of QTLs can be badly overestimated if the size of the mapping population is too small (Beavis, 1994). Second, because QTL analyses essentially locate genomic regions that affect a particular trait, it is unknown how many genes exist within such a region. Third, if QTLs for two different traits map to the same genomic region it is difficult to know whether this is due to multiple linked genes or to a single pleiotropic gene. Fine scale mapping can increase our confidence in the results of QTL mapping, but cloning of QTL is required to be certain. For example, QTL mapping and cloning by Doebley and co-workers (Doebley & Stec, 1993; Doebley, Stec & Gustus, 1995; Doebley et al., 1997) have shown that a single gene, *tb1*, has a major effect on several traits involved in the domestication of maize.

An empirical program

In order to understand how variation within populations relates to divergence between populations, both standard quantitative genetic techniques (Falconer & Mackay, 1996; Lynch & Walsh, 1998) as well as QTL analyses must be applied to the same system. The effects of QTLs can then be reported relative to the standing genetic variation within each parental population. Perhaps more interestingly, patterns of covariance expected to be generated by major QTL when segregating at intermediate frequencies (Eqs. 2–4) can be compared to the patterns of genetic covariance in extant parental populations.

A more direct empirical approach to studying the effects of segregating GOMEs on the **G**-matrix might be informative as well. For example, having identified a prospective GOME with QTL analysis, this region could be introgressed from Parent B into Parent A. In both maize (Doebley et al., 1995) and monkeyflower (H. Bradshaw, personal communication) such introgressions have been accomplished.

A large experimental population (e.g., $N > 500$) of Parent A individuals could then be established with the introgressed GOME segregating at a low initial frequency (i.e., $p(t_0) < \dot{0}.05$). Selection on one (or more) of the traits affected by the GOME could be applied in such a way that the GOME would be predicted to increase in frequency. The strength of selection should not be too strong so that the effective population size remains large and genetic variation is not lost. Selection should continue at least until the GOME has reached high frequency. Ideally, each generation the multivariate mean phenotype as well as the **G**-matrix for the population would be measured. In practice, it would be extremely difficult to measure the **G**-matrix each generation. However, the phenotypic variance-covariance matrix, the **P**-matrix, could be measured relatively easily each generation. Assuming that environmental sources of variation do not change across generations, changes in the **P**-matrix would be reflective of changes in the **G**-matrix (Cheverud, 1988 but see Willis, Coyne & Kirkpatrick, 1991). While measuring the **G**-matrix every generation would be nearly impossible, estimates of the **G**-matrix taken at the beginning and end of the experiment as well as at some intermediate stage(s) would provide stronger evidence for changes in the **G**-matrix during the course of evolution. The joint change in the phenotypic mean and **G**-matrix would be compared to the expectation from the estimated QTL affects.

Conclusions

Genetic studies of adaptive evolution and divergence generally fall into two schools, one that adopts the perspective of quantitative genetics and the view that traits are controlled by many genes of small effect and another that focuses on genes of major effect and classical one or two locus Mendelian inheritance. Both views have strong theoretical and empirical support and have proven their utility through successful application in natural systems. We offer a resolution to this apparent paradoxical nature of genetic architecture by considering the transient effects of GOMEs as they segregate during adaptive evolution. While there are not many examples of segregating GOMEs underlying the variation for continuous traits, our ability to detect GOMEs segregating in natural populations is limited (Mackay, 1996; Lynch & Walsh, 1998). Perhaps it is unsurprising that GOMEs are rarely encountered in intermediate frequencies (but see Lai et al., 1994; Carriére & Roff, 1995), given that they are likely to be quickly selected against when deleterious, or fixed when adaptive (Orr, 1998). However, GOMEs may still play an important role in adaptive evolution and, depending on the factors outlined above, may alter

the dynamics expected when evolution is controlled by their smaller counterparts, GNOMEs.

For two decades, quantitative geneticists have pondered the stability of the **G**-matrix. Comparing **G**-matrices of related taxa provides only snapshots in time. If GOMEs arise rarely and fix rapidly, they can alter the **G**-matrix dramatically but only for brief periods of time. Direct comparisons of **G**-matrices will miss the importance of such events. QTL analysis enables us to look back in time at genes that once segregated within populations. However, we can only assess the importance of such genes if we know the magnitudes of effects of GOMEs as well as the size and shape of **G**-matrix within parental populations. We advocate reporting the magnitude of effects relative to the additive genetic (co)variance within the parental populations. At the very least, magnitudes should be reported relative to phenotypic variance within populations. Introgression experiments allow empirical tests of the effects of GOMEs on the **G**-matrix. By combining QTL and classical quantitative genetic approaches we may be able to assess the relative roles of GOMEs versus GNOMEs in long-term evolutionary divergence.

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