Research review

Gene flow, adaptive population divergence and comparative population structure across loci

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Summary

Many recent studies have sought to identify targets of diversifying selection by testing the neutral expectation that all loci will show similar levels of population divergence (F_{st}). Contrasts between quantitative traits (Q_{st}) and molecular markers (F_{st}) suggest that quantitative traits typically diverge in response to local selection pressures more than do individual genes. Coalescence theory makes it possible to simulate the distribution of F_{st} and Q_{st} expected under neutrality for many situations, including nonequilibrium conditions. Such simulations show that a very high variance of F_{st} and Q_{st} are expected under neutrality, making it difficult to draw firm conclusions about the action of selection on individual loci or traits. Recent quantitative genetic theory shows that, under diversifying selection on quantitative traits, covariances (linkage disequilibrium) among allele frequencies at underlying additive loci contribute a substantial fraction of the among-population trait variance. Thus, adaptive trait divergence can be accomplished, with limited divergence of allele frequencies. However, the contribution of covariances among loci to the divergence of traits depends upon there being multiple loci underlying quantitative trait variation.

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Introduction

The divergence of populations to create local or geographical races within a species forms an intuitive starting point for discussions of speciation (Grant, 1981; Levin, 2000). The creation of distinct gene pools is straightforward in isolation: where a barrier to gene exchange exists, populations are *de facto* independent evolutionary lineages. Without such a barrier (or with only a partial barrier), however, the divergence of populations beyond the expectations of migration drift equilibrium must occur by the differential adaptation of populations to contrasting environmental conditions or ecological niches. Migration is frequently seen as a force that opposes diversification and constrains adaptive response to heterogeneous environments, such that selection must overcome migration to produce adaptive diversification. Understanding how adaptation occurs in the face of gene flow is therefore seen as one of the challenges of ecological genetics (Futuyma, 2001).

The consistent association of particular genotypes or phenotypes with particular environmental conditions makes a strong case that populations are in fact adapted to their local

environments (Linhart & Grant, 1996). Reciprocal transplant experiments have revealed a distinct fitness advantage to local populations compared with immigrants transplanted in from other habitats for many species. Such local adaptation is a widespread – though not universal – phenomenon in plants, having been documented on scales ranging from a few meters to hundreds of kilometers, and in conjunction with a wide range of ecological factors (see reviews in, for example, Heslop-Harrison, 1964; Grant, 1981; Bradshaw, 1984; Levin, 2000; and especially Table 1 of Linhart & Grant, 1996).

It would seem, therefore, that natural selection is generally strong enough to overcome the levels of migration experienced by most plant populations. In many cases such migration will be restricted – seed and pollen dispersal often show strong distance limitation (Heywood, 1991; Levin, 2000, Chapter 4). Nevertheless, distances over which adaptive divergence takes place are often equally short, and species in which wind-dispersed pollen creates apparently very widespread gene flow can exhibit local adaptation (Rehfeldt *et al.*, 1999). Several types of study have documented the action of natural selection eliminating immigrant genotypes from the local population. In *Trillium grandiflorum*, reproductive adult individuals show a greater degree of spatial genetic structure among demes (patch size approx. 3 m) than do the nonreproductive adults or juveniles (Kalisz *et al.*, 2002). This finding is consistent with gene flow among demes eroding genetic differences in the offspring and those differences being recreated by selection between seedling and adult stages. In *Gilia capitata*, Nagy (1997) artificially created crosses between inland and coastal races and documented selection acting on the recombinant F_2 progeny to recreate the native phenotypes. For most traits, the response to this selection was towards the native phenotypes. Numerous examples such as these illustrate the dynamic interplay between migration and diversifying selection.

In this review I raise two general points about the kinds of genetic differences we should expect under a balance between migration and diversifying selection (which here refers to selection favoring different alleles or phenotypes in different environments). First, I highlight the expectation that neutral markers and traits will show considerable heterogeneity of population structure for a given amount of gene flow, such that the targets of diversifying selection will be difficult to identify solely from patterns of divergence. Second I review recent theory on the divergence of genes underlying locally adaptive quantitative traits. This theory shows that when many genes respond to selection in parallel, the linkage disequilibrium among loci accounts for much of the genetic divergence in the traits. I then explore some of the implications of this theory for our understanding of adaptive population differences.

Comparative population structure

The genes involved in electrophoretic differentiation appear to be different from those responsible for most external phenotypic characters. (Grant, 1981, p. 101)

Single loci

The creation of local or geographic races by neutral drift is easily understood in terms of restricted gene flow. Sewell Wright (1951) first derived the inverse relationship that is expected between population genetic differentiation and migration. His famous relationship

$$F_{st} = \frac{1}{4N_e m + 1}$$

(where F_{st} is the proportion of total allelic variation that is attributable to differences between populations) predicts that neutral gene divergence is determined by the number of migrants that are exchanged among populations each generation. Thus, for genes that are known to be neutral (or that can be reasonably assumed to be so) the degree of genetic divergence has become widely used as an indicator of migration rates (Hamrick & Godt, 1990; Ouborg *et al.*, 1999), although these indicators must be used with caution (Whitlock & McCauley, 1999). Limited dispersal can also result in the creation of local demes, genetically differentiated from one another within a continuously distributed population (Turner *et al.*, 1982).

Migration and drift are expected to act equally on all neutral loci. Therefore, neutral loci should all show similar patterns of genetic divergence among populations. It is intuitively appealing to expect that the genetic or phenotypic differences responsible for adaptive population differentiation can be identified by a greater degree of population difference than expected at neutral genes or traits. This approach was originally proposed by Lewontin & Krakauer (1973), who derived the equilibrium expectation for locus to locus variance of F_{st}, and argued that a significantly higher than expected variance of F_{st} among loci is inconsistent with a null hypothesis that all variation is selectively neutral. Variations on this test have seen increasing popularity in recent years (MacDonald, 1994).

However, the Lewontin–Krakauer test is hampered by the considerable variability that F_{st} displays under purely neutral evolution. In particular, Robertson (1975) noted that the Lewontin–Krakauer test was strictly applicable to a large number of populations without phylogenetic structure. Historical structure among populations can inflate the locus to locus variance of F_{st}. This is an important consideration not only on large time-scales such as divergence during the Pleistocene, but also on smaller time scales such as the founding of local demes.

A direct empirical comparison within and between varieties of ponderosa pine (*Pinus ponderosa*) documented this pattern: locus to locus variance of F_{st} is higher when calculated for populations separated by a past historical division than it is for populations (a similar distance apart) within one of the varieties

(Latta & Mitton, 1999). A similar pattern occurs in bishop pine (*Pinus muricata*), where one locus (*Got1*) shows a particularly striking cline in the allele frequencies between Sonoma and Mendocino, California, USA (Millar *et al.*, 1988). In each case, a few highly divergent loci stand out against a background of loci showing lower F_{st} values, suggesting that these loci experience diversifying selection pressures, while the majority (lower F_{st}) reflect extensive migration. However, in both species, paternally inherited (and therefore pollen-dispersed) chloroplast DNA also shows very sharp differentiation (Hong *et al.*, 1994; Latta & Mitton, 1999), indicating that gene flow is in fact quite restricted. Moreover, the variation among nuclear loci is consistent with neutral coalescent simulation results (see below). Therefore, most of the allozyme loci appear to be out of equilibrium with low historical migration rates such that the variation of F_{st} among loci simply reflects stochastic variation in the process of drift, and not selection.

This problem is not one of insufficient sampling – even for large samples, identifying particular loci under diversifying selection is likely to be difficult, because of genuine variation in the actual F_{st} of neutral loci. Coalescence theory has highlighted the extreme variability of outcomes that are possible with neutral evolution (Knowles & Maddison, 2002; Rosenberg & Nordborg, 2002). However coalescence theory also presents a means of directly addressing this uncertainty. Coalescence-based simulation techniques (Hudson, 1990) can be employed to generate the distribution of F_{st} expected under neutrality, and this can permit a more accurate assessment of when the neutral hypothesis can be rejected for particular loci. Figure 1a shows the range of coalescence times (number of generations to the most recent common ancestor of all individuals – technically all alleles – present in a sample) expected under pure drift. Independent loci are simulated by randomly generating independent coalescent trees for each locus. There is a fivefold range between the 95% limits of the distribution. Thus, different loci can have vastly different evolutionary histories without the need to invoke selection. By placing mutations randomly on each simulated tree, allelic states can be simulated and used to calculate the range of F_{st} values expected under neutral drift. Figure 1b shows this distribution following division of an ancestral population into two completely isolated daughter populations. The distribution shows good agreement with the observed distribution across allozyme loci in ponderosa pine. Sampling of additional individuals does little to alter this result, because the probability that all individuals in a sample of size n trace to the same most recent common ancestor (MRCA) as the total population is $(n-1)/(n+1)$, which asymptotes very quickly for moderate n.

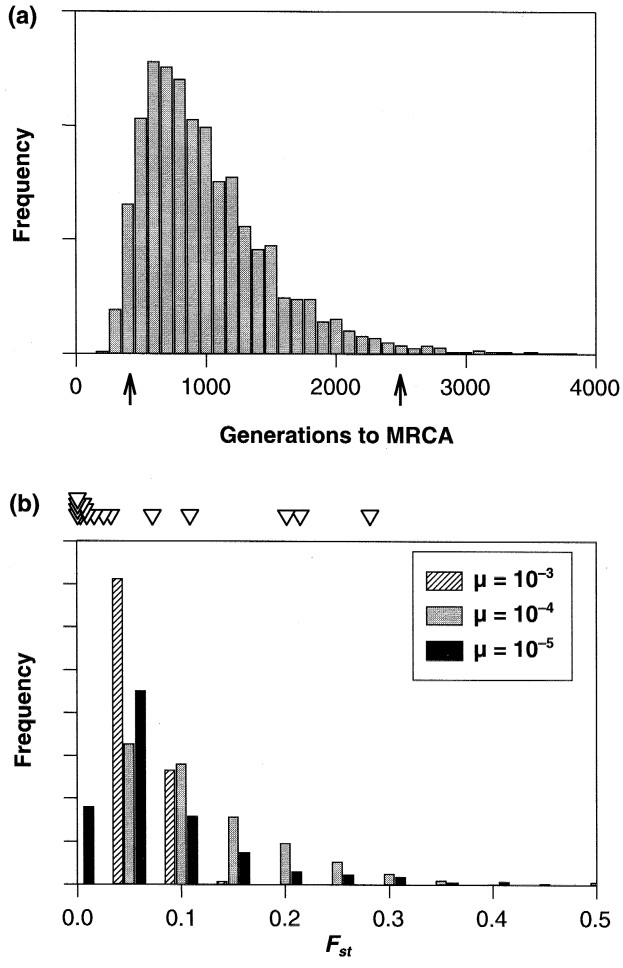

Fig. 1 (a) Distribution of coalescence times (generations to most recent common ancestor, MRCA) for 1000 independent trees of 400 alleles drawn from a single panmictic population with effective population size of 1000. Arrows indicate 95% range of the distribution. (b) Distribution of F_{st} estimates for 200 alleles drawn from each of two populations with effective population size of 10 000. Populations were isolated such that lineages could only coalesce within populations for 5000 generations, and mutations were randomly placed along the branches using the infinite alleles model. Three mutation rates are indicated (hatched bars, $\mu = 10^{-3}$; tinted bars, $\mu = 10^{-4}$; closed bars, $\mu = 10^{-5}$). Triangles represent observed allozyme values in ponderosa pine (cf. Latta & Mitton, 1999).

Quantitative traits

In contrast to single genes, many of the traits that distinguish recognized local or geographical races (alternatively, 'varieties' 'subspecies' or 'ecotypes') are continuously distributed and likely have polygenic inheritance. Evidence for the genetic basis of these trait differences has been accumulating through common garden studies for over a century (Clausen *et al.*, 1948; Heslop-Harrison, 1964; Linhart & Grant, 1996). Direct comparison of quantitative traits with single loci is made possible by the theoretical relationship between single gene F_{st} and the partitioning of genetic variation in quantitative traits (Wright, 1951):

$$\sigma^2_{g(between)} = 2F_{st}\sigma^2_{g(0)}$$

$$\sigma^2_{g(within)} = (1 - F_{st})\sigma^2_{g(0)}$$

$$\sigma^2_{g(total)} = (1 + F_{st})\sigma^2_{g(0)}$$

(where $\sigma^2_{g(0)}$ is the genetic variance expected if all the subpopulations were completely panmictic). Thus,

$$\frac{\sigma^2_{g(between)}}{\sigma^2_{g(total)}} = \frac{2F_{st}}{1 + F_{st}}$$

and by rearranging, it is straightforward to derive an expression (termed Q_{st})

$$Q_{st} = \frac{\sigma^2_{g(between)}}{\sigma^2_{g(between)} + 2\sigma^2_{g(within)}}$$

which is expected to be equal to F_{st} for neutral traits (Whitlock, 1999).

Q_{st} is more difficult to measure than F_{st}. First, it requires randomized common garden experiments, to distinguish genetic differences among populations from environmental influences on the expression of the trait. Second, it requires that the experimenter explicitly partition within population variation into genetic and environmental components, usually by measuring the variation among families. Simply reporting the proportion of total phenotypic variation that is attributable to population differences (i.e. the intraclass correlation coefficient for populations) is not directly comparable to F_{st}, because it includes nongenetic (i.e. environmental) variance with the within-population genetic variance, inflating the denominator of Q_{st}. Therefore, a common approach to measuring Q_{st} is to apply a nested ANOVA design with individuals nested within half-sib families nested within populations of origin (Yang *et al.*, 1996). The mean squares for Population and Family allow the estimation of $\sigma^2_{g(between)}$ and $\sigma^2_{g(within)}$ following standard quantitative genetic methods (Falconer & MacKay, 1996), and hence the calculation of Q_{st}.

Despite the additional effort required, the comparison between Q_{st} and F_{st} has become popular in recent years. If differences between Q_{st} and F_{st} were caused by drift, Q_{st} would be less than F_{st} about as often as it is greater. The common observation is that Q_{st} is highly variable among traits, but that Q_{st} exceeds F_{st}, far more often than the reverse (Merilä & Crnokrak, 2001; McKay & Latta, 2002). It is typically assumed that the electrophoretic markers used to calculate F_{st} are selectively neutral, and therefore that departures of Q_{st} from F_{st} represent selection on traits. Thus, selection on quantitative traits appears to be generally diversifying: that is, quantitative traits have responded to selection, adapting populations to their local conditions. Technically, the comparison allows us to conclude only that quantitative traits and electrophoretic markers experience different evolutionary forces. Since migration and drift must act equally on all nuclear loci, this leaves mutation rate and differences in the rate of approach to equilibrium as a possible cause of the difference. Nevertheless the observation that Q_{st} exceeds F_{st} is consistent with the general ubiquity of local adaptation seen in reciprocal transplants.

The problems associated with the Lewontin–Krakauer test extend to the comparison of F_{st} and Q_{st}. Additive quantitative traits have the same statistical power as single loci (Rogers & Harpending, 1983), and are subject to the same coalescent processes (Whitlock, 1999). As a result, the sampling variance of Q_{st} will be as high as that of F_{st} for single loci and, consequently, Q_{st} can also be extremely variable among neutral traits. This does not hamper the interpretation that mean Q_{st} exceeding mean F_{st} provides evidence for diversifying selection at quantitative traits in general. Podolsky & Holtsford (1995) compared F_{st} of seven allozymes with Q_{st} of 18 discrete and continuous morphological traits in *Clarkia dudleyana*. As a group, the traits (Q_{st} = 0.158–0.611) were overwhelmingly more differentiated than the allozymes (F_{st} = −0.07 to 0.239). Thus, a strong inference can be drawn that selection generally acts to diverge quantitative traits among populations. However, the variability of F_{st} and Q_{st} among loci and traits makes it difficult to draw definite conclusions about which traits are most involved in local adaptation. Four of the traits had Q_{st} values that fell within the range of allozyme F_{st}, and only one trait (pubescence) had broad-sense Q_{st} whose confidence limits did not overlap with any of the allozyme loci.

By contrast, in lodgepole pine (*Pinus contorta*, ssp. *latifolia*) the availability of a large number of allozyme loci, with relatively uniform F_{st} values (0.001–0.065) provides a relatively narrow neutral prediction and, by extension, a relatively high power to reject this hypothesis (Yang *et al.*, 1996). For three of the six traits measured (height, stem diameter and branch length), Q_{st} was significantly greater than even the largest F_{st} value seen at allozymes (and nearly so at a fourth, namely wood specific gravity). Therefore, we can conclude with reasonable certainty that these specific traits have not differentiated among populations because of drift.

Patterns at genes underlying adaptive quantitative traits

For the very loci that influence the trait, it will be more difficult to detect the gene frequency difference than the quantitative trait difference when these genes vary between populations in the same direction over all or most loci. (Lewontin, 1984)

As a quantitative trait diverges in response to local selection pressures, allele frequencies must diverge at each of the underlying genes. When the trait has an additive polygenic basis, each of the underlying loci will respond in parallel across habitats (Latta, 1998; Barton, 1999; Le Corre & Kremer, 2003) and thus allele frequencies will be correlated across loci. That is, in a population or deme where high trait values are

adaptive, alleles that increase the trait will increase in frequency at each of the underlying quantitative trait loci (QTL). This covariance has important consequences for the genetic basis of adaptive divergence.

For an additive trait, the trait value (z) expressed by an individual is the sum of allelic effects, a, across loci, plus environmental deviation (Falconer & MacKay, 1996). Assuming that the environmental deviation has been factored out in an appropriate experimental design,

$$z = \sum a_i$$

The variance of a sum (in this case the additively determined trait) is equal to the sum of the variances at each locus, plus twice the sum of the covariances:

$$\sigma_z^2 = \sum \sigma_i^2 + 2 \sum \sum Cov_{i,j}$$

where σ_i^2 is the variance contributed by the i^{th} locus, and $Cov_{i,j}$ is a function of the linkage disequilibrium of locus i and locus j. Just as the variance of the trait is partitioned into within and between population components to calculate Q_{st}, and the variance contributed by each gene is partitioned to calculate F_{st}, so the covariances can also be partitioned into a within- and between-population component (Latta, 1998). The result is that as the trait responds to diversifying selection, the underlying loci develop linkage disequilibrium across populations, which in turn creates covariance of their effects on the trait (Latta, 1998). The stronger the covariances, the greater the difference between σ_z^2 (and hence Q_{st}) and σ_i^2 (F_{st}). Thus, linkage disequilibrium effectively decouples F_{st} and Q_{st}. This result has been extended to include multi-allelic loci with mutation by Le Corre & Kremer (2003).

This is easiest to see in cases where the covariances are negative. If allele frequencies change in opposite direction, the effects of the change cancel out (Fig. 2a). Thus, the mean trait value remains constant across populations (low σ_z^2, low Q_{st}) despite the changes in the allele frequencies (high σ_i^2, high F_{st}) at each of the underlying loci. In other words, the trait variance across populations is less than the allele frequency variance, and this difference is attributable to the negative covariance of allele frequencies. By the same reasoning, positive covariance of allele frequencies across populations allows the trait divergence to be high, even though allele frequency divergence is relatively small. Simulations show that covariances of allele frequencies do develop as traits evolve towards local optima, permitting allele frequencies to respond to migration drift equilibrium (Latta, 1998; Le Corre & Kremer, 2003). With high gene flow, and diversifying selection pressure, positive covariances develop among QTL allele frequencies. With uniform selection pressure (that is, when each population experiences stabilizing selection to the same optimum trait value), and restricted gene flow, negative covariances of allele frequencies develop. This result provides a unifying framework to explain several observations of adaptive genetic variation.

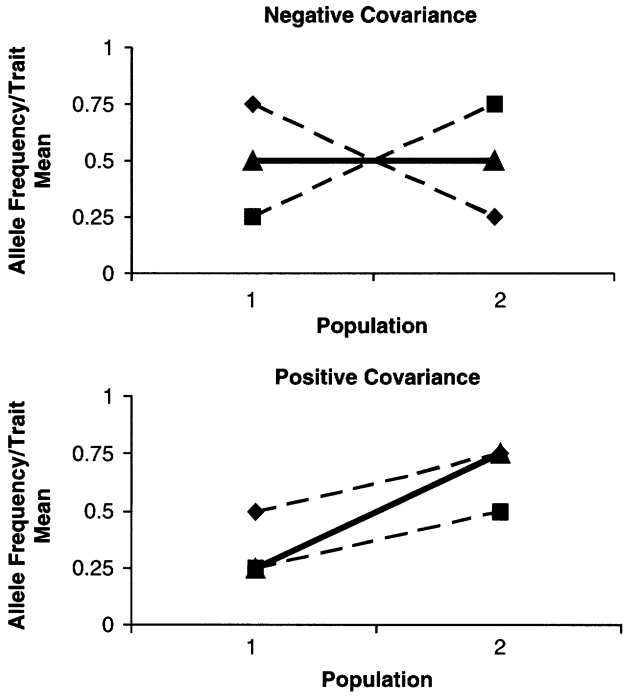

Fig. 2 Hypothetical illustration of negative (a) and positive (b) covariance of allele frequencies (dashed lines) across two loci in two populations. Mean trait values in each population (solid lines) are calculated by assuming an allelic effect of 1/2 with complete additivity.

Adaptive genetic divergence and gene flow

First, the result provides a mechanism by which quantitative traits can diverge among populations (high Q_{st}) despite extensive gene flow homogenizing allele frequencies across gene pools (low F_{st}). Lewontin (1984) argued that allelic differences at QTL will be harder to detect (assuming that QTL can be identified) than genetic differentiation at quantitative traits. While Lewontin couched his argument in terms of the statistical power to detect such differences (i.e. the ability to reject the null hypothesis of no divergence), explicit analysis of linkage disequilibria shows that adaptive population divergence of QTL is not merely harder to detect, it is of a lower magnitude than divergence of the traits themselves. Lewontin highlighted the distinction between cases when all QTL allelic frequencies vary in the same, vs opposite direction – essentially the difference between positive and negative linkage disequilibrium.

Latta (1988) and Le Corre & Kremer (2003) undertook their analysis to explain the high Q_{st} values reported in forest trees. Trees typically show low F_{st} at neutral allozyme or DNA markers, consistent with high gene flow, which is usually ascribed to extensive pollen movement (Hamrick & Godt,

1990). Yet, a broad range of common experiments finds evidence of adaptive population divergence for quantitative traits (Yang *et al.*, 1996; Rehfeldt *et al.*, 1999). It would appear that in high gene flow species, adaptive divergence of polygenic traits is likely caused primarily by the covariance of allele frequencies across populations rather than through high F_{st} of quantitative trait loci.

Hidden variation within and between populations

The general observation that $Q_{st} > F_{st}$ has drawn considerable attention to adaptive divergence in the face gene flow. However, there are at least two cases in which negative associations among quantitative trait loci are likely to develop under reduced gene flow with uniform selection. The first was suggested by Goldstein & Holsinger (1992) who addressed the maintenance of genetic variation in quantitative traits under stabilizing selection to a global optimum. They pointed out the small-scale demic structure that would develop within populations having limited dispersal (Turner *et al.*, 1982), would permit different combinations of alleles to become fixed in different demes, each giving the same trait value when the population as a whole was selected to a constant optimum. On a larger scale, many taxa show transgressive segregation of quantitative traits following hybridization. The most parsimonious explanation in most cases of transgressive segregation is complementary gene action in the parental taxa (Rieseberg *et al.*, 1999) – that is, the fixation of different combinations of alleles in the two taxa, each giving the same trait value.

Both phenomena involve repulsion phase disequilibrium between quantitative trait loci such that each deme or taxon is fixed at one locus for alleles that increase the trait, and that another locus for an allele that decreases the trait. In both cases, this negative covariance results in more uniform trait values than would be expected based upon the allelic divergence. The result from the perspective of Q_{st}–F_{st} comparison is that Q_{st} would be less than F_{st} of the underlying loci but, to my knowledge, no studies have reported Q_{st} in systems showing transgressive segregation.

What distinguishes the formation of positive vs negative covariances of allele frequency among loci is whether the optimal trait values are more variable across environments (diversifying selection – positive covariances) or less (uniform selection – negative covariances) than the variance of population trait means expected under migration/drift equilibrium. From this viewpoint, directional selection is a transient state that occurs when a population trait mean is far from its optimum. During such transient periods, novel mutations that move the population closer to its optimum will rapidly become fixed within a local population. Once the population has evolved to its optimum, however, migration will tend (if it is high) to homogenize allele frequencies and re-establish covariances of allele frequencies across populations.

Discussion

My point here is not to suggest that all traits are neutral, or that they do not diverge under local adaptation, but simply to point out that adaptively diverged genes or traits remain difficult to distinguish from neutral genes or traits by the pattern of divergence alone. On one hand, neutral loci can show a high variance of F_{st} mimicking selection, as in the ponderosa and bishop pine examples mentioned earlier. On the other hand, markers linked to quantitative traits may show no greater F_{st} than neutral loci. For example, in a cross between two subspecies of *Plantago major* (*P. m. major* and *P. m. pleiosperma*) several allozyme loci cosegregate with phenotypic characters diagnostic for the differences between the subspecies (van Dijk, 1984). These single-point analyses (essentially a precursor to more recent and powerful interval QTL mapping techniques; cf. Lynch & Walsh, 1998, Chapter 15), indicate that some of the allozymes are linked to QTL underlying the divergence of subspecies. We would therefore expect these to be more diverged that those that are not linked to QTL. However, when the Lewontin–Krakauer test was applied to the allozyme loci, it was not possible to draw a firm inference about the action of selection (van Dijk *et al.*, 1988). Thus, direct methods for measuring and studying natural selection (e.g. Nagy, 1997) remain a vital tool in understanding adaptive divergence.

More encouragingly, these considerations point to the mechanism by which adaptive divergence can take place in the face gene flow, and particularly how high levels of quantitative trait divergence can be achieved with minimal divergence of single gene allele frequencies. The covariances of allelic frequencies (i.e. linkage disequilibrium) that permit decoupling of Q_{st} and F_{st} depend critically upon there being multiple loci underlying a trait. Determining the number of loci underlying adaptive divergence is therefore of key importance. A number of recent studies have documented that species differences (as well as differences between ecotypes within species) can often be attributed primarily to the action of relatively few major genes (Schemske & Bradshaw, 1999). Even when as few as two loci influence a trait, however, up to half of the divergence in trait values can be attributed to covariance of allele frequencies across loci. As the number of loci increases, the potential for covariances to occur rises exponentially (with the caveat that the magnitude of the covariance between two loci will be limited by the locus contributing a smaller variance to the trait through smaller allelic effects). The contribution of covariances to quantitative trait divergence among natural populations can perhaps most easily be measured by directly surveying allele frequencies at candidate loci. For example, phenology is an ecologically important trait showing adaptive divergence among populations of many species, and candidate genes for phenology are well characterized (e.g. in *Arabidopsis*; Koorneef *et al.*, 1998). Direct allele frequency surveys of multiple candidate phenology loci would

therefore be highly informative, both to assess linkage disequilibria in nature, and to assess the contributions of nonadditive gene interactions to population differences.

It will be interesting to combine the insights of coalescent-based single-locus models, with the analysis of linkage disequilibrium at QTL. If several loci additively determine a quantitative trait that is under diversifying selection, these loci will show relatively little divergence if gene flow is high (Latta, 1998). However, some of these loci might drift to higher levels of divergence than others merely by chance (cf. Figure 1b). This would seem to effectively reduce the number of loci underlying the divergence. It is not clear to what degree a high-F_{st} subset of QTL would become the main target of diversifying selection, reducing the scope for disequilibria to develop. It is plausible that there may be some balance between the uniform response of multiple additive QTL to divergent selection and the heterogeneous patterns expected at neutral loci, but it is not clear whether such a balance would be stable or unstable. What is clear, however, is that underlying adaptive differences of QTL will often show linkage disequilibria more than allele frequency divergence, and will thus be hard to distinguish from the highly variable F_{st}/Q_{st} of neutral loci and traits.

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