Title: Impacts of pleiotropy and migration on repeated genetic adaptation

Short running title: Pleiotropy, migration and repeatability

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Abstract

Studies of trait-mapping and local adaptation often identify signatures of genetically repeated evolution, where different species independently evolve similar phenotypes using the same genes. Such patterns appear incongruent with current estimations of quantitative trait architecture: with hundreds or thousands or genes contributing to a trait, why would selection make repeated use of the same genes? This incongruence is particularly puzzling in light of the Fisher-Orr model, which predicts that repeated use of the same gene should decrease with increasing trait dimensionality, as alleles of large-effect are unlikely to be beneficial when there is high pleiotropy. When adaptation occurs for a single trait in spatially heterogeneous environments with migration, large-effect alleles are more strongly favoured, but it is unclear whether this result would generalize to multiple traits, especially if there are trade-offs between them. Here, we explore this question using individual-based simulations of a two-patch model with multiple quantitative traits governed by mutations with pleiotropic effects. We first confirm that repeatability is lower in spatially homogeneous environments, and then explore the effect of trait dimensionality and pleiotropy in a spatially heterogeneous environment. While repeatability decreases with increasing trait dimensionality, trade-offs in mutation effects on traits do not strongly limit the contribution of a locus of large effect to repeated adaptation, particularly under increased migration. These results suggest that evolutionary convergence will be more pronounced for local rather than global adaptation. Whereas pleiotropy limits repeatability in a single-population model, when there is local adaptation with gene flow, repeatability can be increased if some loci are able to produce alleles of large effect, even with pleiotropic trade-offs.

Keywords: pleiotropy, repeated evolution, repeatability, migration, simulations

Introduction

Studies of adaptation commonly observe convergent genetic responses, where multiple species independently respond to a given selection pressure with mutations in orthologous genes (Bohutínská et al., 2021; Chan et al., 2010; Tittes et al., 2021). These patterns imply a lack of redundancy in the genes available for a selective response (Conte et al., 2012; Yeaman et al., 2018), and at first glance seem inconsistent with another common observation: that variation in quantitative traits is explained by a very large number of alleles of small effect (Boyle et al., 2017; Fisher, 1919), which suggests a high level of redundancy in the genes contributing to quantitative traits.

In the early 20th century, theoretical work by R. A. Fisher demonstrated that the continuous phenotypic variation observed in populations could be explained by a large number of alleles inherited in a Mendelian manner (Fisher, 1919), and that selection would favor small-effect changes at large numbers of loci (Fisher, 1930). Genome-wide association studies in humans have provided empirical observations of standing variation congruent to Fisher's models of adaptive trait architecture (reviewed in Visscher et al., 2017): Associations with hundreds or thousands of genetic variants explain only a modest proportion of trait heritability, with the remaining heritability attributable to even larger numbers of variants with effect sizes too small to detect with current cohorts (or possibly to rare variants that are excluded from many such analyses). But if variation in thousands of genes underpins a given trait, why would we ever observe orthologous genes contributing to adaptation in multiple species, when there are seemingly myriad ways to construct the same traits?

In his revisiting of Fisher's model, Kimura (1983) demonstrated that although smaller effect mutations are more likely to be favourable, beneficial mutations of small effect are less likely to fix, as genetic drift biases the contribution of intermediate-effect loci to adaptation. Later, Orr (1998) showed that effect sizes of fixed adaptive mutations during an adaptive walk should be exponential, illustrating the importance of large-effect mutations early in bouts of adaptation to a new and distant environmental optimum. The omnigenic model (which posits that all genetic variants in genes expressed in the relevant cell type contribute to a phenotype; Boyle et al., 2017; Liu et al., 2019) also makes the distinction between 'core' genes of larger effect and 'peripheral' genes of small effect (although the latter explains the bulk of trait heritability). Perhaps the simplest explanation for convergent genetic adaptation is that alleles of large effect are disproportionately likely to contribute to adaptation (e.g., because of their fixation

probabilities), but only a subset of loci are able to generate alleles of large effect (Orr, 2005). Convergence in gene use would then occur if there is long-term conservation of the genotype-phenotype map and the potential for particular loci to generate alleles of large effect. Certainly, large-effect QTL have been identified in both experimental evolution studies (e.g. McKenzie and Batterham, 1994) and natural populations (e.g. Doebley, 2004; Shapiro et al., 2004), and genomic footprints of selective sweeps (Kaplan et al., 1989; Maynard Smith and Haigh, 1974) provide evidence for strong selection at individual loci (Barghi and Schlötterer, 2020; Schluter et al., 2021). The effects of local adaptation on genetic architecture may further act to increase the likelihood of repeatability, as the contributions of small-effect alleles are disproportionately limited by the swamping effect of gene flow in populations connected by migration (Yeaman and Whitlock, 2011). Consequently, convergence in the genetic basis of local adaptation is expected to frequently involve large-effect mutations, particularly when gene flow is high or drift is strong, yet these processes do not overwhelm selection (Yeaman et al., 2018). It should be noted that repeated adaptation tends to be particularly strong when bouts of adaptation occur from the same pool of standing variation (MacPherson and Nuismer, 2017; Ralph and Coop, 2015), but here we focus on independent bouts of adaptation without such shared variation.

While alleles of large effect may be favoured early in adaptation or when there is migration-selection balance, their contribution to adaptation can be limited by pleiotropy. In both Fisher's (1930) and Orr's (1998) models, mutations are modelled as vectors in multidimensional phenotypic space; therefore mutations with a large effect in a favorable dimension generally deviate too far from the optima in other dimensions, with serious fitness consequences (e.g. Boyle, 1665). Under the Fisher-Orr model where the distribution of mutation effect sizes is homogenous across genes, the repeatability of adaptation should decrease with increasing trait dimensionality (Thompson et al., 2019). Chevin et al. (2010) expanded this model to incorporate distinct genes which could vary in their pleiotropic properties: specifically the number of traits that mutations would affect, and the correlation in effects of mutations on different traits (the latter being a property that can arise from organization of genes into networks; Hether and Hohenlohe, 2014). They demonstrated that repeatability in the genetics of adaptation is an expected consequence of between-locus variation in pleiotropy; convergence may therefore be observed in genes where negative fitness effects of pleiotropy are minimized.

Migration between populations experiencing divergent selection on a single trait can result in the homogenization of small-effect loci, whereas large-effect loci are more likely to be maintained as

differentiated (Yeaman and Whitlock, 2011). While repeatability is expected to decrease with trait dimensionality under a model of adaptation in a single population (i.e., without migration; Thompson et al., 2019), it is unclear how migration-selection balance will affect this, especially if genes differ in their mutational potential (as per Chevin et al., 2010) and if the multiple traits under selection experience different patterns of variation in their respective optima. Previous work on migration-selection focused either on the genetic architecture for a single trait (Tigano and Friesen, 2016) or used G-matrix approaches to explore adaptation at the quantitative genetic level (Guillaume, 2011; MacPherson et al., 2015), so the effect of pleiotropy and migration-selection balance on repeatability at the gene level is unclear. Here, we use individual-based simulations of quantitative trait evolution examining how the interplay between inter-locus heterogeneity in pleiotropy and migration-selection balance affects genetic convergence. We build on previous models, which have considered adaptation in a single population following an environmental shift, by introducing a second population adapting to a divergent environment, and observing interactions between migration, effect size and pleiotropy in bouts of local adaptation. We model different trade-offs in the fitness effects of mutations by varying the values of the trait optima in the two populations, so that divergence among the optima can run counter to the direction of genetic correlation in mutation effects. To simplify the exploration of heterogeneity of mutational effects among genes as per Chevin et al., (2010), we model two kinds of loci: a focal locus that can generate mutations of larger effect, and background loci that generate alleles of smaller effect, and vary both the effect size and mutational correlation separately for these two classes of loci. This approach is not intended to closely model the architecture of a real trait, but rather allows us to focus on the relative contribution of two different classes of locus (e.g. core vs. peripheral genes under the omnigenic model; Boyle et al., 2017) and the effect of varying their characteristics independently. We find that increasing effect size or decreasing deleterious pleiotropy (both the overall dimensionality as well as mutational correlation) at the focal QTL relative to the other QTL will increase repeatability. Moreover we find that increased migration between demes exacerbates the repeatability observed.

Simulations

To study the factors driving repeatability in independent bouts of adaptation, we performed Wright-Fisher, forward-time simulations in SLiM (v. 3.3.1; Haller and Messer, 2019) with adaptation to an environment that was complex and varied across two patches connected by migration. Adaptation within each patch was driven by selection on two (or more) traits: Z_1 with an optimum that varied among the patches, and one or more (e.g. Z_2) with the same optimum in each patch.

To gain insight into the parameters capable of driving repeatability at a particular locus and their interaction, we simulated a simplified genome: Traits could be affected by mutations at five genetically unlinked QTL; within QTL the probability of recombination occurring between one base and the next was 2.5×10^{-7}. Properties were uniform across four QTL, while aberrant properties were assigned to a single 'focal' QTL, where parameter values could be varied independently of the non-focal QTL (for some parameters, simulations were repeated with a total of 20 QTL and one focal QTL). Each QTL consisted of 500 di-allelic loci with genotypic values in [0, a, 2a], at which mutations occurred at a rate of 1×10^{-7} per base pair per generation, resulting in an expected 10,000 mutations in each of two demes over the 20,000-generation simulation. This trait architecture is chosen to facilitate theoretical exploration of the relevant processes when there are two classes of genetic loci, rather than represent a biologically realistic trait.

QTL mutations affected one or more phenotypes (e.g. Z_1 and Z_2); mutational effects for each QTL were drawn from a multivariate normal distribution with variance σ^2, which determines the QTL effect magnitude, and covariance which was equal to the QTL mutational correlation multiplied by σ^2.

The following Gaussian function related individual fitness to phenotype Z_i:

$$w_i = e^{-\frac{(\theta_i - \Sigma a_i)^2}{2V_S}} \qquad (1)$$

where θ_i = the phenotypic optimum and Σa_i = the sum of mutation effects for phenotype Z_i, and V_s = the variance in the fitness function, reflecting the strength of stabilizing selection (set at 125

for all simulations). Overall individual fitness was calculated as the product of w_i across all phenotypes, so there was no correlational selection between pairs of phenotypes.

We simulated two demes (d_1 and d_2), each composed of 1000 randomly-mating diploid hermaphroditic individuals. Phenotypic space was unitless and provided a relative scaling for the width of the fitness function and the magnitude of mutational effects. Both demes began the simulation with phenotypic optima of 0 for all phenotypes and ran with a burn-in for 20,000 generations. After the burn-in, phenotypic optima were shifted and we tracked adaptive evolution over the following 20,000 generations. We focussed on the case where in d_1 the optima for all phenotypes remained at 0, while in d_2, the optimum for Z_1 was shifted to -10, while Z_2 (and optima for any other phenotypes) remained at 0. This configuration of trait optima means that when mutations have a positive correlation in their effects on the two traits, it will be uncommon to have mutations in the direction of the divergence in trait optima among populations (so pleiotropy tends to generate mutations that are deleterious in one dimension). For comparison, we also considered the case where Z_1 and Z_2 in d_2 both shift to -10, wherein pleiotropy generates mutations that are beneficial in both dimensions. We varied the migration rate between d_1 and d_2 (from 0 to 0.05) and α^2 (from 0.1 to 5), mutational correlations (from 0 to 0.99), and the number of phenotypes affected by the QTL.

We investigated three main ways in which the characteristics of the focal QTL could be differentiated from those of the other loci:

1) A change in α^2 by altering the variance component of the variance-covariance matrix used to generate mutations (Fig. 1A cf. B). This parameter was used to model a large-effect QTL at the focal QTL.
2) A change in mutational correlation by altering the covariance component of the variance-covariance matrix (Fig 1A cf. C). This parameter models dependence between phenotypes and determines the probability that a mutation's effect on one phenotype will have a corresponding effect on another.
3) A change in the number of phenotypes affected by a mutation by reducing the dimensionality of the variance-covariance matrix (Fig. 1A cf. D). This models a situation where a QTL has no effect on one or more phenotypes.

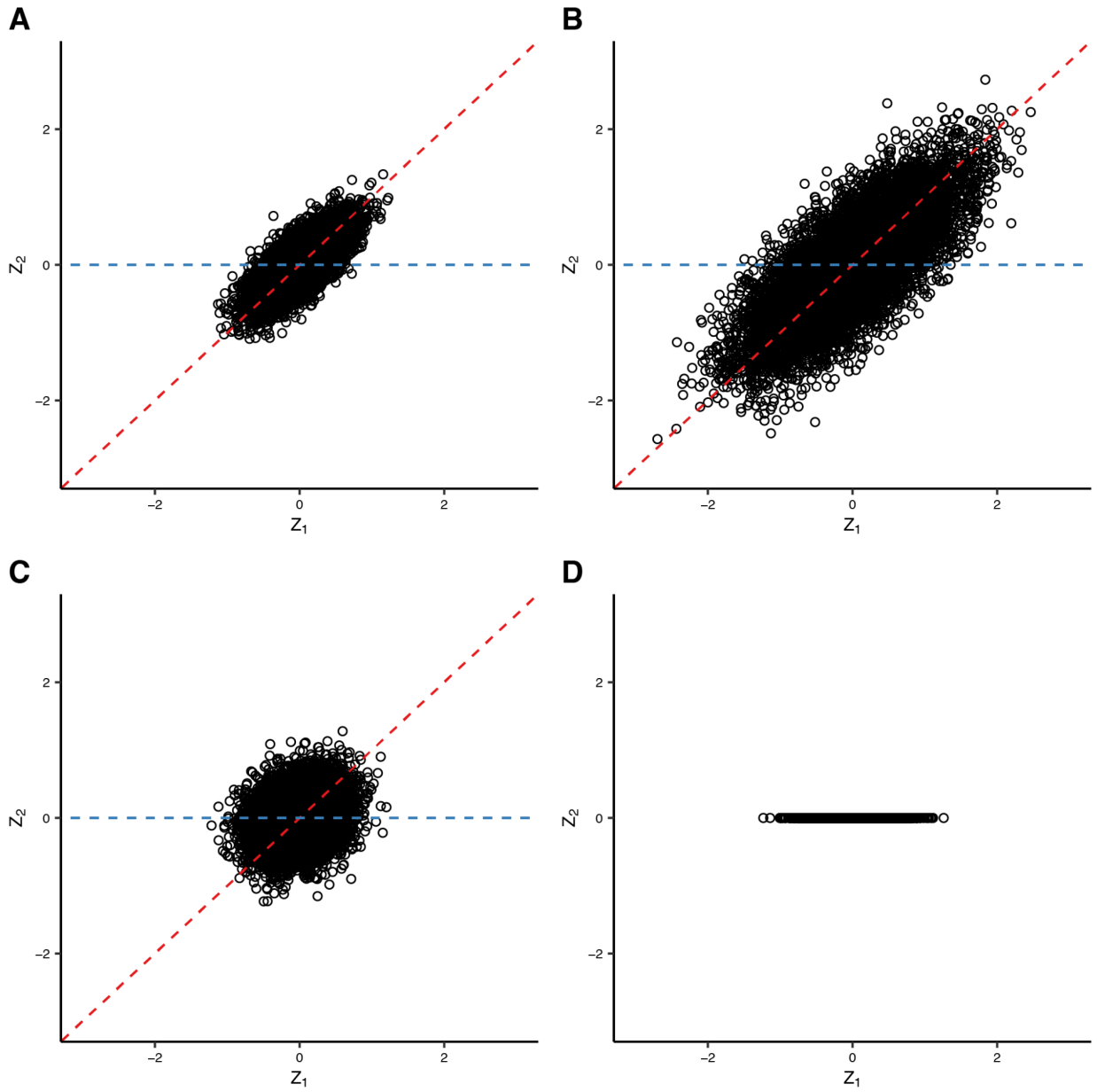

Figure 1. Mutation effect sizes on traits Z_1 (x-axes) and Z_2 (y-axes) for 10,000 draws from distributions used to generate mutations. In A, a^2 is 0.1 and the mutational correlation between traits is 0.75. In B, the mutational correlation is the same as A (0.75) but a^2 is increased to 0.5. In C, a^2 is the same as A (0.1), but the mutational correlation is relaxed to 0.25. In D, mutations have no effect on Z_2. Red lines represent spatial heterogeneity for both traits (i.e. pleiotropy is beneficial), and blue lines represent spatial heterogeneity for Z_1, and spatial homogeneity for Z_2 (i.e., pleiotropy is deleterious).

To interpret the results of each parameter combination, we calculated the genetic value (*GV*) that a given genomic region (e.g., a QTL) contributes to phenotypic divergence using the formula:

$$GV = \sum((p_1 - p_2) \times a) \qquad (2)$$

where p_1 and p_2 are the frequencies of a mutation in each deme, *a* is the size of the mutation's effect on Z_1, and values for each mutation are summed across a genomic region. To compare the relative impact of focal vs. non-focal QTL on divergence, we can then compare GV at these different classes of locus.

For each parameter combination we quantified the divergence (the difference in mean phenotypes) between demes d_1 and d_2 at the divergently selected phenotype with $2 \times GV_{all}$ (*GV* summed across all QTL), and quantified repeatability in the contributions of the QTL to trait divergence (measured by QTL-specific *GV*) across 100 replicates using the C_{chisq} statistic with 1000 permutations (Yeaman et al., 2018), implemented in the dgconstraint R package (Yeaman et al., 2018) with the *pairwise_c_chisq()* function (i.e., each replicate is treated as an independent bout of evolution). Briefly, χ^2 was calculated across simulation replicates with:

$$\chi^2 = \frac{\Sigma(G\bar{V}_n - G\bar{\bar{V}}_n)^2}{G\bar{\bar{V}}_n} \qquad (3)$$

where $G\bar{V}_n$ is the sum across simulation replicates of *GV* for the nth QTL, and $G\bar{\bar{V}}_n$ is the mean $G\bar{V}_n$ across all QTL.

The C_{chisq} statistic was then calculated by using $\chi^2$and χ^2_{sim}, the results of 1000 permutations of the data within each replicate:

$$C_{chisq} = \frac{\chi^2 - mean(\chi^2_{sim})}{sd(\chi^2_{sim})} \qquad (4)$$

By this equation, when C_{chisq}=0 we observe no more repeatability than would be expected by chance. The maximum value of C_{chisq} varies with the number of QTL modelled: C_{chisq}=2 for five QTL and C_{chisq}≈4.36 for 20 QTL.

As an additional measure of the relative adaptive importance of the focal QTL, we calculated GV_{focal} / GV_{all}, the proportion of *GV* summed across all QTL explained by *GV* summed across the focal QTL.

Results

Repeatability of adaptation is uniformly low when all QTL have the same effect size, but increases substantially when the focal QTL has a larger effect size (Fig. 2). When one population adapts to a new environment that differs in one phenotypic dimension but not the other (Fig. 2C, D), the axis of phenotypic divergence between the populations is not aligned with the axis of mutational correlation, and pleiotropy can be detrimental to adaptation (hereafter: deleterious pleiotropy; Fig. 1). Based on Fisher's model, we might expect large effect mutations at the focal QTL to be disfavoured in this scenario, as they would be increasingly likely to have maladaptive effects in one dimension. Surprisingly, we observe substantial repeatability regardless of the alignment between the correlation in mutation effects and divergence and trait optima (Fig. 2A vs. 2C; 2B vs. 2D), with only a slight reduction in repeatability for deleterious pleiotropy under the highest mutational correlations. With both deleterious and beneficial pleiotropy, repeatability tends to be higher with migration (Fig 2; Fig. S1), which again is particularly apparent when mutational correlations are strongest (Fig. 2A vs. 2B; 2C vs. 2D). This repeatability is driven by larger proportional contributions to divergence at the focal QTL, especially under increased migration (Fig. 2 bottom panels). As such, this increased repeatability with migration is likely due to the increased benefit for mutations of larger effect at the focal locus under migration-selection balance (as per Yeaman and Whitlock, 2011). While deleterious pleiotropy with high mutational correlations impedes phenotypic divergence, comparable levels of repeatability were observed between high and low mutational correlations except in the absence of migration (Fig. 2C vs. D). This is because high mutational correlations limit the rate of, but do not completely exclude the occurrence of mutations with fortuitous combinations of effects (Fig. S2A). Our results are somewhat dependent upon the timescale at which we sample: when m=0, repeatability decreases over time, whereas when m=0.005 it increases over time (Fig. S3). Thus, the observed effect of migration on repeatability would tend to increase over time.

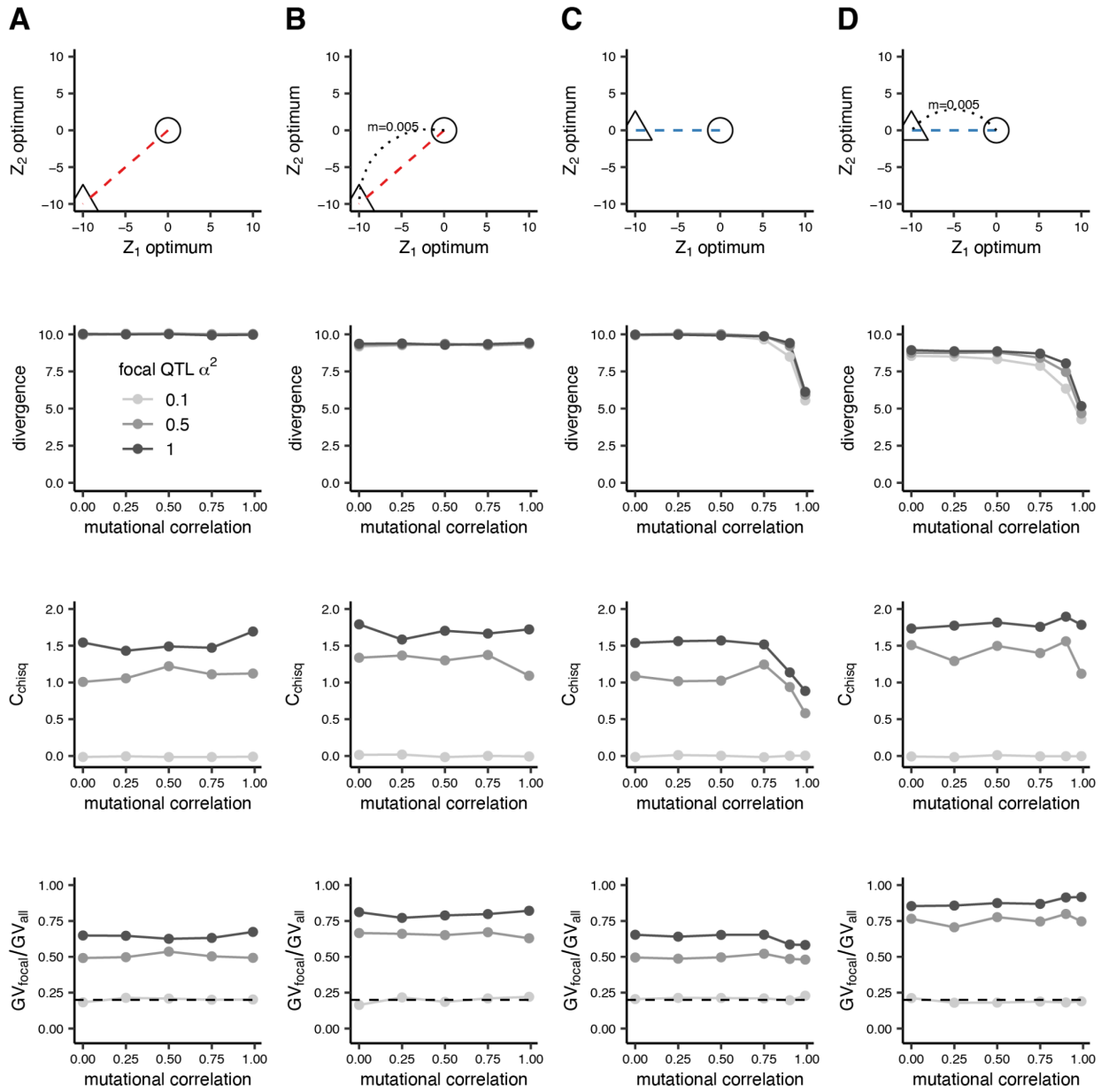

Figure 2. Divergence, repeatability (C_{chisq}) and GV_{focal} / GV_{all} in Z_1 for four relationships between demes (represented in the top row as circles [d_1] and triangles [d_2]): where deme d_2 shifts to a new optimum in only one trait dimension (the environment is homogeneous for one trait dimension and heterogeneous for the other) without (A) and with (B) migration between d_1 and d_2, and where d_2 shifts to new optimum in both trait dimensions (a spatially heterogeneous environment for both traits) without (C) and with (D) migration between d_1 and d_2. α^2 at the focal QTL is varied, while α^2 for non-focal QTL is 0.1. Mutational correlations are uniform at all QTL. These simulations use two phenotypes (one with divergent optima and the other with one non-divergent optima), and were run for 20,000 generations and 100 replicates, with statistics calculated across replicates.

Reducing the correlation in phenotypic effects at the focal QTL may also allow it to more readily acquire adaptive mutations when pleiotropy is deleterious (thereby increasing its repeatability). We modeled this by independently varying mutational correlations at the focal and non-focal QTL (Fig. 3; Fig. S4), and observed repeatability where there were differences between mutational correlation values at focal and non-focal QTL (Fig. 3). As expected, when the mutational correlation at the focal QTL was reduced relative to the non-focal QTL, repeatability of the focal QTL increased. The highest levels of repeatability were seen when the focal QTL had a relaxed mutational correlation against a background of high mutational correlation at non-focal QTL (i.e. 0.75 and particularly 0.9). This reflects the fact that mutational correlations need to be high to significantly limit the availability of mutations with fortuitous combinations of effects at the non-focal QTL and drive extreme repeatability at the focal QTL (Fig. S2B). When both focal and background QTL have the same correlation in their phenotypic effects there is no increase in repeatability, as shown where $C_{chisq} = 0$ and where $GV_{\text{focal}} / GV_{\text{all}}$ crosses the dashed line, and when focal QTL mutational correlations are higher than the non-focal QTL, we observe repeatability from underuse of the focal QTL (Fig. 3).

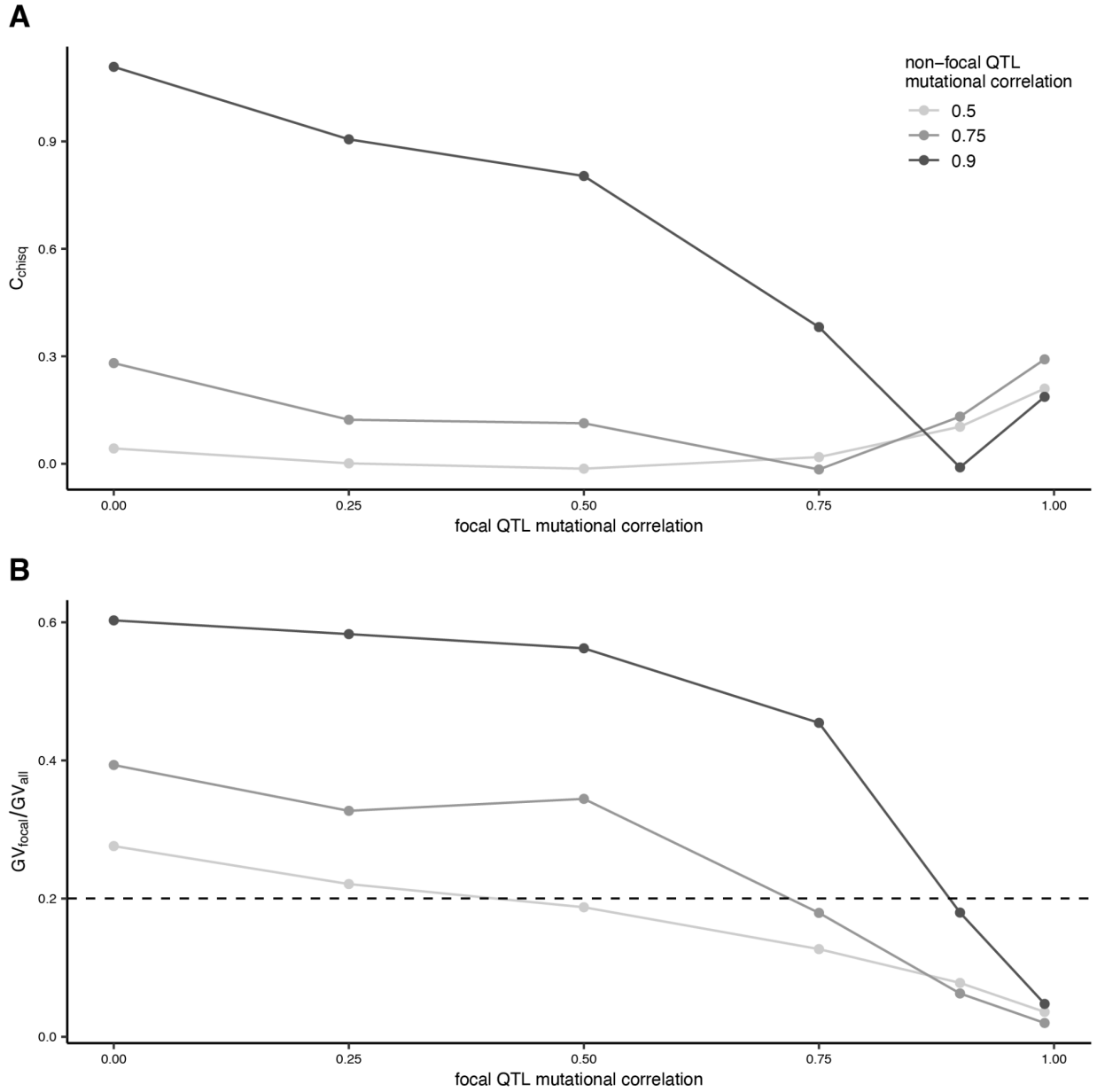

Figure 3. Repeatability (C_{chisq}) in Z_1 against focal QTL mutational correlation for varying values of non-focal QTL mutation correlation (A), and the corresponding mean proportion of all *GV* explained by *GV* at the focal QTL in Z_1 (B). The dotted line indicates $GV_{focal} / GV_{all} = 0.2$, the point at which this value shifts from representing overuse of the focal QTL to underuse of the focal QTL. These simulations use deleterious pleiotropy, a migration rate of 0.005, an a^2 of 0.5 and two phenotypes (one with divergent optima and the other with non-divergent optima), and were run for 20,000 generations and 100 replicates, with statistics calculated across replicates.

To assess the robustness of these observations to an increase in the dimensionality of the phenotypes under selection, we increased the number of non-divergent phenotypes from one to nine and explored the effect of again varying the effect size and extent of pleiotropy at the focal locus. In both cases, when pleiotropy was deleterious (i.e., there was a mismatch between the direction of mutation effects and the axis of divergence in phenotypic optima), we observed a decrease in repeatability with an increase in the number of traits affected by mutations (Fig. 4C, D). This decrease is consistent with the expectation that when mutations can have pleiotropic effects in more dimensions, alleles of large effect experience greater constraints and contribute less to adaptation. However, similar to Fig. 2, the negative effect of pleiotropy on repeatability is less pronounced when migration is higher, presumably offset by the benefit for alleles of larger effect under migration-selection balance. When pleiotropy was beneficial, repeatability was not substantially affected by trait dimensionality (Fig. 4).

Finally, we investigated the case where mutations at the focal QTL affect fewer phenotypes than the non-focal QTL. In the two-phenotype model, this meant focal QTL mutations would only affect the divergent phenotype; in the five and ten-phenotype models, focal QTL mutations affected the divergent phenotype and one fewer non-divergent phenotypes than non-focal QTL. Interestingly, with this difference in breadth of QTL effect between focal and non-focal QTL, the effect of trait dimensionality on repeatability is reversed, with the greatest repeatability seen at the highest number of trait dimensions. As before, with high mutational correlation between phenotypic effects, high levels of repeatability at the focal QTL are observed, however when mutational correlations are weak or absent, very little repeatability is observed (Fig. 5).

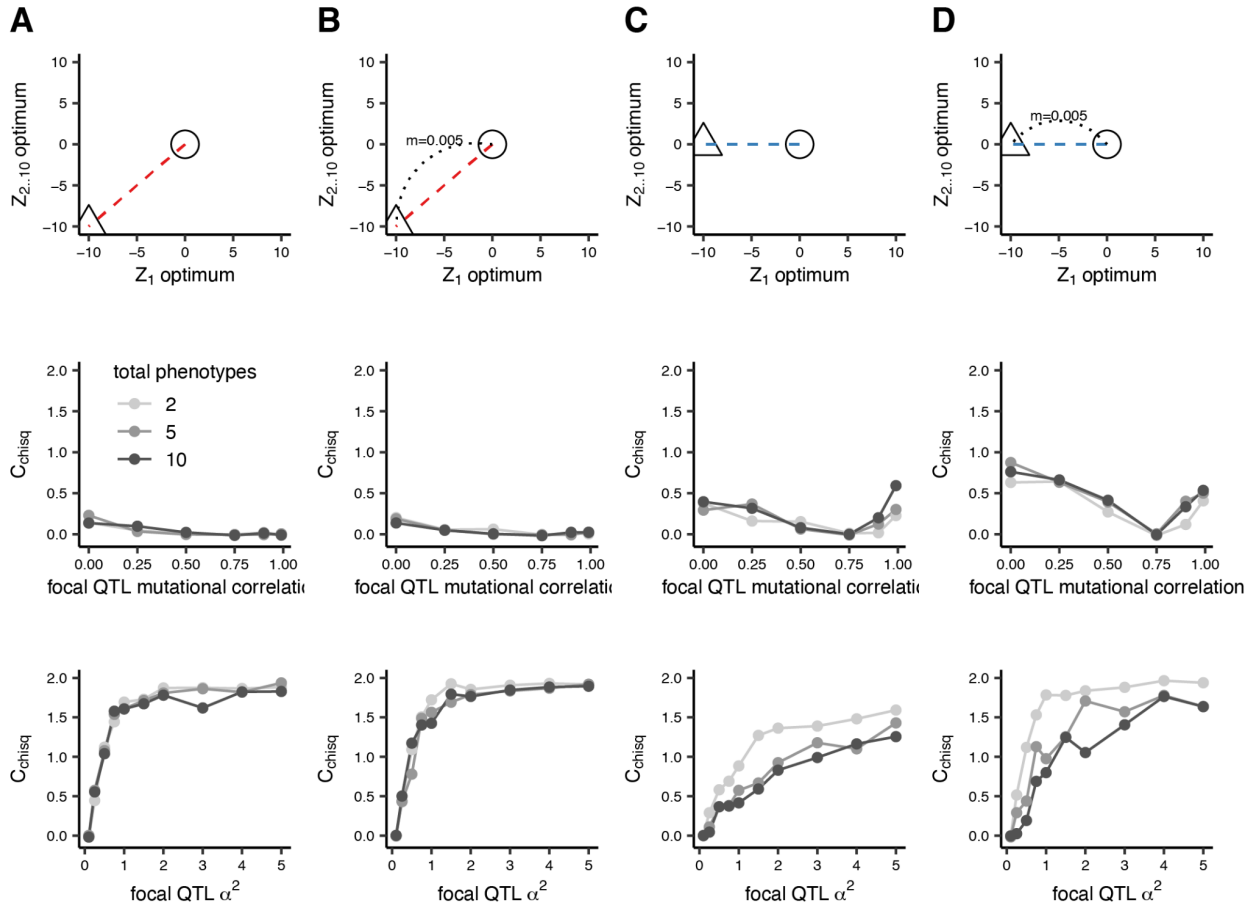

Figure 4. The effects of increasing trait dimensionality on repeatability (C_{chisq}) arising from variation in mutational correlations or α^2 at the focal QTL for four relationships between demes: where deme d_2 shifts to a new optimum in only one trait dimension (the environment is homogeneous for one trait dimension and heterogeneous for the other) without (A) and with (B) migration between d_1 and d_2, and where d_2 shifts to new optimum in both trait dimensions (a spatially heterogeneous environment for both traits) without (C) and with (D) migration between d_1 and d_2. Where α^2 at the focal QTL is varied (middle row), α^2 for non-focal QTL is 0.1 and mutational correlations at all QTL are 0.99. Where mutational correlations at the focal QTL are varied (bottom row), mutational correlations for non-focal QTL are 0.75 and α^2 for all QTL 0.1. Simulations were run for 20,000 generations and 100 replicates, with statistics calculated across replicates.

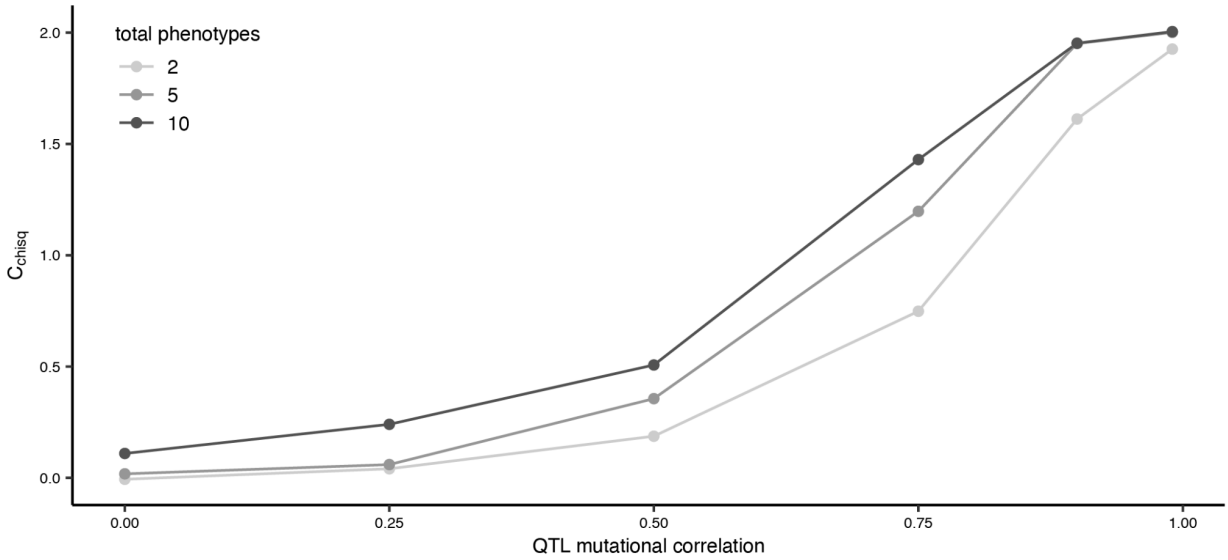

Figure 5. Repeatability against QTL mutational correlation where all QTL share the same mutational correlation, but the focal QTL affects the divergent phenotype (Z_1) and one fewer non-divergent phenotypes than the non-focal QTL. Shades indicate the total number of phenotypes in the simulation (two with one non-divergent phenotype, five with four non-divergent phenotypes and ten with nine non-divergent phenotypes). These simulations use deleterious pleiotropy, a migration rate of 0.005, an α^2 of 0.1, and were run for 20,000 generations and 100 replicates, with statistics calculated across replicates.

Discussion

If all loci have equal pleiotropy and equal effect size, repeatability is not expected (Fig. 2). Thus, the observation of repeated evolution (reviewed in Conte et al., 2012) clearly rejects a simple model where the effects of all loci are equal and interchangeable. While this may seem a "straw-man" model, it helps provide context to interpret theory built on the infinitesimal assumption. Such theories make an unrealistic assumption (that all loci have small and interchangeable effects) in order to generate testable predictions. Models based on the infinitesimal assumption should not be taken to imply that all loci necessarily have equal and vanishingly-small effects, but just that such an assumption allows for tractable analysis. It is therefore critically important to situate the results of this powerful family of models within the problematic observation that some loci clearly have large and repeatable contributions to adaptation. It will be interesting to continue to harmonize results from empirical data, classic population genetic models, and the powerful approximations that can be derived using the infinitesimal assumption (Barton et al., 2017; Hayward and Sella, 2022; Turelli and Barton, 1990).

To explore the effect of variation in pleiotropy on repeatability, we varied the properties underlying the mutations generated at focal vs. non-focal QTL. Firstly, we demonstrated that an increase in effect magnitude (a^2) of a QTL will produce patterns of repeatability, which is consistent with previous theoretical (Chevin et al., 2010) and empirical observations (e.g. Rosenblum et al., 2004; Schlenke and Begun, 2004). Both mutational correlations and migration can force adaptation away from phenotypic optima along ‘genetic lines of least resistance’ (Guillaume, 2011; Schluter, 1996). Correspondingly, when the direction of mutational correlation is counter to the direction of divergence in optima, we see a reduction in trait divergence between demes as mutational correlation is increased, and a reduction in repeatability, which is less pronounced under higher migration, due to the benefit for alleles of large effect (Fig. 2). Similar to previous findings (Thompson et al., 2019), we observe a reduction in repeatability with increased number of traits (Fig. 4), and find this is again less pronounced under higher migration. However, if some loci affect fewer traits than others, we find the opposite pattern with higher repeatability at increasing trait dimensionality (Fig. 5). Congruent with the findings of Chevin et al. (2010) who examined single populations, we also found that repeatability is increased if some loci have reduced mutational correlations (Fig. 2).

By simulating two demes linked by varying amounts of migration, our models address a common situation in local adaptation: Individuals in one population may experience local

environmental shifts; they must therefore adapt to new optima for some phenotypes, while retaining existing optima at others. Previously, Yeaman and Whitlock (2011) demonstrated that migration concentrates the genetic architecture of local adaptation and favors alleles of larger effect. Correspondingly, we find that migration increases the observed repeatability arising from effect-magnitude variation (Fig. 2, Fig. S1), as high migration rates favour adaptation by larger effect alleles, which can most readily occur at the focal QTL when pleiotropy is present. We also find that migration increases repeatability arising from variation in pleiotropy among focal vs. non focal QTL (Fig. S4). This is because repeatability is driven by the net effect of selection on a QTL. Under migration-selection balance those QTL with larger net beneficial effects (i.e., weaker deleterious pleiotropy) will be maintained as differentiated (unless migration is so high that no mutations meet the threshold).

Guillaume (2011) utilized a similar two-patch design to investigate the effects of pleiotropy and migration on population divergence of phenotypes. He demonstrated that combinations of migration and pleiotropy can drive divergence between demes at phenotypes that share the same optima in both demes, as long as the phenotypes are sufficiently correlated with other divergently selected phenotypes. We observe similar patterns in our simulations: increasing levels of mutational correlations and migration reduce differentiation between demes at the divergent phenotype, and increase differentiation between demes in phenotypes not under divergent selection (Fig. S4). Perhaps most surprisingly, we show that this reduced phenotypic differentiation does not necessarily limit genetic repeatability, as high C_{chisq} values are observed in simulations where pleiotropy and migration have substantially limited the divergence between demes (Fig. 2, Fig. S4). It seems that the mutational correlations, despite appearing quite high, do not actually pose substantial constraints to the evolution of genetic architecture, as they basically reduce the effective mutation rate in particular directions, but do not completely prevent such mutations from occurring.

Our simulations provide important insights for studies of local adaptation. Firstly, in the presence of adequate levels of migration, repeatability is expected to occur across lineages undergoing local adaptation to similar optima, even if strong pleiotropic relationships oppose the direction of divergence in phenotypic space (Fig. 3). Secondly, repeated use of a QTL in multiple lineages may arise if the QTL has a disproportionately large effect size (Fig. 2), or if deleterious pleiotropy at the QTL (either the amount of correlation between traits or the number of traits affected) is relaxed (Fig. 3, 5). Finally, for mutational correlations between divergent and non-

divergent traits to influence repeatability, the correlations must be very high, so that fortuitous pleiotropy-breaking mutations are substantially limited (Fig. S2).

However, our simulations make a number of assumptions that are almost certainly violated in natural populations exhibiting evolutionary convergence. Firstly, we treat each simulation replicate as if it were a different species representing an independent bout of adaptation, and we assume complete orthology between QTL in replicates and that orthologous QTL retain corresponding effect magnitude and pleiotropic properties. In nature, divergence between species limits studies of convergence to the orthologous portions of their genomes and the effects of adaptation in non-orthologous regions has not been addressed here. Secondly, we have simulated both the initial phenotypic optima (to which both demes start our simulations adapted) and the divergent phenotypic optima as identical between replicates. Populations adapting to similar environments will not share identical phenotypic optima, which is important for the interpretation of our results, as Thompson et al., (2019) observed that repeatability declines rapidly as the angle between phenotypic optima increases, a pattern that is exacerbated by increased trait dimensionality. Furthermore variation between QTL in mutation rate, retention of standing variation and patterns of linkage disequilibrium may all affect the likelihood of repeatability, but we have held these parameters constant in our simulations.

The simulations presented here also use a simplified genome architecture: four QTL with uniform properties and a single QTL with aberrant properties, and between two and ten traits. This system pales in comparison to the thousands of genes (exhibiting near-global pleiotropy) which contribute to traits under the omnigenic model (Boyle et al., 2017; Liu et al., 2019). Contrastingly, a metaanalysis of gene knockout experiments in *Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Mus musculus* (Wang et al., 2010) estimated pleiotropy to be far less pervasive: a median gene affects only one to nine percent of traits. (Wang et al., 2010) also detected significant signals of modular pleiotropy (where subsets of genes affect subsets of traits), which would serve to simplify the architecture available for evolutionary convergence. Simple genetic architecture enhances repeatability at a genome-wide level, and this study suggests that an even more modular architecture at some QTL will act to further magnify repeatability. While the nature of pleiotropic, quantitative traits in higher organisms remains unresolved, we expect our simple model to be applicable to more complex architectures (Yeaman et al., 2018), and repeating our simulations on models with 20 QTL yields comparable results (Fig. S5). Traits in real organisms will often be much more polygenic, with considerable

variation among genes in the extent and direction of pleiotropy in their mutations, as well as the average effect size. If such the differences in mutational characteristics of genes are conserved across deeper evolutionary time, then variation in their pleiotropic effects will strongly affect their contribution to repeatability.

Supplementary figures

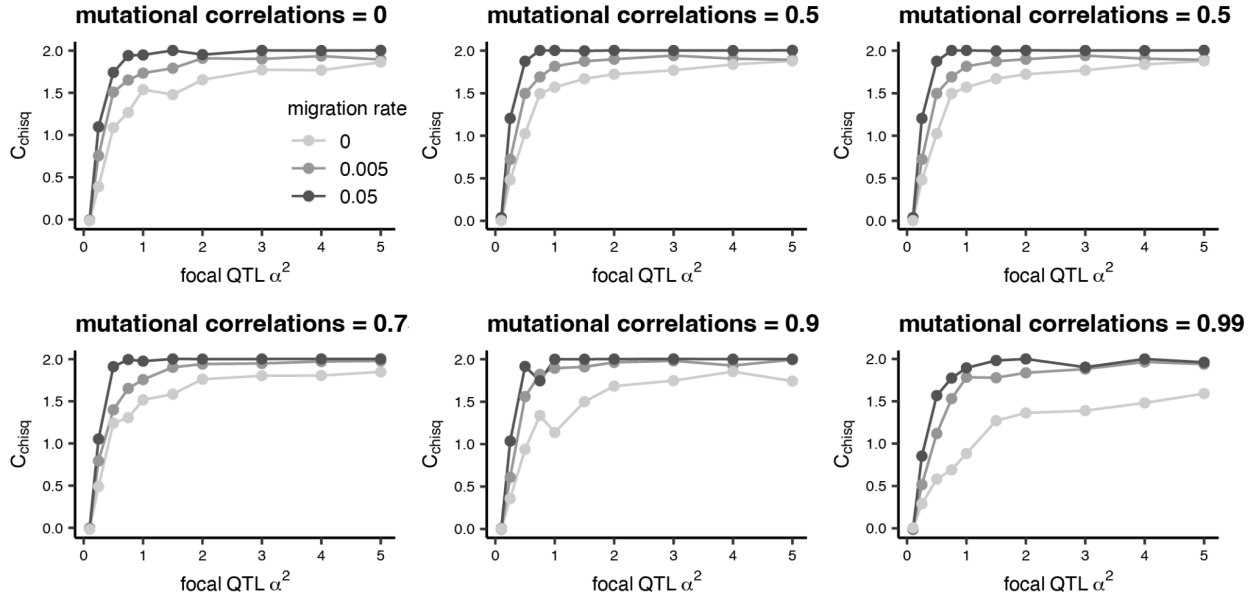

Figure S1. Repeatability (C_{chisq}) in Z_1 against focal QTL a^2 where the a^2 for non-focal QTL is 0.1. These simulations use deleterious pleiotropy, two phenotypes (one divergent and one non-divergent), and were run for 20,000 generations.

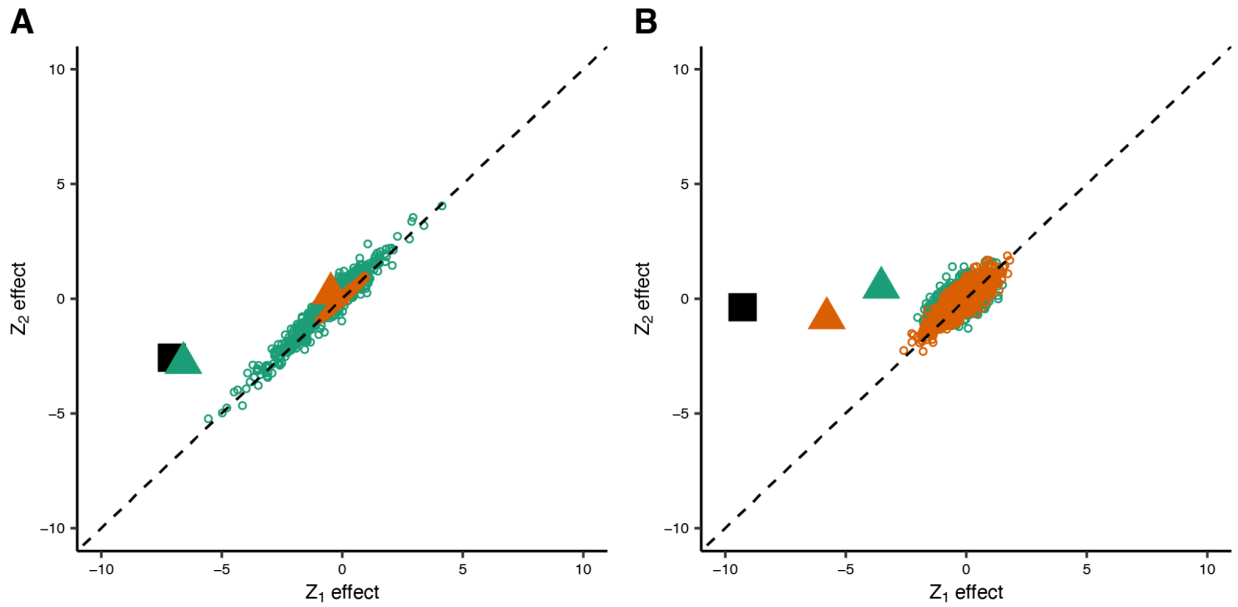

Figure S2. Phenotypic effects for all mutations occurring in d_2 across 100 replicates for single combinations of parameters (A: focal QTL a^2 = 5; non-focal QTL a^2 = 0.1; mutational correlations = 0.99 at all QTL;B: a^2 = 0.5 for all QTL; focal QTL mutational correlations = 0.75; non-focal QTL mutational correlations = 0.9). Green points represent mutations at the focal QTL; orange points represent mutations at non-focal QTL. The mean divergence across replicates for focal and non-focal QTL is represented by green and orange triangles respectively, and the mean overall divergence by the black square. In both panels there are five QTL and migration rate = 0.005.

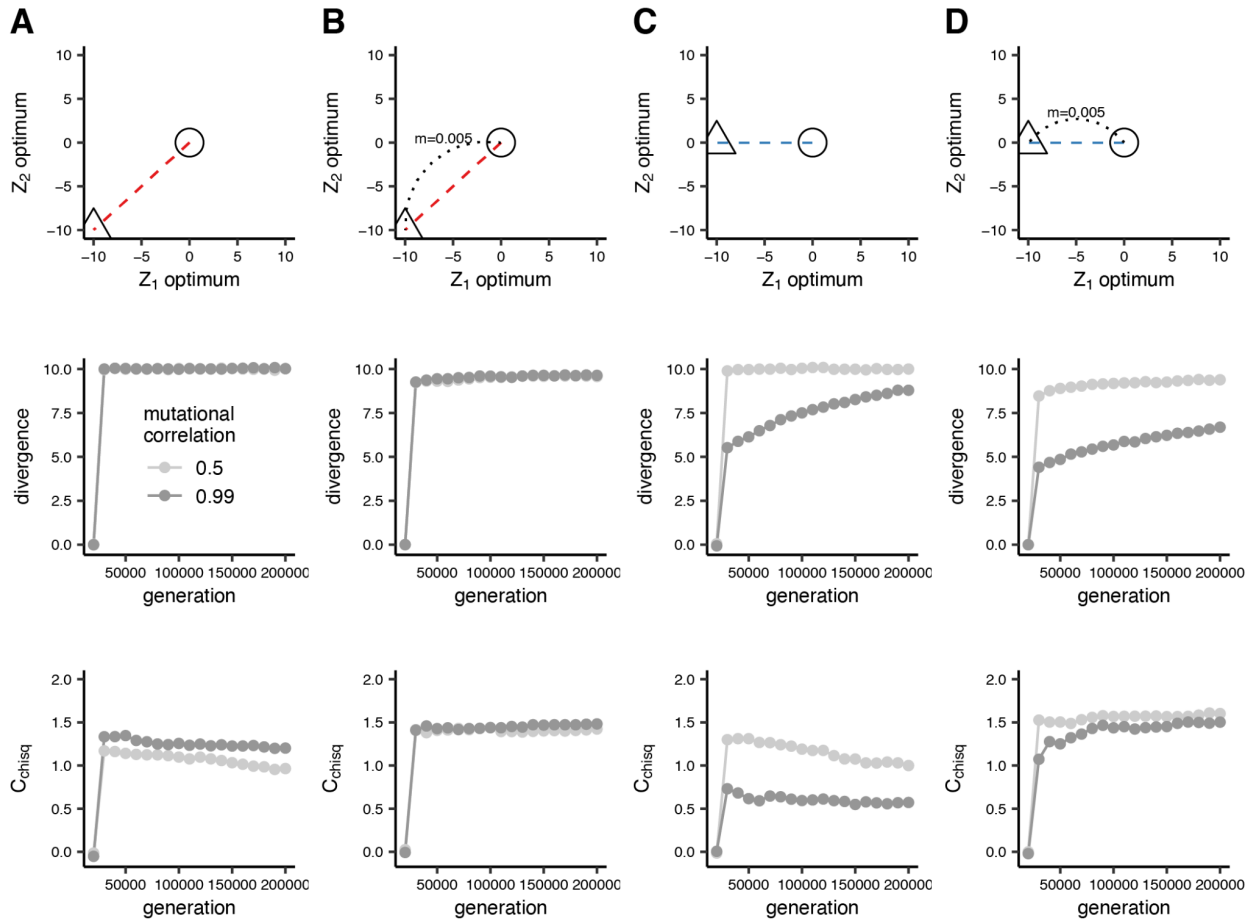

Figure S3. Divergence in Z_1 and repeatability (C_{chisq}) over generations for four relationships between demes: where deme d_2 shifts to a new optimum in only one trait dimension (the environment is homogeneous for one trait dimension and heterogeneous for the other) without (A) and with (B) migration between d_1 and d_2, and where d_2 shifts to new optimum in both trait dimensions (a spatially heterogeneous environment for both traits) without (C) and with (D) migration between d_1 and d_2. a^2 is 0.5 for the focal QTL and 0.1 for non-focal QTL. Mutational correlations are uniform at all QTL. These simulations use two phenotypes (one with divergent optima and the other with one non-divergent optima), and were run for 200,000 generations.

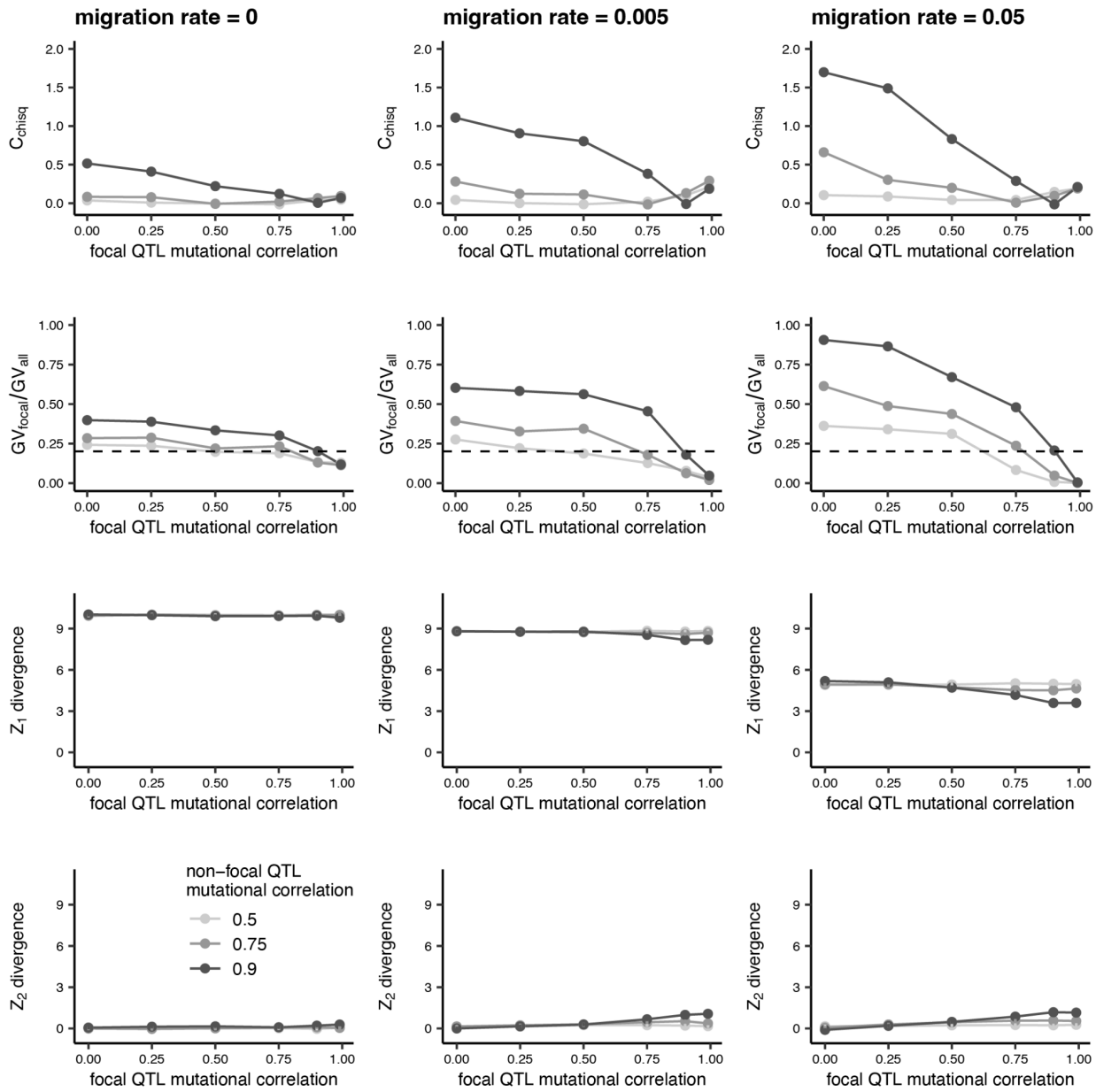

Figure S4. Repeatability (C_{chisq}) in Z_1 against focal QTL mutational correlation for varying values of non-focal QTL mutation correlation (top row), the mean proportion of all *GV* explained by *GV* at the focal QTL (second row), and divergence between demes in Z_1 (third row) and Z_2 (bottom row). These simulations use deleterious pleiotropy an α^2 of 0.5 and two phenotypes (one divergent and one non-divergent), and were run for 20,000 generations.

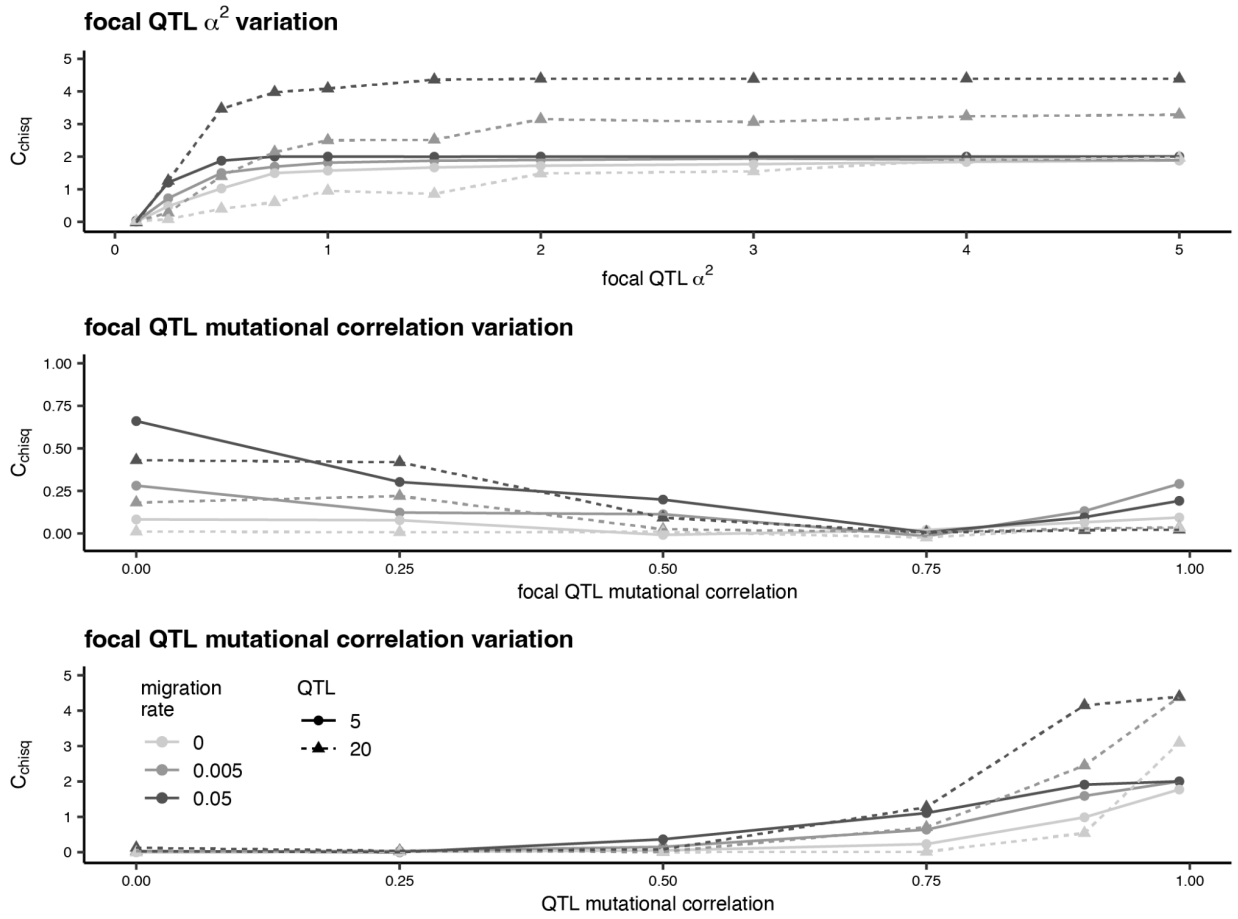

Figure S5. Effects of increasing the number of QTL modelled from five (solid lines, circle points) to 20 (dashed lines, triangle points). In the top pane we examine effect-magnitude variation at the focal QTL (as in Fig. 2), with mutational correlations for all QTL fixed at 0.5. In the middle pane we examine mutational correlation variation at the focal QTL (as in Fig. 3), with mutational correlations at non-focal QTL of 0.75 and α^2 at 0.5. In the lower pane we examine a reduction in dimensionality at the focal QTL (as in Fig. 5), where the total number of phenotypes is two and α^2 is 0.5. These simulations use deleterious pleiotropy and two phenotypes (one divergent and one non-divergent), and were run for 20,000 generations.

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