What fraction of the genomic basis of local adaptation are we missing?

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Abstract

How will species adapt to changing environments? To what extent does adaptation to previous conditions maintain the variation needed to adapt to future conditions? To answer these kinds of questions, we need to identify locally adaptive alleles and quantify their effects. Theory shows that the architecture of adaptation can depend upon the nature of mutation and on how ecology shapes the processes of migration and selection. Depending on this interplay, adaptation can be driven by few alleles of large effect or many alleles of small effect, but little is known about the relative prevalence of such architectures in nature. Unfortunately, our statistical methods are also biased: it is much easier to identify loci of large effect that contribute repeatedly across populations or species, while alleles of small effect are all but invisible to genomic analysis. There is, therefore, a gap between the total amount of locally adaptive variation and that which is explained by genomic studies. To quantify this missing local adaptation, future studies require a deep integration of genomic and phenotypic analyses.

Molecular adaptation to changing environmental conditions can be achieved either through the spread of new mutations or through shifts in the frequency of alleles present as standing variation. As the former pathway depends critically on mutation supply, it tends to occur more slowly in all but the largest populations (Charlesworth and Charlesworth, 2010), so short-term adaptive change in most plants and animals will likely be driven more by response through standing variation (Barrett and Schluter, 2008). The question of what maintains standing variation therefore has particular relevance to understanding the response to future changes in environment. Whereas adaptation towards a single optimal trait value is thought to maintain variation mainly under a balance between mutation and selection, various forms of selection can substantially alter the persistence of alleles that could contribute to adaptation following a shift in environment (Felsenstein, 1976; Hayward and Sella, 2022; Johnson and Barton, 2005). Spatial variation in selection is very common, with extensive evidence from natural populations showing trade-offs between traits and fitness mediated by the different environments encountered across a species' range (Hedrick et al., 1976; Hereford, 2009; Leimu and Fischer, 2008). If the environmental pressure in a focal population shifts in time towards the regime that was present in a neighbouring population, then their coupled evolutionary history can maintain alleles in the focal population that were received from the neighbouring population and are pre-adapted for this change. To what extent does this shape the capacity to respond to environmental change? The answer depends on the details of a species' genetics and its ecology.

Population genetics predicts that long-term maintenance of local adaptation can be achieved if the alleles underlying it have a strong enough local advantage to persist in the face of gene flow, which tends to homogenize populations (Charlesworth and Charlesworth, 2010). But local adaptation can also be maintained if traits have a high mutational target size or mutation rate such that many alleles distributed across species' genomes contribute to local adaptation simultaneously. In such cases, individual alleles are not necessarily expected to be maintained over the long-term and will often be replaced by new mutations (Sakamoto et al., 2024; Yeaman, 2015).

These two types of architecture represent extremes of a continuum and natural populations may commonly exist somewhere in the middle, but the relative contribution of the two patterns to local adaptation in natural systems is basically unknown.

To understand the genomic basis of local adaptation, we need to identify the alleles that underly it, how much local adaptation they are responsible for and how such alleles are maintained in populations over time. An allele can be considered locally adaptive if it increases the carrier's fitness in its home range. A comprehensive understanding of the locally adaptive effects of individual alleles would then require detailed experimentation across the range of environments in which they are found, and on the various genetic backgrounds in which they are found. While detailed quantification of the locally adaptive effects of individual loci may be overkill in certain contexts, knowledge of effect sizes could be leveraged in conservation or breeding programs (Aitken et al., 2024). For example, the degree to which the additive genetic variance for fitness can be increased by assisted gene flow will be related to the effect sizes and allele frequencies of locally adaptive alleles in donor populations (Grummer et al., 2022). While genomics has given us the tools to identify locally adaptive alleles, we are far from a detailed understanding of this important aspect of biodiversity.

Identifying locally adaptive alleles

There are two main paradigms for identifying locally adaptive alleles from patterns of genetic variation. First, one could do a genome wide association study (GWAS) on traits that are subject to spatially varying selection to identify the genomic regions underlying locally adaptive phenotypic variation. A limitation of this approach is that a phenotypic effect is not, in and of itself, sufficient evidence to declare an allele locally adaptive. If the selection maintaining local adaptation were stabilizing, mutations that increase or decrease trait values would contin-

ually arise, but for an allele to be locally adaptive it needs to, on average, increase its carrier's fitness in its home range with trade-offs elsewhere in the range. The second paradigm is to examine patterns of allele frequency over space. Population genomic analyses have been devised to identify extreme patterns of allele frequency variation or particularly strong associations with environmental variation, i.e. F_{ST} outlier scans and genotype-environment association (GEA) tests (reviewed in Lasky et al., 2023). Estimating phenotypic or locally adaptive effect sizes from allele frequency patterns is complicated by genetic drift that may vary from place to place. Additionally, strong selection may generate linkage disequilibrium (LD) among alleles. For example, if all Northern populations had X, Y, Z alleles and all Southern populations had x, y, z alleles, it would be impossible to tell whether X had a bigger or smaller effect than Z if their frequencies covaried. Experiments that break up this LD would be needed to estimate individual effect sizes in such cases. Nevertheless, genome scans have been widely adopted, at least in part, because they do not rely on assumptions of which traits are the basis of adaptation.

Many studies have used GWAS and/or genome scans to identify locally adaptive alleles. There is evidence that the locally adaptive variation identified via GEA analysis tends to have large phenotypic effects, consistent with the predictions that selection on such alleles needs to be strong to withstand gene flow (Whiting et al., 2024). Furthermore, numerous genome scan studies have found strong evidence for polymorphic inversions or other structural variation involved in local adaptation (Le Moan et al., 2024; Todesco et al., 2020). Polymorphic inversions reduce recombination in heterozygotes that can lead to the evolution of supergenes with large fitness effects (Kirkpatrick and Barton, 2006; Wellenreuther and Bernatchez, 2018). These are compelling cases, but unambiguous results are the exception in genome scans – often, smoking guns are not found.

Statistical issues at the heart of genome scans prevent us from using them to identify the total genetic basis of local adaptation. It has long been recognised that correcting for population

structure when attempting to study the genetic basis of local adaptation is vital (Meirmans, 2012). Correlations between ancestry and environmental variation tend to arise in spatially distributed species because both factors tend to be spatially autocorrelated. Unless controlled statistically, this can generate signals that resemble adaptation. This problem is particularly important because such conditions are also most conducive to the evolution and maintenance of local adaptation, which will tend to be strongest when closely related individuals tend to experience similar environments (Booker, 2024; Slatkin, 1973). On the other hand, methods that control for population structure may reduce the power to detect true positives in locally adapted species where the environment covaries with ancestry (Meirmans, 2012). Indeed, in red spruce Capblancq et al. (2023) found that alleles identified via population structure corrected GEA explained less local adaptation (as measured in common gardens) than did alleles identified using an uncorrected approach. Of course, in such cases it would be difficult to disentangle the true and false positives from uncorrected GEAs. At an even more fundamental level though, identification of locally adaptive alleles based on allele frequency patterns requires that the alleles are at sufficiently high frequencies in the sample in the first place. If local adaptation were maintained by alleles at low frequencies, genome scan approaches may simply have no power.

Complex trait variation probably underlies a lot of local adaptation

Phenotypic variation underlying local adaptation may be morphological, phenological, behavioural or physiological. While there are clear cases where local adaptation involves discrete characteristics (e.g. industrial melanism in peppered moths, presence/absence of armour plates in the three-spine stickleback), there are many cases where locally adaptive traits are complex. Species have been shown to exhibit locally adaptive quantitative trait variation in bud burst, flowering time, and cold tolerance among many others (Table S1).

Complex traits are likely composites, representing the integration of numerous developmental pathways, processes and aspects of physiology. Indeed, genome-wide association studies (GWAS) in many different organisms have led to the view that such complex traits tend to be extremely polygenic, with the variation underlying them distributed widely across species' genomes (Boyle et al., 2017). In a GWAS, phenotypic variation is regressed on genotypic data for genome-wide markers. From a marker's estimated effect on the phenotype, one can obtain an estimate of its contribution to phenotypic variation. Summing up across GWAS hits, one can obtain an estimate of the narrow sense heritability ($h^2 = V_A/V_P$) for the trait. Marker-based estimates of h^2 are routinely found to be lower than estimates obtained using traditional quantitative genetic approaches. In humans, for example, GWAS conducted on samples of millions of individuals are only able to explain around 40% of pedigree-based heritability for height and other complex traits in particular populations (Yengo et al., 2022). Many factors may contribute to this missing heritability, but recent studies suggest that a substantial portion is likely due to alleles segregating at very low frequencies in populations (Wainschtein et al., 2022). These alleles will be virtually invisible to GWAS due to an almost total lack of statistical power to identify their effects through regression.

If the genetic component of complex trait variation is often due to alleles at low frequencies and such complex traits often drive local adaptation, it would hardly be surprising if a substantial portion of the variation that underlies local adaptation is also due to alleles at low population-level frequencies. With a highly polygenic basis of complex trait variation, selection on those traits can lead to rapid phenotypic change via allele frequency shifts at many loci across the genome. Evidence consistent with this can be seen in the sustained response to selection for agriculturally desirable traits in breeding populations (Barton and Keightley, 2002), as well as in many other cases of selection on complex traits. Examples include selection for increased limb length in mice (Castro et al., 2019), increased intensity of colouration in guppies (van der Bijl et al., 2025), and resistance to the fungal pathogen that causes ash dieback (Metheringham

et al., 2025). Spatially varying selection acting on such complex traits can lead to phenotypic differentiation among populations with only slight fluctuations in allele frequency from place to place (Le Corre and Kremer, 2003; Lotterhos, 2023).

Just as there is the missing heritability for phenotypic variation in GWAS, we should also consider the missing basis of local adaptation in genome scans. If, for a particular species, there was locally adaptive phenotypic variation for traits that are extremely polygenic, what proportion of that variation would be identifiable via genome scan approaches? What proportion of locally adaptive phenotypic differentiation would we be missing by using genome scan methods?

How can we estimate the magnitude of the unknown?

Quantifying the "missing genetic basis of local adaptation" is difficult, but some suggestive evidence comes instead by looking for the reverse: how well can we predict local adaptation from genomic data without doing a genome scan? Genetic drift across a landscape will lead to spatial variation in allele frequencies. If locally adaptive phenotypic differentiation were maintained by slight fluctuations in allele frequency from place to place for many polymorphisms in the genome, the effects of selection on allele frequencies may be very difficult to distinguish from localised genetic drift. In such cases, genome scans would have very low power (Lotterhos, 2023), but general patterns of spatial ancestry may provide a means to predict local adaptation. The genealogical process shapes co-ancestry among individuals and populations, which is reflected in variation in allele frequencies across the genome (McVean, 2009). Kinship matrices, population covariance matrices or principal components analyses are all commonly used to model such co-ancestry or population structure. Population structure is usually treated as a statistical baseline against which to identify alleles involved in local adaptation (Meirmans, 2012). Indeed, outliers from genome scans are detectable because they have patterns that are extreme relative

to the overall pattern of population structure. But if local adaptation were maintained by loci spread widely across the genome, population structure itself could approximately characterize local adaptation.

Several recent studies found that genomic relatedness (i.e. population structure) provides better predictions of local adaptation than do predictions made from alleles identified via GEA. Studies in Jack Pine, Douglas-fir and balsam poplar used genomic offset approaches to model climate adaptation across those species' ranges and validated their predictions using common garden data (Fitzpatrick et al., 2021; Lind et al., 2024). For all three species in those studies, genomic offset models were built using either randomly chosen SNPs or SNPs identified using GEA. In all cases, genomic offset models fitted using random SNPs had equal or greater ability to predict local adaptation than did models based on GEA outliers. Using different approaches, recent analyses on maize (Li et al., 2025) and Black Cottonwood (Slavov et al., 2025) both found that population structure, as captured by principal components analysis, provided better predictions for phenotypic variation than did environmental variation or GEA outliers.

That the general pattern of population structure seems to predict adaptation does not imply that all the SNPs that went into the analyses described contribute to phenotypic variation themselves . Indeed, Lind and Lotterhos (2025) used simulations to show that offset models built using explicitly neutral markers for species where local adaptation is maintained by alleles at 1,000 loci provide almost identically good predictions as models built using all the causal markers themselves. With strong selection on a single locus, the impacts of selection on neutral sites can extend to distances that are proportional to the ratio of selection to recombination (Barton, 2000). With many loci under selection across the genome, each locus could exert a forcing effect on allele frequencies at neighbouring neutral loci via linkage. Therefore, the observation that general patterns of population structure predict local adaptation suggests that a substantial fraction of the phenotypic variation underlying local adaptation is maintained via selection on sites

distributed widely across the genome. Note, this same line of reasoning is the basis of genomic prediction, where relatedness computed from genome-wide markers is used to estimate breeding values.

In some of the cases described above, local adaptation was better predicted by randomly chosen SNPs compared to GEA outliers. This seems to imply that local adaptation is highly polygenic in those cases, with causal loci widely distributed across the genome. However, those studies were not designed to determine the genomic architecture of local adaptation *per se*. Future studies, perhaps combining theory and simulation, specifically aimed at understanding how different architectures of local adaptation can be characterised from genomic data are needed.

Inferring what is missing by quantifying what is known

Despite a sophisticated body of theory and advanced techniques for sequencing and analyzing genomes, we are still faced with two central problems in our understanding of local adaptation. First, genomic approaches to catalog locally adaptive variation are likely only capturing a subset of the variation that underlies local adaptation. Second, while genomic approaches can identify locally adaptive alleles, they cannot measure locally adaptive effects on their own. To understand the genetic basis of local adaptation, genomic studies need to be integrated with phenotypic studies that measure local adaptation.

Accurate measures of local adaptation are difficult to obtain because quantifying local adaptation requires measures of fitness. It is notoriously tricky and time-consuming to measure fitness, especially for wild populations and long-lived organisms for whom selection may operate on different life stages (McGraw and Caswell, 1996). Experiments to quantify fitness are unlikely to fully reflect the conditions individuals face in their native habitats. For example, biotic interac-

tions are difficult to control and are thus usually excluded and rare climatic events that shape long-term adaptation they may not occur within the timeframe of a common garden experiment. Despite such limitations, local adaptation can be measured in a variety of ways, from provenance trials to reciprocal transplant experiments to F_{ST}/Q_{ST} comparisons (Wadgymar et al., 2022).

Linking genomic and quantitative genetic methods with phenotypic data can give us more detailed understanding of what fraction of the architecture of local adaptation is explained by our observations. For example, Wang et al. (2018) made a detailed study of locally adaptive phenological variation in *Poplulus tremula*. With a combination of quantitative genetics, GWAS and GEA approaches, Examining individuals distributed from Northern to Southern Sweden, Wang et al. (2018) found that variation in *PfFT2* explained about 65% of the variation in the timing of bud set. Wang et al. (2018) used an RNAi approach to validate the allele they found at the *PfFT2* gene and demonstrated that it had extremely large phenotypic effects, altering the timing of bud set by about a month. Other studies have taken a quantitative-trait mapping approach to studying local adaptation (for example Fournier-Level et al., 2011; Lowry et al., 2019), and we predict that developing on such studies is a promising direction for understanding genetic architectures of local adaptation.

If local adaptation is often due to differentiation in quantitative traits (Table S1), limitations inherent to the study of quantitative traits also apply to the study of local adaptation (e.g. identifying alleles with small effect sizes or low at frequencies). Our understanding of the genomic architecture of local adaptation will remain limited to an unknown extent unless there is a deep integration of phenotypic and genomic analysis. Devising creative ways to integrate phenotypic and genomic data with the environmental variation causing local adaptation represents the key challenge for the future. For example, an ideal experiment might see crosses of multiple families derived from locally adapted populations planted in common gardens where local adaptation can be quantified. Experimental designs such as multi-parental advanced generation intercrosses

(Scott et al., 2020) or X-QTL mapping (Macdonald et al., 2022) could break up LD among locally adapted alleles and/or narrow down effect size estimates to precise genomic regions. By quantifying the proportion of overall fitness variation attributable to loci discovered through genome scans, we can estimate how much lies beyond the reach of our methods. Because of the correlation between statistical detectability and effect size, quantifying the proportion of unknown unknowns actually tells us something about their genetic architecture (i.e. what proportion of local adaptation is driven by alleles of small effect). While such approaches may be difficult to scale and apply in some organisms (e.g. long-lived species or those with large complex genomes), integrating phenotypic, environmental and genomic data is the most promising way to more fully understand how local adaptation evolves and is maintained.

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TRB wrote the original draft. ABM compiled the examples shown in Table S2. All authors reviewed and edited the writing at all stages.

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