PNAS COMMENTARY

# Joining forces to push past paradoxes: Combining quantitative genetics and genomics shows evolution hiding in plain sight

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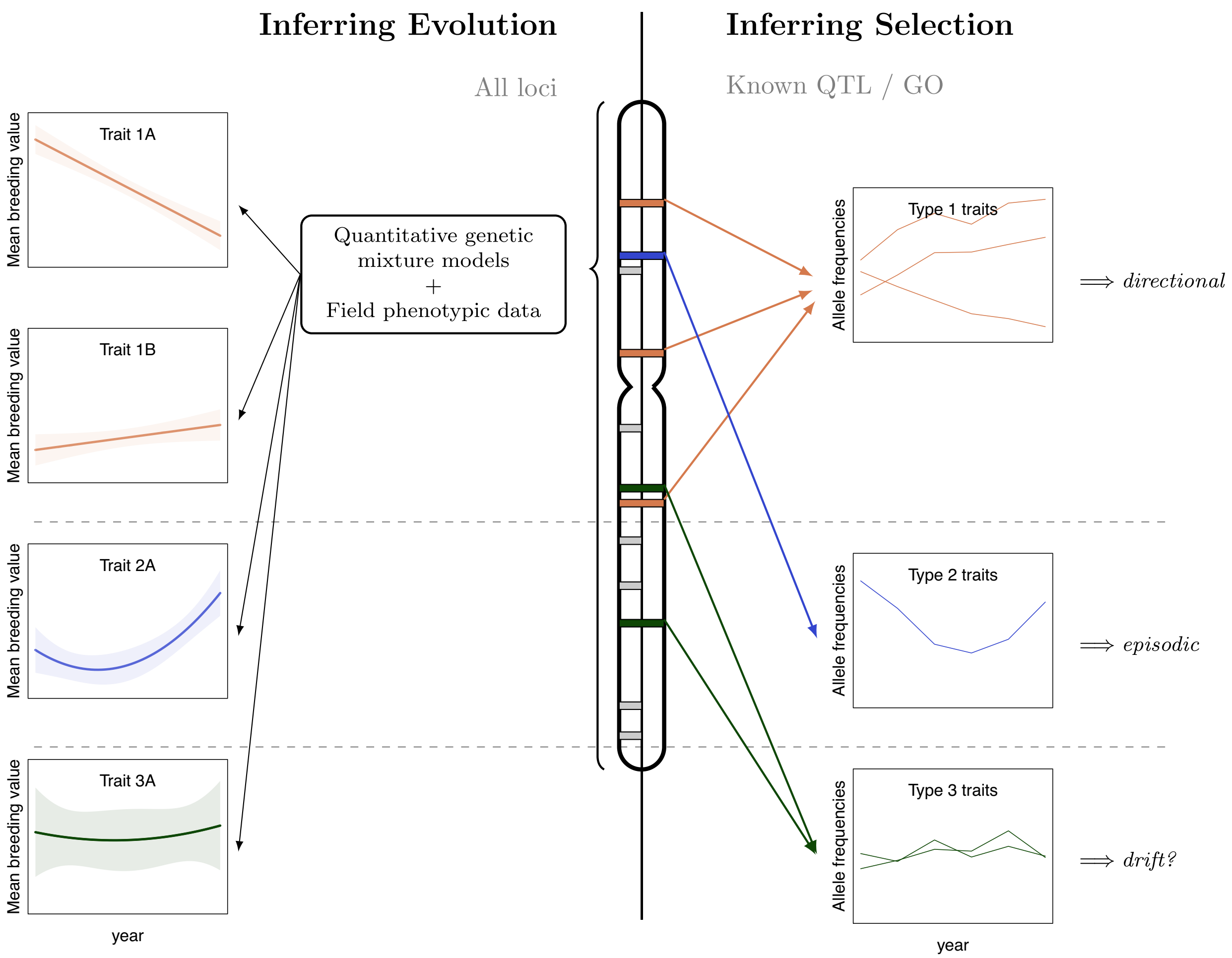

**Fig. 1.** Schematic representation of Strickland et al. approach. To the *Left*, individual-level genomic data are combined with field phenotypic data to estimate changes in average breeding values for each trait through time, which is a direct measure of how much genetic change across all loci contributed to phenotypic change. Breeding values agglomerate information from all genotyped loci, but without explicit reference to the role of each locus. To the *Right*, the same genomic data are used to infer modes of selection acting on types of traits. A trait type can include one or several traits measured in the population. First, patterns of changes in allele frequencies through time are tested against expectations to detect modes of selection at the level of SNPs. Then, some SNPs (in blue, orange and green) can be assigned to a type of trait based on previous QTL and GO studies of the species. Thus, modes of selection are assigned for trait types. For simplicity, a single chromosome is represented.

Evolution by natural selection is a deceptively simple process: In a given environment, some trait values make survival and reproduction more likely, and if trait differences are in part inherited across generations, then the trait will evolve toward those trait values. This principle has been used effectively to quickly shape domestic species to human will in farms and in the lab (1, 2).

Yet, students of evolutionary ecology will know that when it comes to natural populations there is nothing simple about disentangling the yarn of ever-changing and correlated environments, selective pressures, phenotypic distributions, and

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genotypic distributions. Looking at quantitative traits (that is, traits that are continuous rather than having a few possible discrete states), there is widespread evidence of rapid phenotypic changes in quantitative traits over the last decades (3), combined with heritable genetic differences (4) and strong selective pressures (5). Taken together, these suggest that many quantitative traits should currently be evolving in response to natural selection with nontrivial changes every generation. This is not what is observed: In most cases, studies of heritable quantitative traits under strong selection fail to conclusively infer a genetic response to selection (6–8). As we will see below, it remains unclear to what extent this paradox is due to biological properties or method limitations.

> **The study by Strickland et al. is part of a trend towards integrating quantitative genetics and genomics in wild populations.**

Among chief biological hypotheses explaining the paradox is the fact that natural populations are subject to complex, variable, and multivariate selective environments (7), in stark contrast with captive populations in which humans generally implement a single and well-defined selective pressure on a target trait. With natural selective environments, it is difficult to know a priori which traits are subject to selection, and which ones may evolve given that several traits may be influenced by the same genes (i.e., pleiotropy). Additionally, multivariate selection may simultaneously affect different traits in different modes (e.g., directional, stabilizing, episodic). If the mode of selection is not known, then neither is the shape of the expected response to selection, which further complicates the ability to identify entangled responses to selection. However, testing biological explanations for the mismatch between genetic change and selection is made complicated by 1) a tendency for studies to focus on the evolution of one trait at the time, 2) technical difficulties in inferring genetic change for any given trait, and 3) challenges in demonstrating the role of selection in that change.

To tackle these challenges, in PNAS Strickland et al. (9) used a combination of quantitative genetics and genomic methods (Fig. 1) applied to a population of threespine stickleback and provide one of the most comprehensive studies of multitrait contemporary evolution by natural selection in the wild to date. To start with, they tested for contemporary evolutionary change and signals of natural selection in eight traits at the same time, a high number by the standard of microevolutionary studies of wild population. Moreover, they choose to study traits related to feeding and defense against predators, which was opportune since the traits are relevant to environment variables that changed sharply during the study period (densities of predators, prey, and conspecifics), thus making selective pressures likely.

Strickland et al. first found that in this stickleback population, the average of several traits changed strongly through time, but phenotypic change may be driven by nongenetic plastic processes (i.e., direct responses to the environment), so the changes cannot be directly ascribed to genetic change. It could be tempting to look directly at changes in gene versions (alleles) at the molecular level, but variation in quantitative traits is typically caused by a large number of genetic loci, most of them having a small effect (1). In the best-studied wild organisms, we may be able to classify what kind of trait a particular genetic locus is more likely to influence by matching those loci to databases of known phenotypic effects or molecular functions [e.g., quantitative trait loci (QTL) or gene ontology (GO) analysis]. Even then, the references were derived in different populations and different environments from the focal ones, and the effect of a genetic locus in the context at hand is only speculative and its direction unknown. Therefore, usually changes in allele frequencies cannot be directly linked to phenotypic change in a particular trait.

To test for evolutionary change, for each trait Strickland et al. estimated individual genomic breeding values, a quantitative genetic metric that represents the influence of all the genome on traits' phenotypic variation (2, 10). In wild populations, the estimation of breeding values has traditionally been allowed by the construction of multigenerational pedigrees over many years of individual-based monitoring in the wild, a resource that is available only in a small set of populations (4, 11). In the absence of a multigenerational pedigree, Strickland et al. used a mixture model for genomic breeding values, which combines individual phenotypic measurements from the field and relatedness between individuals at many genetic loci, but without explicit reference to the potential effect of each locus (Fig. 1). They then looked at patterns of change in average breeding values through time. Interestingly, they find evolution was fast and directional for some traits, in particular feeding-related traits which changed as much as 25% of the trait mean in 10 generations, not detectable for other traits, and fluctuating in one trait (with an initial genetic change being then reversed). Thus, the presence of strong adaptive genetic change could have been missed if a single trait had been studied, or in the case of episodic evolution, if evolution had been estimated between two time points rather than continuously. In another recent study of wild vertebrate populations, substantial rates of overall genetic response to selection, without reference to which traits are being selected and evolving (12), were detected in about half the populations, including some in which former studies had failed to detect substantial evolution for specific traits (13). Both studies suggest that substantial contemporary adaptive evolution may indeed be common, but that we need to study many traits simultaneously to detect and characterize it properly.

Changes in breeding values are an ideal measure of the evolution of phenotypic traits, but in themselves do not identify the cause of evolution. In studies of microevolution in the wild it has generally been challenging to distinguish a genetic change in response to selection from changes due to genetic drift, the random sampling of chromosome fragments across generations (10). To address this, in a second set of analyses, Strickland et al. tested for the mode of selection (directional, stabilizing, episodic, or neutral) in type of traits. To achieve this, they compared patterns of change in allele frequencies to theoretical expectations for each Single-Nucleotide Polymorphism (SNP). But how did they associate those loci to the evolving traits? The effect of each SNP on each trait is typically null or very small and estimating those effects within the focal population would require mapping genotypes and phenotypes on orders of magnitude more individuals than exist in the population. Fortunately, threespine stickleback is a favorite of evolutionary genomics studies and a substantial proportion of SNPs sequenced in this study were located at or around genetic loci that have previously been associated with a type of traits (QTL) or to a molecular function that can be related to a type of trait (GO analysis). By classifying SNPs having a putative effect on types of traits, Strickland et al. were able to test for associations between the dominant modes of selection identified at the SNP level and the types of traits associated to those SNPs (Fig. 1). They find feeding traits were significantly overrepresented in genomic regions under directional selection, aligning with the result of directional evolution inferred for feeding traits using breeding values.

The study by Strickland et al. is part of a trend toward integrating quantitative genetics and genomics in wild populations, also exemplified by tests of selection combining genomics data and pedigree analysis in scrub-jays (14) or the revisiting of evolutionary trends using pedigrees and genomic prediction in Soay sheep (10). This integration comes with the challenges of mastering multiple sets of concepts and methods full of hurdles (e.g., ref. 15) that require conversation and transfer of expertise between research communities. Ultimately the benefit of this integration seem likely worth the effort, shedding light on perceived paradoxes and brings a richer, more accurate, picture of evolution in the wild.

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