



Behavior and the Dynamic Genome

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with the type of epistasis found among adaptive mutations within a single protein (11). Notably, Weinreich *et al.* studied mutations in an antibiotic resistance gene, β -lactamase, and found a prevalence of sign epistasis, which limits the number of genetic paths that evolution can follow (11). In contrast, the epistasis documented by Khan *et al.* and Chou *et al.* exerts less constraint on the order of substitutions that increase fitness, so that the specific path that evolution will take is less predictable. At the same time, the prevalence of antagonistic epistasis measured by the two groups ensures a predictable tempo of adaptation characterized by diminishing marginal returns (10).

Although these new experiments suggest a consistent principle of how epistasis shapes the pattern of adaptation, many questions must be answered before their results can be extended to evolution outside the laboratory. It remains unclear, for instance, whether these results would be altered by changing fundamental evolutionary parameters, such as population size, rate of mutation, and rate of recombination. Likewise, it is unclear

whether experiments in simple environments, with only one or a few niches for coexisting strains, will reflect the pattern of adaptation in more complex ecologies, such as *Pseudomonas fluorescens* in structured environments (6). Nonetheless, the compelling consistency between these two studies should inspire efforts to test the generality of their findings, by measuring epistasis in a wide range of experimental and even natural systems.

These studies, and the long-term laboratory evolution experiments from which they derive, represent a resounding achievement for the reductionist approach to studying biology. The mechanistic picture they paint of evolution is complex but not incomprehensible; although epistatic interactions lead to surprising phenomena, the advantages of a frozen “fossil record” of laboratory-raised isolates, and the ease of manipulating—and, now, fully sequencing—evolved strains enables researchers to tease apart and examine the underlying causes of these phenomena. Moreover, the theory and concepts developed to explain these simple experiments may have broad payoffs. Already,

epistasis has been implicated in the evolution of drug resistance in influenza viruses (12) and in bacterial pathogens (13). Ultimately, populations of bacteria tediously propagated in the lab may be key to predicting the next moves of the most mutable and dangerous human pathogens.

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GENOMICS

Behavior and the Dynamic Genome

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When circumstances change, an organism's first response is often behavioral. But how does adaptive behavior evolve, given that it requires constant and often instantaneous interactions between an individual and its environment? The dominant view emphasizes new random DNA mutation as the starting point. This may lead to behavioral variation. If the resulting variants have different fitness values, then natural selection could result in behavioral evolution through changes in allele frequencies across generations. An alternative theory proposes environmentally induced change in an organism's behavior as the starting point (1), and “phenotypic plasticity” that is inherited across generations through an unspecified process of “genetic assimilation” (2). Despite numerous exam-

ples (3), the latter as a driver of behavioral evolution has never been widely accepted, perhaps as a reaction against Lamarckianism—the idea that characteristics acquired by habit, use, or disuse can be passed on across generations. However, behavioral genetics and genomics, especially for animals in natural populations, lend some plausibility to the phenotypic plasticity view.

The ability to analyze genome-wide gene expression through “transcriptomics” has shown that the genome responds dynamically to stimuli (4). One illustrative example is the honey bee. The African honey bee (*Apis mellifera scutellata*) responds much more fiercely when its hive is attacked than do other subspecies of honey bee. Evolutionary changes in brain gene expression may have resulted in an increase in responsiveness to alarm pheromone (the chemical bees use to alert each other to danger) for African honey bees (5). About 10% of the same genes regulated in the brain by alarm pheromone are also differentially expressed between African and the less aggressive European honey bees. These genes, acting

Does behavior evolve through gene expression changes in the brain in response to the environment?

over both physiological and evolutionary time scales, provide a possible mechanism for how behavioral plasticity might drive rapid behavioral evolution through changes in gene regulation. In an environment with more predators, colonies producing more bees with lower thresholds for responding to alarm pheromone would have fared better, which would then result in a population with patterns of gene expression whose output was an “aroused” behavior, even in the absence of alarm pheromone. Although this view does not rule out the possibility that these differences in aggression arose through new mutation, the transcriptomics agrees with the idea of “genetic accommodation” (3), the modern, more inclusive version of genetic assimilation, which could involve either evolutionary increases or decreases in plasticity. In certain environments, plastic genotypes might be favored, but in other environments, nonplastic genotypes might be preferred instead. Future studies will determine whether differences in honey bee aggression can be explained by selection on regulatory regions of the

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Behavioral evolution. Male dung beetles with horns (**left**) fight for mates, whereas hornless males (**right**) sneak copulations. The morphs show different patterns of gene expression in developing brain tissue. Genes that are differentially expressed between these two morphs have diverged among two species.

genome, epigenetic (chemical) modifications to the genome, or both.

Genes that are responsive over different time scales also may be involved in the evolution of animal personality (6). For example, after the retreat of the glaciers during the early Holocene ~12,000 years ago, marine stickleback fish (*Gasterosteus aculeatus*) invaded new freshwater environments filled with predators they had never encountered before. Some sticklebacks must have changed their behavior in response to this threat, and over generations, those behaviors that enhanced survival were favored. As with the African honey bees, their survival might be attributed to behavioral changes that resulted from genetic accommodation of a plastic response to predation risk through selection on gene regulation. Presently, there are genetically distinct populations of “bold” and “shy” stickleback fish adapted to different predation regimes that exhibit different baseline levels of antipredator behavior, even when predators are not immediately present.

These examples suggest that genes with expression differences along the temporal continuum are candidates for driving evolutionary divergence through phenotypic plasticity. The mating behavior in dung beetles (*Onthophagus taurus*) reflects this possibility. Male beetles with prominent horns fight for access to females, whereas hornless males attempt instead to mate surreptitiously, without challenging other males (see the figure). The genes that are differentially expressed between these two male morphs are also evolutionarily divergent (7). Given the ever-increasing cases of genetic accommodation in natural populations, including feeding-induced changes in head shape in snakes (8) and sticklebacks (9), behavioral innovation in Darwin’s finches (10), and range expansion in house finches (11), genomic analyses could clarify whether phenotypic plasticity is often a driver of behavioral evolution.

Transcriptomics and analysis of genetic variation may reveal whether genes linked to phenotypic plasticity and behavior are common or rare; epigenomics can explain how they might go from inducible to constitutively expressed; and molecular systems biology can identify their positions in regulatory networks (12). These kinds of genes might be used repeatedly in evolution to build the circuits and systems underlying certain types of behaviors, even though they do not directly encode behavior.

The dynamic genome also generates testable evolutionary hypotheses about **which genes might be most important for human health**. Genes that are important over different time scales might be expected to be held in check by stabilizing selection, and to be buffered from developmental perturbations over a lifetime. But from the perspective of “Darwinian medicine,” **the genes that facilitate plasticity over multiple time scales might also cause maladaptation when the environment changes**. If so, then genes acting over the temporal continuum, or the networks they operate in, may be disproportionately involved in **disease conditions such as mental illness**. A case in point is *CNTNAP2*, which encodes a neuronal cell adhesion protein. *CNTNAP2* functions in a network that includes the transcription factor Forkhead box protein P2 (*FOXP2*). Mutations in *CNTNAP2* are linked to language delay in children with autism spectrum disorder (13, 14), and *FOXP2* is involved in auditory communication in a variety of vertebrates, including humans (4). Disrupting the expression of *FOXP2* in the basal ganglia in mice (15) and song birds (16) causes communication deficits, and there is evidence for a selective sweep for a *FOXP2* allele in primates that is associated with the evolution of human speech (17).

The relationship between behavioral plasticity and the dynamic genome should become clearer as brain transcriptomics spreads to more species. Similar advances

can be expected for the relationship between gene expression and genetic variation, including cryptic genetic variation, which does not influence the phenotype unless there is a change in the environment (18). With the imminent sequencing of genomes of thousands of species, as well as thousands of individuals of the same species, there will be ample new evidence to test these ideas, but with a twist. Given that genes that are more plastic in their expression can also be more sensitive to mutation (19), there likely will be examples where phenotypic plasticity “lit the match” for adaptive behavioral evolution (3) but cryptic genetic variation provided the fuel.

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