

THE EPIGENETICS OF ADAPTATION: FOCUSING ON EPIGENETIC STABILITY AS AN EVOLVING TRAIT

Kathleen Donohue^{1,2}

¹Department of Biology, Duke University, Box 90338, Durham, North Carolina 27708

²E-mail: k.donohue@duke.edu

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“Epigenetics” refers to changes in gene expression that occur through changes in DNA methylation, histone modification, small or micro-RNAs, or most inclusively, other mechanisms that alter how DNA sequences are translated into functional gene products. With the discovery that epigenetic modifications to gene expression can be inherited across cell lineages or even across organismal generations, enormous interest has been generated in the potential evolutionary consequences of epigenetic inheritance. This collection of articles addresses how epigenetic inheritance may influence adaptive evolution, focusing on epigenetic stability and inheritance itself as a potentially evolving trait.

It has frequently been argued that epigenetic modifications that are stable across multiple generations can act as an important source of heritable phenotypic variation upon which natural selection can act, and that such variation, unlike random genetic mutation, may even be nonrandom with respect to environmental context and adaptive value. This bold hypothesis raises a number of compelling questions. First, when changes in gene expression are not caused by changes in DNA sequence, what sort of epigenetic changes are stochastic versus environmentally induced, and do they differ in their stability of inheritance? Second, what is the adaptive value of such random and environmentally induced epigenetic modifications in the wild? Third, is the stability of epigenetic alterations itself heritable and is it adaptive, and if so, under what conditions? Does natural selection actually favor epigenetic stability, or not, and does selection for or against stability determine how frequently we may observe adaptation via epigenetic inheritance? These articles begin to address these questions

by reviewing recent advances in studies of epigenetics in natural populations.

To start, Turck and Coupland explain the molecular basis of two major mechanisms of epigenetic regulation of gene expression: DNA methylation and histone modification. By reviewing case studies in plants, they argue that these two modes of epigenetic regulation can differ in stability and environmental sensitivity. DNA methylation has the potential to be mitotically and meiotically stable, and methylation states can even be passed to homologous alleles or orthologous genes in a genome. Histone modification, in contrast, is involved with environmentally induced epigenetic regulation that can be reversible. Using a case study, the authors show that interspecific differences in the reversibility of environmentally induced gene repression via histone modification are associated with the difference between annual and perennial life histories, and thus likely to have significant adaptive consequences. The authors also hypothesize that the degree of DNA methylation and the stability of environmentally induced changes in gene expression via histone modification may both be associated with changes in the DNA sequence, whether through transposon insertions, tandem duplications, or DNA sequence variation in promoter regions. Such alterations to DNA can cause heritable variation in epigenetic regulation, and thereby be the basis of the evolution of such regulation.

Although Turck and Coupland show that differences in DNA methylation and stability of histone modifications can lead to distinct changes in plant life histories, Herman et al. directly address the adaptive value of epigenetic stability by reviewing theoretical

insights regarding the evolution of phenotypic plasticity both within and across generations. Theoretical treatments of the adaptive value of plasticity suggest that the degree of epigenetic stability or reversibility is likely to be under selection, when changes in epigenetic state cause changes in adaptively relevant phenotypes. They argue that the adaptive value of epigenetic stability is expected to depend on scales of environmental variation and predictability, accuracy of environmental cues and the ability to respond to them, and modes of selection, such as density/frequency dependence and hard/soft selection. One proposition is that epigenetic changes that persist for multiple generations are unlikely to have an adaptive advantage beyond changes that persist for a single generation of parent–offspring transmission, and may actually be less adaptive—unless there is a cost of epigenetic resetting. Thus, costs of epigenetic resetting are an interesting target for investigation when epigenetic changes persist for multiple generations.

Next, Verhoeven and Preite examine epigenetic variation specifically in asexual organisms. Because asexual organisms can reproduce without meiosis, when many epigenetic marks are reset, the stability of epigenetic changes may differ between sexual and asexual organisms. Moreover, because sexual populations can acquire genetic variation through gene flow and recombination, but asexual populations do not, the adaptive value of epigenetic variation may differ between asexual and sexual organisms, with stable epigenetic changes contributing phenotypic variation to asexual populations that would otherwise not be present. They review evidence for differences in epigenetic stability between sexual and asexual organisms, evidence for epigenetic variation within natural populations of asexual organisms, and evidence of epigenetic differentiation between populations inhabiting different environments. What is apparent is that, while trends suggest that epigenetic variation may be adaptively significant in asexual populations, few studies have directly tested the fitness consequences of known epigenetic changes. Moreover, none have specifically sought to directly compare the stability of epigenetic changes and the adaptive value of such stability in sexual versus asexual organisms. The review exposes a rich area for future research on natural selection on epigenetic changes and their stability, especially within the context of differences in mating system.

Schlichting and Wund's review pertains to what can be considered an extreme case of the evolution of stability of gene expression: when environmentally induced epigenetically (broadly defined) controlled changes in phenotypes evolve into stable, genetically determined phenotypes via genetic accommodation and the evolution of reaction norms. These authors review empirical evidence for different mechanisms of genetic accommodation, what ecological conditions favor the transition from environmentally induced to stably inherited phenotypes, and more generally

how phenotypic plasticity influences evolutionary trajectories. As such, the review provides a link between former analytical treatments of genetic accommodation via the evolution of reaction norms, with analysis of factors that influence how labile gene expression can evolve into gene-expression states that are stably inherited across generations—that is, the evolution of epigenetic stability.

Finally, Furrow and Feldman provide a new theoretical examination of the evolution of epigenetic regulation. They show that the degree of environmental variation and the degree of genetic variation at epigenetically modified loci are both key parameters that determine the epigenetic regulatory properties that evolve. They also show that the rate of fluctuation of environments influences how faithfully epigenetic modifications are predicted to be inherited across generations.

Combined, these articles support the view that epigenetic stability itself may evolve, in part, through changes in the DNA sequence of genes involved in regulating methylation and histone modification or, in a more fine-tuned manner, in promoter regions of epigenetically regulated genes in the form of transposons, tandem duplications, or targets of modified histones. The rate of evolution of epigenetic regulation and its stability is predicted to be highly sensitive to the degree of such genetic variation.

These articles therefore bring into focus the genetic and ecological basis of epigenetic stability per se. Natural variation in epigenetic stability provides a useful tool for such investigations, and methods such as Quantitative Trait Loci analysis and Genome-Wide Association Studies could be effectively applied to this question—with epigenetic stability as the target of surveys of natural variation. Studies that seek to analyze the genetic and environmental basis of variation in epigenetic stability, and to quantify that variation in natural populations, would provide essential information both on the molecular and environmental processes that determine epigenetic stability as well as the evolutionary processes that shape it. Identification of loci associated with natural variation in epigenetic stability would also provide valuable resources for both genetic and ecological studies of adaptation. Such studies have the potential to quantify selection on stable versus unstable variants in different ecological contexts, including quantification of potential costs of epigenetic reversibility.

The other recurrent theme of this collection is that studies of the molecular genetics of epigenetic regulation are not always conducted within the context of observable whole-organism phenotypes, and studies of the adaptive significance of plastic phenotypes have not identified the molecular basis of the phenotypic changes that likely depend on changes in gene expression. What is needed are studies of epigenetic variants that have been characterized at the molecular level, the phenotypic level, and the adaptive level; otherwise put, we need studies of adaptively plastic phenotypes that have been genetically and epigenetically

characterized down to their molecular basis. Only then can we address the adaptive significance of epigenetic changes and their stability.

Once the adaptive value of epigenetic stability is the focus of investigation, it is apparent that multigenerational epigenetic inheritance may not actually be adaptive in itself. To the extent that it is observed, it may indicate costs or constraints on epigenetic resetting. Discovering potential sources of such costs of and constraints on epigenetic resetting could be a new focus for studies of epigenetics. Moreover, examples of genetic assimilation, whereby formerly environmentally induced phenotypes evolve to become stably expressed without the environmental stimulus, could provide especially interesting cases in which to study ecological and genetic conditions under which stably inherited epigenetic changes are most likely to be adaptive.

The observed variation in epigenetic stability within individuals, within populations, and among species provides the opportunity to study the adaptive significance and underlying genetic

and ecological basis of epigenetic stability. This stability is likely to be under selection, just as phenotypic plasticity and maternal effects are under selection. Epigenetic stability is itself a phenotype worth focusing on, both in terms of its molecular basis and its adaptive consequences.

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