COMMENTARY

PERSPECTIVES

EVOLUTION

Divergent destinies of polymorphism

Lizards maintain or lose color variation through interactions between genetics, selection, and plasticity

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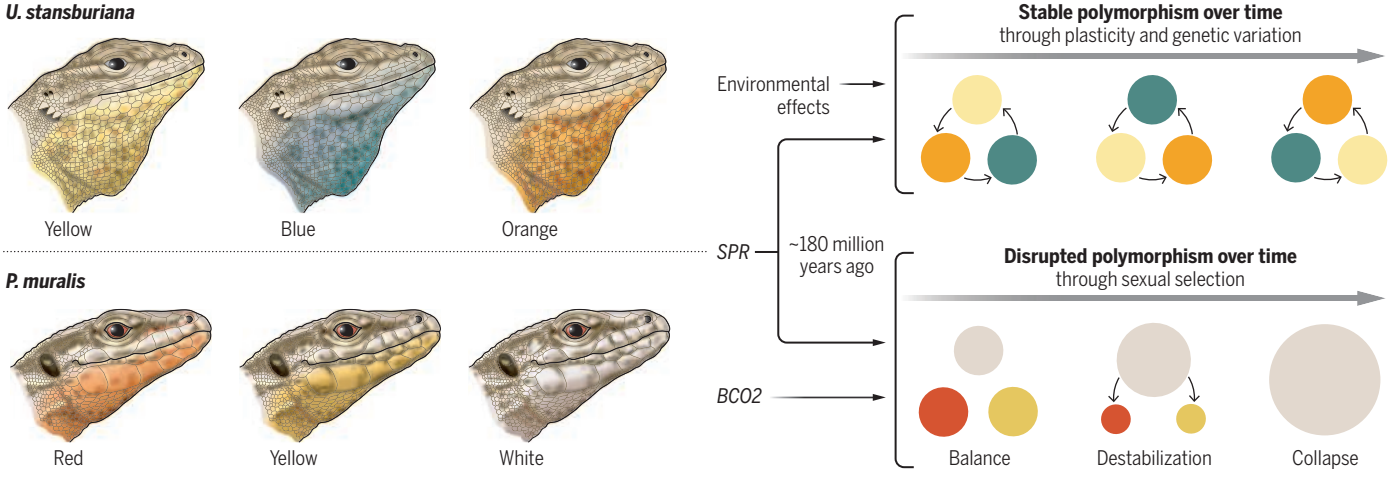
Understanding why polymorphic traits—color, shape, or behavior differences across individuals—persist within a species is a long-standing challenge. Such variation is expected to disappear as selection favors a single optimal form. Yet despite this expectation, polymorphism occurs frequently across the tree of life. Geneticist Theodosius Dobzhansky argued that diversity could be actively maintained through "balancing selection," which prevents genetic variants from becoming dominant or being lost (*1*). Early empirical studies did not clearly support this model (*2*–*4*), but evidence for balancing selection has since accumulated (*5*). Nevertheless, the persistence of polymorphisms often depends on complex, dynamic interactions between genes, phenotypes, and environments that are challenging to study (*6*). On pages 64 and 69 of this issue, Uller *et al.* (*7*) and Corl *et al.* (*8*), respectively, report on the mechanisms that govern the origins, maintenance, and loss of color variation in lizards.

Dobzhansky proposed that heterozygote advantage (benefits of having two variants of a gene, or alleles), frequency-dependent selection (the frequency of a trait in a population depends on that of other traits), and environmental heterogeneity promoted balancing selection (*1*). Several real-world estimates of trait fitness seemed too context-dependent and unstable to sustain balancing selection (*9*–*11*), but other observations supported its existence. For example, despite the burden of sickle-cell anemia in people with two copies of the sickle-cell allele of hemoglobin, this variant persists at high frequencies in some regions because people with only one copy have increased resistance to malaria. This example supported Dobzhansky's hypothesis while highlighting the population and ecologically contingent nature of the mechanisms that maintain polymorphisms. Is balancing selection alone sufficient to maintain polymorphisms in nature? Why some polymorphisms persist whereas others vanish and how ecological, genomic, and developmental processes interact to sustain or erode this variation are also unclear.

Coloration has long fascinated evolutionary biologists because it is a visually conspicuous trait often associated with ecological, reproductive, and behavioral fitness. Recent genomic advances have identified specific loci underlying pigment variation, as well as their relevance across diverse species. Corl *et al.* focused on the iconic color polymorphism of the side-blotched lizard, *Uta stansburiana*. In this species, male individuals have alternative mating strategies that correspond to the color of their throat—orange, yellow, or blue—and these strategies are maintained through frequency-dependent selection (*12*, *13*). Corl *et al.* found that allelic differences at the sepiapterin reductase (*SPR*) gene, coupled with environmentally modulated plasticity in gene expression, generate and maintain polymorphism (see the figure). Plasticity, in which a genotype produces different phenotypes (observable characteristics) depending on the environment, can suppress variation under selection or expose this variation to new selective filters. Contradicting long-standing assumptions that three distinct genetic variants underlie throat color, Corl *et al.* found that two *SPR* alleles produce two alternative color states, whereas the third color state arises through plasticity. This finding reframes a textbook example of a stable polymorphism and

One gene, two outcomes

Throat color polymorphism in *Uta stansburiana* and *Podarcis muralis* lizards is encoded by the same gene, sepiapterin reductase (*SPR*) [coupled with β-carotene oxygenase 2 (*BCO2*) in *P. muralis*], despite the distant relationship of these species. In *U. stansburiana*, the polymorphism is maintained in the population through the influence of plasticity alongside genetic variation. By contrast, in *P. muralis*, strong sexual selection for a new suite of body traits disrupted the maintenance of the previously balanced polymorphism, so only one throat color remained. The sizes of the circles in the image represent the proportion of lizards with each throat color in the population.



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illustrates how balancing selection and plasticity may interact to maintain polymorphisms at a stable equilibrium in nature.

Uller *et al*. analyzed the common wall lizard, *Podarcis muralis*. In this species, an orange, yellow, and white color polymorphism maintained for millions of years by variation at two genes, *SPR* and β-carotene oxygenase 2 (*BCO2*) (*14*), has recently collapsed. The emergence and rapid spread of the "nigriventris syndrome"—characterized by darker and greener body color, larger body and head size, and dominant behavior—apparently disrupted the equilibrium that once maintained color variation. Sexual selection on this phenotype seems to have overridden the dynamics that stabilized the ancestral polymorphism. As the syndrome spread, the polymorphism disappeared, and a single white form was fixated across populations. Notably, genomic analyses indicate that the loci underlying nigriventris traits do not overlap with the genomic regions that determine the orange and yellow forms. This finding suggests that the loss of color polymorphism associated with selection of nigriventris traits was not driven by genetic linkage (when genes are affected by selection at a locus nearby in the genome). Instead, this outcome seems to be due to shifts in ecology and sexual selection that disrupted the mechanisms that had previously stabilized this polymorphism.

The studies by Corl *et al*. and Uller *et al*. show contrasting examples of how plasticity and selection on a shared genetic substrate may promote or erase morphological and genetic diversity. In *U. stansburiana*, plasticity allows color and behavior to shift with environmental conditions, supporting the coexistence of multiple reproductive strategies and polymorphic phenotypes. In *P. muralis*, however, sexual selection favored the emergence of a new phenotype that swept rapidly through populations, disrupting the equilibrium that had maintained polymorphism.

The *SPR* gene underlies color variation in both lizards, whose lineages diverged ~180 million years ago. This shows that the mechanisms that modulate coloration have been highly conserved over time. However, despite this shared genetic basis, plasticity and genetic variation at *SPR* support long-term color diversity in one system, whereas variation is overwritten by sexual selection in the other system. This difference shows that evolutionary paths depend on the genes involved but also on their plasticity and behavioral, social, and ecological contexts.

The findings of Corl *et al*. and Uller *et al*. lend weight to a more integrative model of how polymorphisms arise and are maintained. Rather than being static genetic states, polymorphisms may represent transient outcomes of dynamic interactions between genomes, plasticity, behavior, and ecology. The long-term maintenance of polymorphisms is also likely to result from these dynamic interactions and is unlikely to be explained by the sole effects of balancing selection on genetic variation. The next frontier will be to understand how multiple processes interact to determine whether polymorphisms arise, persist, or collapse. □

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CANCER

Genetic resistance to leukemia

A genome-wide association study identifies a genetic variant that reduces the risk of leukemia

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Noninheritable (somatic) mutations occur frequently in the tissues of mammals and can accumulate over their lifetime. Advances in the sensitivity and efficacy of DNA sequencing technologies have enabled the early detection of somatic mutant cell populations in otherwise healthy people. Mutations in stem and progenitor cells that impart a competitive advantage over nonmutated cells cause the mutated population to grow by clonal expansion. In blood, this process is called clonal hematopoiesis and is associated with an increased risk of leukemia, as well as cardiovascular and inflammatory diseases. Although multiple causes and mechanisms of clonal hematopoiesis have been identified, the factors preventing or delaying this process have been more difficult to pinpoint. On page 52 of this issue, Agarwal *et al*. (*1*) report a genome-wide association study (GWAS) that identified an inheritable genetic variant that protects against clonal hematopoiesis and its progression to leukemia.

The hematopoietic system, which generates blood cells, is easy to sample. It has, therefore, become a focus of clonal expansion studies, which have led to the identification of aging-associated clonal hematopoiesis of indeterminate potential (CHIP). CHIP is defined by the presence of somatic mutations in at least one gene associated with cancer in white blood cells (the most frequently mutated genes being DNA methyltransferase 3 α, or *DNMT3A*; tet methylcytosine dioxygenase 2, or *TET2*; and ASXL transcriptional regulator 1, or *ASXL1*), with a proportion of cancer-associated variant copies of a gene (variant allele frequency) of at least 2% in blood and bone marrow cells, and in the absence of another blood disorder. Most CHIP mutations give a competitive advantage to hematopoietic stem cells (HSCs) over normal HSCs, particularly in eroded and aged hematopoietic systems exposed to inflammation (*2*). The size of the mutant clone population is a major predictor of poor outcomes in CHIP carriers (*3*). In particular, CHIP is associated with a 10- to 12-fold increased risk of developing myeloid malignancy (*4*), a group of blood cancers. Notably, mutant HSC populations can stagnate and even shrink in an individual over a long period of time (*5*). Environmental inherited factors that prevent or slow mutant clonal expansion may explain these variations.

Agarwal *et al*. performed a GWAS meta-analysis based on a population-based search for associations between variant genomic regions and CHIP in three cohorts comprising 43,619 CHIP carriers and 598,761 controls. They sought to identify inheritable genetic regions associated with protection against CHIP. A common DNA sequence at the 17q22 locus was associated with a 16% or 29% reduced risk of CHIP when one or two copies (alleles) of the sequence were present, respectively, and with a 20% reduced risk of myeloid malignancy when one allele was present. Further analysis