Received: 14 September 2021 | Accepted: 17 December 2021

DOI: 10.1002/ajb2.1822

ON THE NATURE OF THINGS: ESSAYS

# The quiet evolutionary response to cellular challenges

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**KEYWORDS**
adaptive evolution, evolution, evolutionary cell biology, genome scan, meiosis, polyploid, protein evolution, trait maintenance

Like many evolutionary geneticists, I am fascinated by genes underlying potentially adaptive traits that differentiate populations. While such traits are obviously important, I have, in part through my own work on adaptation to whole-genome duplication, become interested in traits that *do not* differ in obvious ways between populations. There is good evidence that such traits are also important and can leave signatures of selection in genomes. This idea is not a new revelation—in the vast literature on protein biophysics there is keen awareness that evolutionary adjustments are often needed to keep essential proteins functioning in new conditions. However, this concept has not been employed extensively outside that field to, for example, interpret genome scans for selection. Things written off as false positives in genome scans may actually be critical for adaptation; evolutionary adjustment of proteins underlying conserved traits may explain otherwise puzzling footprints of selection and may help explain why adaptation is often multigenic. The general conclusion that selection can act on trait maintenance rather than change, is likely broadly relevant.

## POLYPLOIDY AND "TYPE A" TRAITS

Polyploids arise from whole-genome duplication, either involving genetically similar chromosomes (autopolyploidy) or distinct sets of chromosomes (allopolyploids) (Ramsey and Schemske, 1998). One strength of autopolyploidy as a model for adaptive evolution is that we can directly compare diploids, lab-generated neo-autotetraploids, and evolved (established) autotetraploids (Ramsey and Schemske, 2002; Hegarty et al., 2013; Bomblies, 2020); put more generally, we are directly comparing ancestral, "challenge", and derived states (Figure 1). Many cellular traits are altered immediately by genome duplication, particularly cell size, which affects a wide range of physiological traits (Doyle and Coate, 2019). A comparison of diploid, neo-tetraploid, and evolved tetraploid plants (67 species) shows that, in many cases, cellular traits that are consistently affected by genome duplication (i.e., differ between diploids and neo-tetraploids), are ultimately not dramatically different when comparing diploids and evolved autopolyploids, suggesting that over evolutionary time they return to a diploid-like state (Bomblies, 2020). Thus, neo-polyploids appear to represent a transient "challenge" state that necessitates evolutionary retuning to return many traits to the ancestral state, an evolutionary pattern I previously called "Type A" (Bomblies, 2020; Figure 1). It is now also clear that genes encoding proteins that affect traits showing this "Type A" pattern, can be outliers in genome scans for selection in tetraploids (Hollister et al., 2012; Yant et al., 2013; Bomblies, 2020).

Meiotic recombination in *Arabidopsis arenosa* provides one empirical example of a "Type A" trait: We previously proposed that a reduced recombination rate might be important in meiotic stabilization of autopolyploids because it can prevent formation of deleterious multivalents (Bomblies et al., 2016). This idea was inspired by our finding that meiotic genes that affect recombination rate show signatures of selection in autotetraploid *A. arenosa* (Hollister et al., 2012; Yant et al., 2013; Wright et al., 2015). It was then initially puzzling to find that recombination rate does not in fact differ significantly between diploid and tetraploid *A. arenosa*. However, when we examined neotetraploids, we found that these have increased

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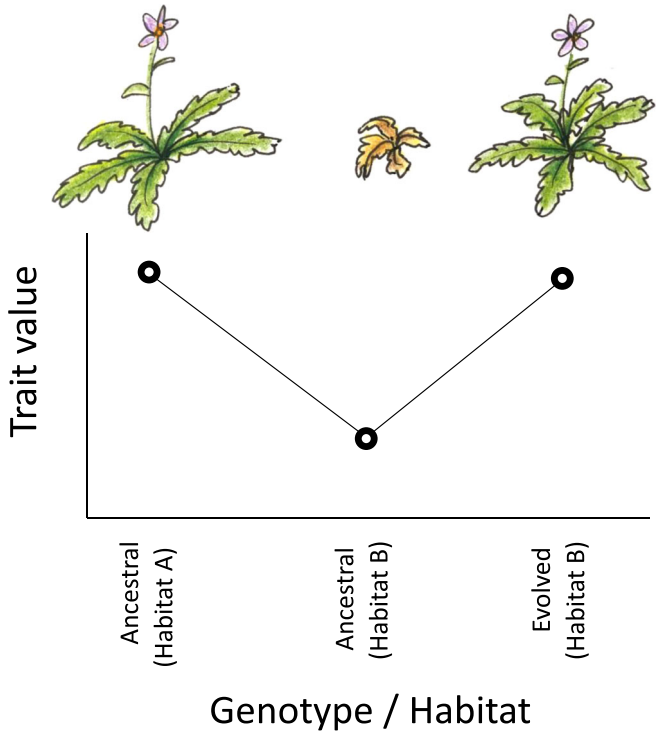


**FIGURE 1** "Type A" traits are those that do not cause obvious phenotypic differences between ancestral and derived types in their native habitats (habitats A and B, respectively). Only when the unevolved (ancestral) type adapted to habitat A is exposed to the "challenge" situation (habitat B; middle), to which the evolved type is adapted, does it become clear there is a difference. Thus, such traits will not show up as differences between populations in obvious ways unless we also test the "challenge" situations

recombination relative to both diploids and evolved tetraploids (Morgan et al., 2021). Thus, the signatures of selection on meiotic genes in tetraploids likely reflect a response to novel challenges caused by genome duplication, rather than diploid and tetraploid *A. arenosa* having distinct optima. The adaptive value of the changes in these proteins thus seems to be that they allow the phenotype to play out in a broadly unchanged manner, despite the altered cellular context, something the proteins encoded by diploid alleles are not capable of (Morgan et al., 2020, 2021).

Importantly, the above observations highlight that when we just compare the phenotypes of ancestral (i.e., diploid) and derived (i.e., evolved tetraploid) states, a clear explanation for why some genes might be under selection does not readily present itself. The existence of such "type A" traits raises the question of how much evolutionary change we might not be explaining when we overlook traits that do not differ between populations. As an aside, it is important to recognize that whether we consider something "different" depends on what we understand as a "trait"—if in this example the trait is recombination frequency, diploids and tetraploids do not differ, but if it is molecular function of the underlying proteins, then there are differences (Morgan et al., 2020).

## GENOME SCANS AND THE POTENTIAL FOR A RELATIVELY UNBIASED VIEW OF ADAPTATION

High-throughput sequencing has revolutionized how we can understand adaptation. We can now "scan" entire re-sequenced genomes of alternately adapted types, and the goal of explaining many genetic changes that differentiate populations is at least theoretically within reach. While this approach has already given important insights, there are still uncertainties, for example, which tests to use, how test statistics are affected by population structure and history, where to draw cutoffs, and, not least, how to interpret genes that show up on lists without biasing ourselves to favor obvious candidates (Tiffin and Ross-Ibarra, 2014). In choosing which genes to get excited about, there is an inherent bias: we often gravitate to candidate genes we can explain by traits that differ between populations. For example, if flowering time differs between two populations, a previously known flowering time gene will jump out from a list, even if that list contains hundreds of other genes. Much more puzzling would be, for example, a subunit of polymerase II or a tubulin gene. But while the corresponding traits may not differ, the processes these proteins are involved in are challenged by factors (like temperature) that do vary among habitats, and thus we may be detecting the evolutionary footprint of re-tuning of these essential processes to maintain function in a novel context.

## ADAPTIVE EVOLUTION MIGHT COMMONLY INVOLVE "TYPE A" PATTERNS

Though there can be false-positives in genome scans, I think that evidence for selection on genes where associated traits remain unchanged could in many cases be real, arising from something analogous to what we see in polyploids. This is something that the protein evolution field is keenly aware of: Cellular challenges are common and important factors in evolution since biophysical properties of proteins (e.g., stability, folding, interactions, aggregation) are affected by factors such as temperature, redox status, or pH (e.g., Zavodszky et al., 1998; DePristo et al., 2005). Indeed, there is evidence that even relatively small differences in thermal environment can cause selection to favor substitutions that cause amino acid changes that affect the stability or flexibility of proteins. Interestingly, selection in such cases often targets only part of the proteome, at least in the short to medium term (Zavodszky et al., 1998; Gu and Hilser, 2009; Saarman et al., 2017). It seems a general property of many essential proteins to undergo "functional maintenance" evolution, helped by the fact that the scope of amino acid changes that stabilize or destabilize proteins to temperature is vast, much larger than those that directly cause functional changes (e.g., DePristo et al., 2005; Saavedra et al., 2018). Thus, in interpreting signatures that adaptive evolution

leaves in genomes, we cannot ignore biophysics or the importance of functional maintenance. As an organism shifts to a new environment, a substantial fraction of its proteome and many critical cellular processes may be perturbed. Knowing this, many patterns we see in lists of genes putatively under selection from genome scans become more predictable: we would *expect* to find many genes that are relatively subtly altered, genes that encode "core cellular process" proteins, and genes that encode proteins controlling traits that—at least in the gross sense—do not differ between populations.

The kind of genetic retuning to an altered environment envisioned here has some parallels with key features with the Red Queen hypothesis, where genes evolve rapidly in response to factors such as pathogens or selfish genetic elements, also without causing obvious phenotypic change (e.g., McLaughlin and Malik, 2017; Brockhurst et al., 2014). While the Red Queen dynamic can similarly drive adaptive gene evolution to initiate cell-level changes without an obvious larger-scale phenotypic effect, a key distinction is that the evolution of genes underlying the core cellular traits envisioned here do not involve a constant "running" evolution or coevolution as envisioned in the Red Queen hypothesis.

## OUTLOOK

"Type A" evolutionary trajectories that do not lead to clear phenotypic changes may be responsible for a large amount of adaptive evolutionary change. The need to retune multiple essential protein "machines" without damaging function may also be part of the explanation for why adaptation is often multigenic. Of course, maintenance traits can be hard to detect, since obvious phenotypic differences between ancestral and derived forms are lacking. Something comparable to the power of the diploid–neopolyploid–evolved polyploid comparison would be to investigate (at the cellular or protein level) why non-adapted genotypes fail (or fail to thrive) when exposed to the habitat of an adapted genotype and how these problems are "fixed" in adapted genotypes (Figure 1). A challenge is that it can be hard to determine exactly what the problem is, since cellular or protein failures may cause global and seemingly nonspecific effects, and multiple processes may be affected. What exactly to measure is daunting in such cases (it could be anything), but choices can be guided by what we find in genome scans. What is then needed is a careful micro-evolutionary implementation of "evolutionary cell biology" (Lynch et al., 2014). With such an approach we can answer questions such as: How common or important are "Type A" traits in adaptation? Are some adaptations (e.g., to temperature or polyploidy) that are more prone to show this kind of "Type A" pattern than others? Can "unchanging" traits explain some of the unexplained in genome scan lists? Do the types of changes that accumulate in genes fundamentally differ between "Type A" and other types of evolution?

## ACKNOWLEDGMENTS

The author thanks two anonymous reviewers for generous feedback and suggestions, Prof. Alex Widmer (ETH Zürich, Switzerland) and Dr. Christine Faulkner (JIC, Norwich, UK) for helpful discussions and critical reading of the manuscript, and the Bomblies lab for helpful discussions. The lab's work on meiotic adaptation to habitat is funded by a Swiss National Science Foundation grant (SNSF; grant 310030_192671). Open access funding provided by Eidgenossische Technische Hochschule Zurich.

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K.B. conceived of, wrote, and edited the manuscript.

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**How to cite this article:** Bomblies, K. 2022. The quiet evolutionary response to cellular challenges. *American Journal of Botany* 109(2): 189–192. https://doi.org/10.1002/ajb2.1822