

Predicting the basis of convergent evolution

Convergent adaptive traits do not always arise from the same genetic changes

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Repeated evolution of similar traits in organisms facing the same ecological challenges has long captured the interest of evolutionary biologists (1–4). Naturally occurring examples of “convergent evolution” offer new opportunities to ask about predictability in evolution. Do complex genomes mean that there are endless possibilities for adapting to an ecological challenge? Or must evolution target the same genes, or even the same amino acids in the same proteins, in order to increase the fitness and therefore survival of different species facing similar challenges? Natarajan *et al.* (5), on page 336 of this issue, provide an example of an integrated approach to answer these questions. By using a combination of genetic data with experimental tests, they show that evolution of a new protein function in response to low-oxygen, high-altitude conditions can occur through different genetic mechanisms across a wide diversity of avian species living at high and low elevations.

Hemoglobin proteins found in different vertebrate species living either at low or high altitudes provide classic examples of convergent protein evolution. Natarajan *et al.* sequenced, expressed, and measured oxygen affinity for hemoglobins isolated from 56 species of birds clustered into related low- and high-altitude-species pairs. They found convergent evolution of high-oxygen affinity in proteins from high-elevation species. They then determined the genetic basis for this functional shift in hemoglobin oxygen affinity. Evolution of new protein functions is thought to be under biophysical constraint, limiting genetic changes to certain portions of proteins, or to specific amino acid substitutions (6, 7), potentially making evolution largely predictable. On the other hand, evolutionary trajectories have been shown to be historically contingent, with possible evolutionary paths being dependent on the ancestral starting point (8, 9), resulting in relatively unpredictable, distinct genetic changes in different lineages subjected to similar evolutionary pressures.

Were there common genetic changes in the hemoglobin from high-elevation-avian species? Amino acids were identified that

diverged between low- and high-elevation-species pairs and were associated only with high-altitude environments. Although many amino acid differences were found between species pairs, only four were replicated in different lineages. Two of these positions are known to play key roles in protein function, yet these changes occurred in only two or three species pairs. The single most common substitution was found primarily in hummingbird species pairs but was also seen in one species of flowerpiercers. Was this change responsible for the convergent evolution of high-oxygen affinity? Natarajan



Convergent evolution of high-oxygen affinity in hemoglobin from high-altitude-dwelling bird species (including some hummingbirds, shown) occurred through different amino acid substitutions. Historical contingency limits predictability.

jan *et al.* introduced the substitution from high-altitude-adapted species into a reconstructed ancestral hummingbird hemoglobin protein and found an increase in oxygen affinity. However, when they introduced the same substitution into more ancient avian hemoglobins, there was no change in protein function. Additional genetic differences prevented this substitution from having the same functional consequences in more distant ancestral backgrounds. They concluded that historical contingency constrained the potential evolutionary pathways for hemoglobin adaptation to high-altitude conditions.

Furthermore, a much wider taxonomic sampling, including perching birds and waterfowl, found many distinct and no common genetic substitutions in high-oxygen-affinity hemoglobins among the other high-altitude-adapted birds. By sampling many pairs of

widely divergent avian lineages, Natarajan *et al.* discovered that although most high-altitude-adapted birds have hemoglobin with higher-oxygen affinity, this convergent evolution in protein function resulted from different genetic changes.

Evolutionary biologists have identified cases of predictable convergent evolution involving adaptations in single proteins (6, 7), as well as cases in which evolutionary paths were less predictable because of historical differences in genetic backgrounds (9). The careful examination of convergent hemoglobin evolution across an extensive taxonomic scale by Natarajan *et al.* provides an elegant example of how the predictability of genetic evolution may change depending on the scale of the investigation.

They found contrasting results concerning genetic convergence depending on how closely related the species were. Among many hummingbirds, a single substitution was associated with high-altitude adaptation, and that amino acid substitution was sufficient to change hemoglobin oxygen affinity. However, no genetic convergence was seen between more distantly related high-altitude-adapted birds.

The genetic basis of convergent evolution may only be predictable when looking at the appropriate scale. Smaller-scale convergence between closely related organisms or specific proteins may occur through predictable genetic changes. Larger-scale convergence across taxonomic orders may only be predictable at larger genetic scales, targeting whole proteins or functional complexes (10, 11). ■

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