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Digest: Know your poison: Predictable molecular changes confer toxin resistance in snakes*

Kalina T. J. Davies[1,2]

[1]*School of Biological and Chemical Sciences, Queen Mary University of London, London E1 4NS, United Kingdom*

[2]*E-mail: k.t.j.davies@qmul.ac.uk*

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The repeated independent evolution of similar features in divergent lineages, a process known as convergent evolution, has long been a source of fascination for both naturalists and evolutionary biologists. Until recently, this active area of research had been focused principally on the evolution of physical characteristics associated with novel traits (e.g., the independent evolution of wings in birds, bats, and pterosaurs).

Since molecular mutations are assumed to be largely random, we might not expect similar substitutions in unrelated genomes (even of phenotypically convergent taxa) to occur more frequently than would be expected by chance. However, other factors such as genetic drift, selection, and recombination also play a role in sequence evolution. The advent of high-throughput sequencing technologies and the subsequent increase in data has allowed molecular biologists to study genetic variation across progressively larger numbers of taxa and loci. Consequently, it has become clear that convergent molecular evolution does indeed occur. Furthermore, researchers have detected several forms of convergent molecular evolution, such as shared selection pressures acting on the same gene (e.g., Chikina et al. 2016) and identical amino acid substitutions at the same locus in unrelated taxa (e.g., Li et al. 2008).

In this issue, Hague et al. (2017) used an elegant predator–prey study system to investigate the historical order of molecular substitutions associated with convergent adaptation of toxin resistance in two lineages of common garter snakes (*Thamnophis sirtalis*). Both lineages developed resistance to tetrodotoxin (TTX), a deadly neurotoxin found in the snakes' prey, Pacific newts (*Taricha* spp.). Toxin resistance in this snake species is largely mediated by amino acid substitutions in the skeletal muscle sodium channel ($Na_V1.4$) that prevent TTX from binding (Hague et al. 2017).

The authors used a combination of population genetic and phylogenetic techniques to reconstruct the evolutionary history of amino acid substitutions in $Na_V1.4$ across geographically widespread snake populations. Phylogenetic reconstructions indicate that TTX resistance in the two snake lineages evolved independently, and occurred in both instances through an amino acid substitution of isoleucine to valine at position 1561 (I1561V) of $Na_V1.4$. Through the use of ancestral sequence reconstruction, the authors were able to infer that the I1561V change preceded the other nonshared substitutions found in the protein. This result suggests that the presence of the I1561V substitution in $Na_V1.4$ may be critical as the first-step mutation to TTX-resistance. Therefore, it appears that TTX-resistance in garter snakes evolved via a certain order of substitutions.

Previous studies hypothesized that structural, functional, and mutational biases may all limit the number of possible routes to adaptation (for review, see Storz 2016). In the case of $Na_V1.4$-mediated TTX resistance, Hague et al. (2017) suggest that permissible substitutions may be limited, as those that may be beneficial in terms of toxin resistance must also not disrupt the sodium channel's function. Recent molecular studies of functional convergence in the haemoglobin of high-altitude adapted bird species have also highlighted the importance of genetic background and the context-dependent effects of historic mutations (Natarajan et al. 2016).

Despite the growing number of cases of molecular convergence linked to phenotypic adaptations, molecular evolution

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remains far from predictable. For example, Eastern hog-nosed snakes are also TTX-resistant, but not via substitutions in $Na_V1.4$ (Feldman et al. 2016), suggesting that we have much to learn concerning the factors governing convergent molecular evolution.

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