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Convergence and parallelism reconsidered: what have we learned about the genetics of adaptation?

Jeff Arendt[1] and David Reznick[2]

[1] Department of Biology, University of California – Riverside, 900 University Avenue, Riverside CA 92521, USA
[2] Department of Biology and Center for Conservation Biology, University of California – Riverside, 900 University Avenue, Riverside CA 92521, USA

Biologists often distinguish 'convergent' from 'parallel' evolution. This distinction usually assumes that when a given phenotype evolves, the underlying genetic mechanisms are different in distantly related species (convergent) but similar in closely related species (parallel). However, several examples show that the same phenotype might evolve among populations within a species by changes in different genes. Conversely, similar phenotypes might evolve in distantly related species by changes in the same gene. We thus argue that the distinction between 'convergent' and 'parallel' evolution is a false dichotomy, at best representing ends of a continuum. We can simplify our vocabulary; all instances of the independent evolution of a given phenotype can be described with a single term – convergent.

Patterns in the genetics of adaptation

A recent study of the evolution of pigmentation in beach mice sheds light on a long-standing assumption in evolutionary biology concerning the distinction between convergent and parallel evolution. Hoekstra *et al.*'s [1] primary result was to functionally verify that a single nucleotide substitution in the gene encoding the melanocortin-1 receptor (*Mc1r*) had a major role in the evolution of lighter coats in mice that inhabited sand dunes on Florida's Gulf Coast (Figure 1). This study represents yet another observation in a remarkable tale of convergent evolution because this same gene has been implicated in the evolution of pale or dark coloration in lizards [2], several birds [3,4], various felids [5], pocket mice [6], and the black bear [7], and has even been implicated in the evolution of blonde wooly mammoths [8]. Perhaps a more surprising result of this study, reported inconspicuously at the end of the article, was the independent evolution of light coat coloration in a geographically isolated population of pale beach mice found on the dunes of Florida's Atlantic coast. Because the Atlantic beach mice are a different population of the same species, inhabit a similar selective environment, and have an extremely similar pigmentation phenotype, and because *Mc1r* has been implicated in pigment variation in so many other organisms, one might expect that *Mc1r* would also have a primary role in the evolution of pale coloration in the Atlantic population. However, the *Mc1r* mutation implicated in light coloration on the Gulf Coast was not present in the Atlantic Coast mice. The molecular mechanism that caused the evolution of their pale pelage must lie elsewhere in the genome.

This simple result raises an important issue. We have long distinguished between the phenomena of parallel and convergent evolution as labels for the independent origin of phenotypic similarity among populations or species, respectively. Why make the distinction between parallel and convergent evolution? It is often assumed that if the same phenotype evolves multiple times independently within a given species or among closely related species then the same genetic and developmental pathways are responsible for the phenotypic similarity because the traits evolved from a similar genetic starting point [9,10]. This is often termed 'parallel evolution'. By contrast, when unrelated species achieve a similar phenotype, it is thought that the similarity often arises via different genetic and developmental pathways because the common phenotype evolves from such different genetic starting points [9,10]. This has, in turn, been defined as 'convergent evolution'.

It is enlightening to consider how these terms are currently used in the literature. A review of the use of the terms in 200 papers published since 2005 (Box 1) highlights that the distinction between parallel and convergent is most often defined solely by the taxonomic relationships between the groups being compared: 'parallelism' is applied to close relatives and 'convergence' to more-distant relatives. A smaller number of papers use parallel or convergent evolution in reference to whether the underlying genetic mechanisms that cause phenotypic similarity are the same (parallelism) or different (convergence), usually without regard to phylogenetic relationships. Current usage thus supports the argument that, in most peoples' minds, 'parallel evolution' refers to the evolution of similar phenotypes among close relatives and 'convergent evolution' refers to the evolution of similar phenotypes among distantly related organisms.

Some studies of the genetic basis of phenotypic similarity among close relatives do fit the expectation that the underlying genetic mechanism is the same [11]. As a consequence, some have argued that parallel evolution is a signal of genetic constraints [12–16]; similar phenotypes evolve in parallel simply because genetic and developmental constraints limit the organism to a few alternative

Corresponding author: Arendt, J. (Jarendt@ucr.edu).

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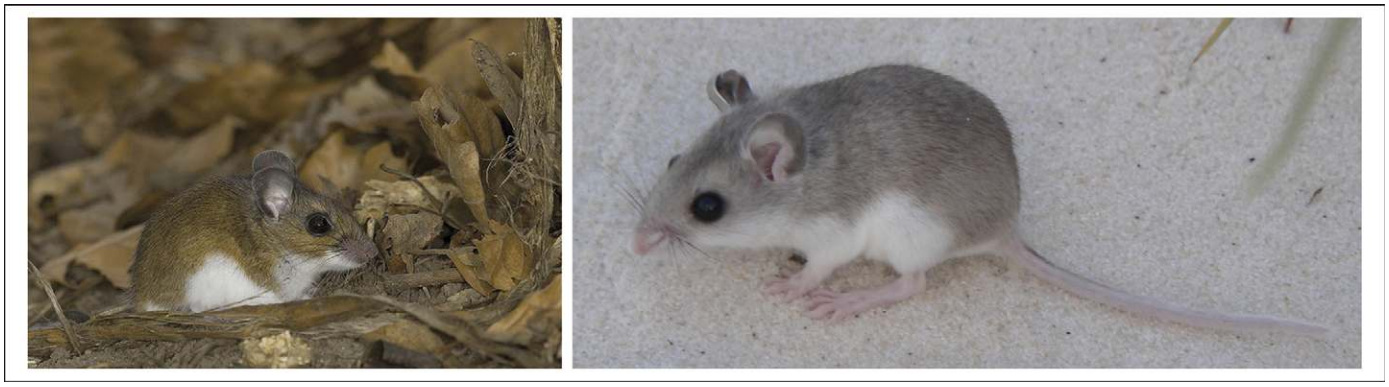

Figure 1. Color polymorphism in *Peromyscus poliotiotus*. A mutation in the *Mc1r* gene results in the lighter coloration of beach mice on islands along the Gulf Coast of Florida in comparison with the darker mainland mouse. Dark mouse photograph by Shawn Cary and light mouse photograph by Matt Falcy.

phenotypes [12,17,18]. Others argue that if multiple developmental pathways can lead to the same phenotype, then parallel evolution might instead reflect attaining the same phenotype via different genetic changes, even among closely related taxa [19–21] and therefore parallel evolution is a signal of adaptation. Until recently, these arguments have been made in the face of little or no empirical data because we did not have the ability to define the genetic basis of independently evolved phenotypic similarities. Our capacity to study the genetics of adaptation has expanded rapidly over the past two decades, leading to a growing number of studies that define the genetic source of these similarities. Given the growing amount of new data, the time has come to take stock of what we are learning about the genetics of adaptation, to consider whether or not the distinction between parallel and convergent evolution is valid and hence whether or not the use of these labels for the path to phenotypic similarity carries biological meaning.

Even though the number of cases where the genetic mechanisms have been uncovered is still limited, it is clear that the data do not support a distinction between convergence and parallelism associated with the taxonomic relatedness of the groups being compared: closely related organisms often evolve the same phenotype via different mechanisms and distantly related organisms often evolve the same phenotype via the same mechanism. A further issue that is implicit in our argument is that the genes responsible for the development of a phenotype are often parts of developmental networks rather than simple pathways [22], raising the question of how close is close enough to consider the roles of individual genes or genetic pathways to be the same or different.

Closely related taxa use different developmental pathways

Presumed examples of parallelism involve groups of organisms that are so closely related that the evolution of phenotypic similarity is assumed to be via a homologous developmental or genetic pathway. Such groups might be species within a genus, populations within a species or, in the extreme case of laboratory experiments, different replicates derived from the same clone. We begin with examples derived from studies of adaptive pigmentation.

As previously discussed, light-colored beach mice occupy the light-colored sand dunes on both the Gulf and Atlantic Coasts of Florida. In the Gulf Coast population, a single derived amino acid change in the coding region of *Mc1r* causes a reduction in *Mc1r* function leading to light-coloration; however this mutation was not present in the Atlantic beach mice that had a similar phenotype [1]. Closer examination of the *Mc1r* coding region did not identify any new mutations that cause light-coloration, suggesting that a completely different gene or genes are responsible for similar adaptive coloration [1]. A similar pattern is seen in the complete loss of pigment in Mexican cavefish (*Astyanax spp.*). Here, two unpigmented cave populations harbor deletions in the ocular albinism 2 (*Oca2,* GenBank accession number DQ232591) coding region, although not the same deletion, which suggests that although the same gene is involved, the loss of pigmentation has occurred independently in these two populations [23]. However, other populations of cavefish show full complementation (Box 2) for pigmentation loss [24], which argues that either different mutations in *Oca2* complement each other or, more likely, different genes are involved in the loss of pigmentation in different populations. Given that more than one hundred genes contribute to the production of pigmentation and that the disruption of many of them could result in the loss of pigmentation, there is potential for attaining the same phenotypic endpoint via many different pathways.

The 'gain' of pigmentation has been studied in populations of rock pocket mice (*Chaetodipus intermedius*) that recently invaded geographically distant lava flows in the southwestern U.S deserts [25,26], where melanic pelage provides protection from visual predators [27]. In one Arizona population, four linked amino acid mutations in *Mc1r* are perfectly associated with the melanic phenotype [6], but in three other lava-dwelling populations in New Mexico, the four derived mutations are absent and no new mutations in *Mc1r* are statistically associated with melanism [28]. As is the case with the Atlantic Coast beach mice, the mutation or mutations that cause increased pigmentation must lie somewhere other than in *Mc1r*. Clearly, in nature, independent populations can have different genetic solutions to similar ecological problems.

Examples of closely related taxa using different genetic solutions to solve similar ecological problems need not rest on cases where the specific molecular mechanisms have been elucidated. For example, several species and popu-

Box 1. Use of the terms 'parallel' and 'convergent' evolution

The phylogenetic and mechanistic aspects of parallel and convergent evolution are usually both incorporated in definitions of the terms, although which aspect is emphasized has changed over the years. For example, in the three editions of Futuyma's *Evolution* textbook [62]:

'Parallel evolution occurs when a feature evolves independently in closely related species, but how closely related they need be before it is parallelism rather than convergence is unclear and probably immaterial. (p. 143, 1st edition, 1979) That parallel evolution should be common is not surprising. If related species have similar patterns of development, they are likely to be modified in similar ways if subject to similar selection pressures.' (p. 145, 1st edition, 1979)

'Ideally, 'convergent evolution' described cases in which similar phenotypes have evolved by different developmental pathways, whereas 'parallel evolution' refers to independent developmental modifications of the same kind. Because related species have similar developmental programs, parallelism is frequent among closely related species.' (p. 295, 2nd edition, 1986)

'In convergent evolution (convergence), independently evolved features are superficially similar, but arise by different developmental pathways...Parallel evolution (parallelism) is thought to involve similar developmental modifications that evolve independently (often in closely related organisms, because they are likely to have similar developmental mechanisms to begin with).' (p. 110, 3rd edition, 1996)

What matters, however, is not the textbook definition but how a term is used in practice. We examined usage patterns by entering the key words 'parallel evolution' and 'convergent evolution' into Web of Science and examining the 100 most recent citations for each. Papers covered the past two years (March 2005 to March 2007). Of the 200 papers, 83 either were not biological in nature, were misidentified by the search engine, or used the terms in an unconventional way. Of the 117 remaining studies only one was found in both lists. In total, 72 used either term in a strictly phylogenetic fashion, meaning that clades were described as examples of parallel evolution if they were closely related (40 times) or convergent if the trait was considered to have evolved independently in different lineages (33 times), often without regard to relatedness. Only 44 papers referred to the underlying molecular or developmental mechanism. Of these, 27 used 'parallel' and 10 used 'convergent' evolution when the molecular mechanism was similar (i.e. the terms seem to be treated as synonymous) and 7 studies used 'convergent' evolution when the mechanism was different. On this basis, we conclude that the topic of parallel and convergent evolution remains one of great interest because we only had to go back to mid-2005 to find many references. In addition, the original definition of the term, which is based on morphology and relatedness, is in predominant use today, whereas the molecular definition is less likely to be used.

Box 2. Common methods for determining if the same genes underlie similar phenotypes

Hybrid complementation

This method relies on a genetic cross between diploid organisms each with derived phenotypes that are recessive. If the derived phenotype is due to the same gene in each population, then the hybrids will be homozygous at the causal locus and express the derived phenotype. If the derived phenotype is due to different genes, the hybrids will be heterozygous at the causal locus, express the dominant ancestral genes, and the hybrid will express the ancestral phenotype. Interpretation of the results might be complicated because different mutations at a single locus and even mutations at different loci might sometimes complement. Hawley and Gilliland [63] review common pitfalls of this method.

Quantitative trait loci (QTL)

This is statistical analyses of genome-wide molecular markers and phenotypes measured in progeny of controlled crosses to identify chromosomal regions contributing to phenotypic differentiation. QTL studies done in parallel can often determine if chromosomal regions harboring causal alleles are distinct. However, if the same chromosomal regions are implicated, determining if the same genes or mutations within that region are responsible for similar phenotypes is a considerable challenge. Studies of moderate sample size also run the risk of mis-identifying minor genes as having major phenotypic effects [64].

Gene expression

Macro-arrays make it possible to screen thousands of genes for changes in gene expression. Importantly, expression patterns represent a molecular phenotype, not a genotype. The expression level of a gene might be because of mutations in the *cis*-regulatory elements or in *trans*-regulatory genes that influence the expression of the causal gene. Thus, this approach alone does not directly test whether similar mutations are occurring or not.

Gene sequences

Candidate genes with known function can be sequenced directly. This approach requires a detailed knowledge of candidate loci and a method for functional verification. Because candidate genes must be examined one at a time, this approach is necessarily limited in scope. In addition, population structure can often cause spurious associations between genotype and phenotype and therefore must be taken into account [6].

Transgenes

A candidate gene is transferred into a host in which expression of the gene has been knocked-out. If the donor phenotype is induced, the candidate gene is probably responsible for that phenotype. This approach is similar to complementation except that test subjects might be reproductively isolated. To date, we know of only two studies using this approach to test parallel evolution [57,16].

lations of *Drosophila* adhere to Bergmann's rule, which states that body size increases with latitude. Larger body size has evolved independently in different species of *Drosophila* on three continents; however, the mechanism by which the increase in body size is achieved varies. Larger body size can be achieved by increasing the number of individual cells or by keeping cell number constant and increasing cell size, or by a combination of both processes. Different genetic mechanisms probably contribute to these different paths. In *D. melanogaster*, Australian [29] and European [30] body size clines depend solely on variation in cell number – larger flies have more cells, whereas in South America cell number and cell size contribute equally to body size variation [31]. In *D. subobscura,* two recent invasions of the New World have produced similar body-size clines. In this case, the South American cline resembles the native European cline with larger flies having more cells, whereas in the North American cline larger flies have the same number of cells but the cells are larger [32].

If there is one instance in which we might expect to see the same genes and pathways respond to a selection pressure, it is in experimental evolution studies of prokaryotes in which replicates can be derived from a single clone, the potential targets of evolutionary change are small (i.e. prokaryotes have few genes), and identical selection pressures can be applied in controlled laboratory conditions. An ongoing study of adaptation to low glucose medium in *Escherichia coli* represents such a controlled study, but surprisingly not all replicates share the same genetic response. Twelve lines of *E. coli* were derived from a single ancestral clone and have been allowed to evolve for 20 000

generations. 'Parallel' evolution was evidenced by a progressive increase in fitness, measured as rate of population increase relative to the common ancestor, but also by an increase in cell size in all 12 replicates. A macro-array analysis of gene-expression patterns using two of these lines identified 59 genes with significantly different levels of expression in both lines relative to their common ancestor. All 59 genes changed expression in the same direction in both lines, suggesting that these changes are adaptive [33]. The expression of most of these genes is regulated by two transcription factors, *relA* and *spoT*. The nucleotide sequence of *relA* had not changed from the ancestral condition, but there was a single amino acid substitution in *spoT* in one line. When the mutated copy of *spoT* was transformed into the common ancestor of the 12 lines, it caused a significant increase in fitness, thus demonstrating that this mutation had a functional role in adaptation. When the same allele was transformed into a second clone that did not have a *spoT* mutation, it had no impact on fitness, showing that the same endpoint had been attained in a different way. More importantly, *spoT* had no role in adaptation in four of the twelve lines. This experiment shows that even under this most extreme form of selection on replicate genotypes (genetically identical replicates exposed to identical selection), the same derived phenotype can be attained via different genetic pathways.

Table 1 provides additional examples from natural population comparisons and selection experiments in which different genetic changes have been implicated in similar phenotypic changes. This list is intended to be representative rather than exhaustive.

Table 1. Representative examples in which similar phenotype evolved within a species by different genetic changes

Organism	Character	Comparison[a]	Refs
Virus	Novel host	3	[49]
(ΦX174)	Novel host, temperature	4	[50]
Bacteria	Glucose limited media	3,4	[33]
(*Escherichia coli*)	Novel carbon source	3	[51]
	Thermal adaptation	4	[52]
Fungus	Carbon source	3	[53]
(*Saccharmoyces*)			
Fruit fly	Wing vein	1	[19]
(*Drosophila* spp.)	Knockdown resistance	1	[20]
	Learning	1	[54]
Atlantic salmon	Domestication	3	[55]
(*Salmo salar*)			
Mexican cavefish	Pigment loss	1	[24]
(*Astyanax* spp.)	Eye loss	1	[24]
White fish	Body size	3	[56]
(*Coregonus lavaretus*)			
Threespine stickleback	Lateral plate reduction	1,4	[57]
(*Gasterosteus aculeatus*)	Pelvic reduction	5	[39]
Domestic mouse	Nest building	1	[58]
(*Mus domesticus*)			
Rock pocket mouse	Pigment gain	4	[28]
(*Chaetodipus intermedius*)			
Beach mouse	Pigment reduction	4	[1]
(*Peromyscus polionotus*)			

[a]Method of Comparison: 1 = hybrid complementation; 2 = QTL analysis; 3 = patterns of gene expression; 4 = sequencing of candidate genes; 5 = phenotypic comparison.

Distantly related taxa use the same developmental pathway

Although pigmentation studies provide clear examples of how populations within a species can use distinct mechanisms to produce similar phenotypes, these studies also provide examples of how distantly related taxa can use the same genes to produce similar phenotypes. One dramatic example is the observation that the exact same amino acid polymorphism in *Mc1r* that is found in beach mice [1] also segregated within a population of wooly mammoths [8], raising the possibility that mice and mammoths have achieved polymorphic coloration by the identical genetic mechanism.

The observation that distantly related organisms use the same genetic mechanisms to attain the same phenotype is not limited to studies of pigmentation. Threespine stickleback (*Gasterosteus aculeatus*) sometimes show a reduction in pelvic structures when they invade freshwater habitats (Figure 2) [34,35]. Loss of pelvic structures is often associated with a change in expression patterns of the *Pitx1* gene and complementation tests show that the same gene is affected in populations along the west coast of Canada and populations in Iceland [36] and quantitative trait loci (QTL) analysis implicates this gene in several Alaskan populations [37]. Recently, Shapiro *et al.* [38] used expression patterns and intergeneric hybridization to show that *Pitx1* is also important in loss of pelvic structures in some populations of the distantly related ninespine stickleback (*Pungitius pungitius*). A peculiar feature of the *Pitx1* allele for pelvic reduction is a tendency for the resulting vestigial pelvises to be larger on the left side. This pattern is seen not only in both species of sticklebacks but also in manatees [38] (*Trichechus manatus*), an aquatic mammal that has no external pelvic structures. It is possible, therefore, that alterations in *Pitx1* expression are associated with loss of pelvic limbs in other, distantly related vertebrates. Although *Pitx1* might often be recruited independently in different species,

Figure 2. Cleared and stained photos showing a threespine stickleback with full pelvic skeleton (upper image) and one with no pelvic girdle (lower image). Photograph by Mike Shapiro and David Kingsley.

Bell *et al.* [39] found that some freshwater populations of threespine sticklebacks with reduced pelvises had a bias for the right side of the pelvis to be larger, which suggests that there might also be multiple genetic mechanisms associated with pelvic reduction in this species.

Another example of distantly related species sharing the same genetic mechanism is seen in the shift in diet by vertebrates that have evolved specialized forms of herbivory. Distantly related vertebrates have independently evolved foreguts, which are chambers in the anterior portion of the stomach used for bacterial fermentation of ingested plant material. In several species, such as ruminants and leaf-eating colobine monkeys, lysozymes – a bacteriolytic enzyme usually expressed in tears, saliva and other bodily fluids, has independently been recruited to the stomach, where it releases the nutrients assimilated by bacteria that pass through the guts of these species. Once recruited for this new function, stomach lysozymes acquired similar biochemical properties and functions [40], underwent bouts of rapid evolution [41–44] and experienced similar amino acid substitution patterns [41], presumably as adaptations to the stomach environment. Furthermore, the same amino acids have changed independently in langurs (*Presbytis entellus*) and cows (*Bos taurus*), presumably because they are important for enzyme function [45]. Perhaps even more striking, a paralogous calcium binding lysozyme was recruited in the avian foregut-fermenting species, the hoatzin (*Opisthocomus hoatzin*) [46]. This lysozyme has undergone similar evolution following recruitment to the stomach as that seen in mammals [46]. Thus, lysozyme evolution provides a striking example of how divergent species (in this case, separated by more than 300 million years) use similar genetic solutions to solve the same ecological challenge. It can thus be demonstrated that even distantly related taxa can evolve a similar phenotype via the same genetic and developmental mechanism (see Table 2 and [11] for additional examples).

Table 2. Representative examples in which similar phenotype evolved among species by similar genetic changes[a]

Gene[a] (character)	Organism	Comparison[b]	Refs
Mc1r	Pocket mice	4	[6]
(pigmentation)	Several felids	4	[5]
	Little striped whiptail lizard	4	[2]
	Lesser earless lizard	4	
	Snow goose	4	[3]
	Arctic skua	4	
	Beach mice	4	[1]
	Mammoth	4	[8]
Opsin	Various birds	4	[59]
(UV color vision)			
Pitx1	Threespine stickleback	3	[38]
(pelvic reduction)	Ninespine stickleback	3,5	
	Manatee	5	
Lysozymes	Leaf monkeys	4	[45]
(digestive enzyme)			
Ion channels	*Drosophila melanogaster*	4	[60]
	Homo sapiens		
Knox-Arp	Lycophytes and euphylophytes	4	[61]
(leaf formation)			

[a]GenBank accession numbers: *Mc1r* pocket mice AY247560-AY247635; felids AY237394-AY237399; little striped whiptail lizard AY586032-AY586157; lesser earless lizard AY586159-AY586162; snow goose AY521182-AY521209; arctic skua AY521214-AY521217; beach mice DQ482848 and DQ482850; mammoth DQ648859 and DQ648866; opsins AJ277922, Y11787 and M92039; Pitx1 DQ779175-DQ779182; ion channels in *D. melanogaster* NM_078578, NM_107164, NM_168322, and NM_135472 in *H. sapiens* PF02931 and PF03493; lysozymes DQ516063-DQ516065; Knox-Arp AY667449-AY667453.
[b]See Table 1 for methods of comparison.

Difficulties in interpreting genetic changes: how close would be close enough for parallelism or distant enough for convergence?

Trying to distinguish parallel from convergent evolution is further complicated by the incorporation of the terms into studies of genetic change. Recent uses of parallelism versus convergence often address whether the same or different genetic pathways produce some feature of the phenotype, rather than the same or different genes (e.g. [16]). Different genes that affect the production of melanin, for example, might still be part of same biochemical pathway. One might argue that the independent evolution of pale coloration in multiple populations of beach mice or dark coloration in pocket mice inhabiting different lava flows represent parallel evolution if the evolution of pigmentation involved a change in the same biochemical pathway, regardless of whether or not the change could be traced to *Mc1r* [16]. However, the production of a phenotype even as simple as coloration involves a network of genes rather than a simple linear pathway [1,22,47]. Consequently, different genes yielding the same endpoint might be associated with a different spectrum of pleiotropic effects. For example, pigmentation is the product of a series of events that include first the development and then the migration of pigmentation cells to the appropriate position on the body and in the integument, then the actual production of pigment. The loss of pigmentation could be caused by a loss of function anywhere in the sequence of events from cell migration to development and function. Hoekstra *et al.* [65] reported that 'hundreds of genes...encode different developmental mechanisms and are known to affect pigmentation' (p. 231), so there is no reason to assume *a priori* that a gene other than *Mc1r* that caused coat color evolution was exclusively part of the same or a different developmental pathway. Asking whether or not the same or different genes or genetic pathways cause the repeated evolution of dark coloration in pocket mice, light coloration in beach mice, or increased fitness in *E. coli* thus highlights an additional problem with trying to distinguish between parallelism and convergence; because phenotypes are often the product of multiple, interacting mechanisms, there will rarely be a clear distinction between 'same' and 'different' genetic pathways. Assigning such similarities to either parallelism or convergence is thus analogous to divining between shades of gray rather than discerning black from white. Incorporating terms that traditionally refer to phylogenetic relationships into molecular comparisons (Box 1) leads only to confusion.

Conclusions

Empirical studies of the genetics of adaptation show that there is no predictable association between taxonomic affinity and similarity of the genetic basis for the same phenotype that evolved independently. Closely related

species of different populations might evolve the same phenotype using different genes (Table 1). Distantly related organisms, even ones in different classes, might do so using the same genes (Table 2). In the former case, the evidence for different genes or genetic pathways yielding the same phenotype in different populations of the same species or closely related species argues against the role of constraints in shaping how specific features of the phenotype evolve [48]. At best, the association between taxonomic affinity and the similarity of the mechanism that causes the independent evolution of phenotypic similarity might be a probabilistic one – more closely related species might be more likely to evolve phenotypic similarity via the same mechanism than more distantly related species. If the use of the terms 'parallelism' and 'convergence' cannot be associated with a clear dichotomy, either at a phylogenetic level or a molecular level, then their continued use is not justified and can even be misleading. They are relics of a time when we could not evaluate the underlying causes of phenotypic similarity and were confined to inferences based on comparative anatomy. These terms are also relics of a time when there was not an appreciation of the complexity of genetic and developmental networks that underlie the determination of simple phenotypic traits, such as coloration. We argue that this might be a good time to simplify our vocabulary. We need only one term to describe the independent evolution of phenotypic similarity. 'Convergent evolution' will do nicely. If one is interested in how phenotypic similarity evolved, then we have the toolkit to find out.

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