Trends in Ecology & Evolution

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Opinion

Phylogenetics is the New Genetics (for Most of Biodiversity)

Stacey D. Smith,[1,6,*,@] Matthew W. Pennell,[2] Casey W. Dunn,[3] and Scott V. Edwards[4,5]

Despite substantial progress in understanding the genetic basis for differences in morphology, physiology, and behavior, many phenotypes of interest are difficult to study with traditional genetic approaches because their origin traces to deep nodes in the tree of life. Moreover, many species are not amenable to either large-scale sampling or laboratory crosses. We argue that phylogenetic methods and theory provide tremendous power to identify the functional genetic variation underlying trait evolution. We anticipate that existing statistical comparative approaches will be more commonly applied to studying the genetic basis for phenotypic evolution as whole genomes continue to populate the tree of life. Nevertheless, new methods and approaches will be needed to fully capitalize on the power of clade-scale genomic datasets.

Highlights

Genome sequencing is rapidly spreading beyond model organisms, opening the door to comparative studies that can reveal the genetic basis for phenotypic variation across species. Nevertheless, statistical comparative methods have not been frequently applied to these data.

New phylogenetic methods have been developed with the explicit goal of linking genes and even specific mutations to species differences ('PhyloG2P'). Applications of these methods show great promise for uncovering new sources of functional variation and tackling traits beyond the reach of traditional genetic approaches.

Parallel advances in statistical comparative methods present new avenues for expanding the phylogenetic toolkit and creating tailored approaches for mapping genotype to phenotype.

Most of Biodiversity Is Beyond the Reach of Classical Genetics

One of the fundamental goals of biology is to connect variation across genomes to differences in phenotypes. With advances in sequencing and molecular genetic techniques, this area of biology has blossomed in recent years, revealing the genetic basis for traits ranging from floral scent [1] to sociality [2] to herbivory [3]. At the same time, statistical methods for analyzing these data have also proliferated [4–6]. At their core, however, all classical and population genetic methods for **genotype-to-phenotype mapping** (see Glossary) work by associating genetic variation with differences in the trait of interest. Thus, they require a population with segregating phenotypic variation, which could be produced artificially through crosses or mutagenesis or could occur naturally, such as in polymorphic species or hybrid zones between species. As with any statistical approach, association methods [e.g., **genome-wide association studies (GWASs)**] have significant challenges and pitfalls [6,7]. Still, the loci uncovered by association mapping and similar methods have often been validated in subsequent functional studies [8,9], confirming their ability to identify regions of the genome that contribute to phenotypic differences.

Despite the success of this population genetic program for genotype–phenotype mapping, it presents significant limitations for understanding the genetic basis of phenotypes for most of biodiversity. First, many species cannot be propagated artificially or sampled in the wild at the scale needed for association mapping (usually hundreds of individuals, depending on the trait of interest). Second, and more importantly, many traits of interest are not found segregating in nature nor can different species with contrasting phenotypes be crossed. For example, mammals with and without pouches cannot be crossed, precluding the creation of a mapping population segregating for pouches. As a consequence, our understanding of the genetic basis for phenotypic diversity is concentrated around a narrow range of species and traits – often those that vary in model organisms amenable to genetic studies. Although loci discovered through genetic studies of model species often later help to explain variation at deeper phylogenetic levels (i.e., across species [10,11]), we wonder what we might discover if this research program were inverted (Figure 1). We suggest, and recent studies confirm, that beginning from a phylogenetic

[1]Department of Ecology and Evolutionary Biology, University of Colorado, Boulder, CO 80309, USA
[2]Department of Zoology and Biodiversity Research Centre, University of British Columbia, Vancouver, BC V6T 1Z4, Canada
[3]Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT 06520, USA
[4]Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138, USA
[5]Museum of Comparative Zoology, Harvard University, Cambridge, MA 02138, USA
[6]http://www.colorado.edu/smithlab

*Correspondence: Stacey.D.Smith@colorado.edu (S.D. Smith).
@Twitter: @iochromaland (S.D. Smith).

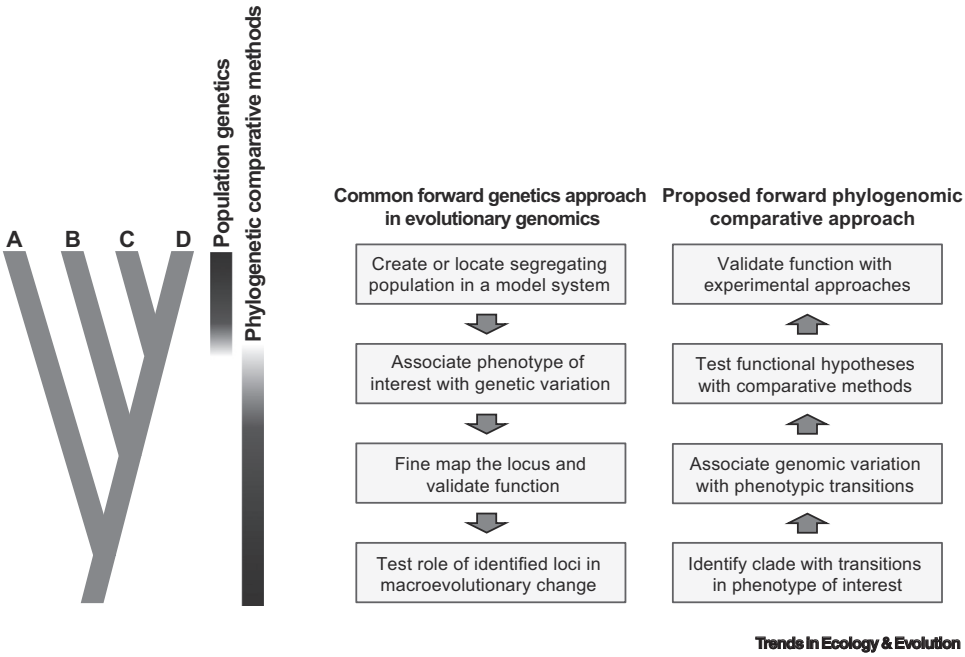

Figure 1. Approaches to Identify the Genetic Basis for Trait Evolution. Both population genetic and phylogenetic comparative approaches can be used to identify candidate genetic changes underlying phenotypic differences, although the former are generally applicable only at shallow timescales while the latter are applicable across entire clades (depicted with the phylogeny of four species, A, B, C, and D). In the traditional approach (left flow chart), the genes found to underlie phenotypes of interest through classical population genetic approaches are then used as candidates for between-species transitions. An alternative PhyloG2P approach (right flow chart) begins at the macroevolutionary scale, searching for genes linked to phenotypic transitions in a target clade. Functional tests can be conducted with additional comparative analyses (e.g., Figure 2) and/or with experimental studies in one or more species (e.g., gene knockouts with **CRISPR-Cas9**).

perspective, without the aforementioned limitations on focal traits and taxa, might reveal not only new mechanisms for trait evolution, but also new perspectives on longstanding questions (see Outstanding Questions).

Putting the Comparative into Comparative Genomics

Enabled by recent advances in sequencing technology, comparative genomic studies have emerged as an important avenue for detecting genetic changes responsible for trait variation across species. These studies fall into two broad categories: genome sequence evolution and comparative functional genomics. Genome sequence evolution studies directly consider the DNA sequence of the genome itself. They often leverage models of molecular evolution to test for specific patterns of sequence change across species, such as signatures of changes in selection that are coincident with a change in a trait of interest. Statistical tools like PAML [12] have made this a productive and popular approach to find genomic changes associated with phenotype changes across species. These studies are strongly rooted in phylogenetic theory and methods, in part because phylogenetic methods for DNA analyses are so well developed.

By contrast, comparative functional genomics compares functional genomic traits, such as gene expression or genome content, across species. These studies often rely on pairwise comparisons to identify candidate genetic changes for species differences [13,14]. It remains uncommon, however, for comparative functional genomic studies to apply **phylogenetic comparative methods (PCMs)**, which offer the possibility of disentangling similarity due to **convergent evolution** from similarity resulting from shared common ancestry. In phylogenetics, the term

Glossary

Convergent evolution: the independent evolution of the same or similar character states in different lineages (e.g., the repeated origins of wings in vertebrate animals).
CRISPR-Cas9: a technology used to edit specific DNA sequences and to test the effect of those targeted changes; for example, on the development of physiological or morphological traits.
Genome-wide association studies (GWASs): a statistical approach for associating genotypic variation and phenotypic variation; most commonly used when artificial crosses are not an option (e.g., in human genetics).
Genotype-to-phenotype mapping: efforts to link or 'map' differences in observable phenotypes (e.g. differences in an organism's form or function) to differences at the genetic level.
Incomplete lineage sorting (deep coalescence): refers to genetic (allelic) variants that fail to coalesce in a common ancestor between lineage splitting events (Box 2); will be more common when internal branches of the phylogeny are short and/or population sizes are large and often results in gene trees that differ from species trees.
Independent contrasts: a statistical method developed by Felsenstein in 1985 [46] that transforms observations for species (tip data) into statistically independent contrasts that can be used in a range of standard statistical analyses (e.g., regression, correlation).
PhyloG2P: a research program of phylogenetic genotype-to-phenotype mapping that can be used to identify the genetic basis of traits in species that are not amenable to traditional genetic crosses and mapping.
Phylogenetic comparative methods (PCMs): a body of statistical approaches, mostly model based, that are used to test evolutionary hypotheses (e.g., the relationship between trait variation and environmental differences) while accounting for the nonindependence of species due to common ancestry.
Phylogenetic generalized least squares (PGLS): a statistical method used to test for associations between one or more variables; accounts for phylogenetic history through a covariance matrix and a specified model of trait evolution.
Pleiotropy: refers to genes or mutations that affect multiple traits.

'comparative methods' refers to statistical methods that compare variables across species while incorporating the fact that species share many features owing to the process of descent with modification; the closer two species are related, the more similar they are expected to be. For most biological questions involving interspecific variation, statistical analyses can be severely misleading if they do not account for evolutionary history [15,16]. Applications of PCMs to functional genomics data could include testing for evolutionary associations between variables (e.g., the correlated changes between gene expression and a particular trait) or identifying shifts in the rate of evolution for a single variable. PCMs have seen rapid development over the past few decades, but have mostly been applied to morphological, physiological, and ecological traits. Although comparative functional genomic studies consider quantitative traits to which these methods also apply, they are rarely used to study such traits. This bias is not driven by biological or theoretical reasons; PCMs often apply just as readily to quantitative functional genomic data as they do to morphological data. The reason is in part technical – the software designed for functional genomic analyses and PCMs are rarely interoperable, necessitating custom coding – but is also intellectual, reflecting the domains of two communities, genomics and comparative biology, that communicate less than they should.

Species tree: the branching or reticulating history of species; used in contrast to gene trees (the history of genes within species).

Although failing to account for this shared history can lead to incorrect conclusions in comparative genomics [17], designing studies around an explicit phylogenetic context can provide novel and robust insights into the origins of trait differences across lineages [18]. Thus, we argue that the field of comparative genomics has much to gain from the application of PCMs and derivative models, just as the field of phylogenetics will benefit from developing new models and PCMs optimized for linking genomic variation to phenotypic differences. In the following sections, we outline the role of phylogenetics in tracing the evolutionary history of traits and highlight the potential of PCMs for the identification of the genetic mechanisms underlying trait variation across species.

Phylogenetics Provides the Necessary Framework for Understanding How Traits Evolve

Although comparative approaches have been underutilized in mapping genotypes to phenotypes, phylogenetics as a field has been critical in dissecting the evolutionary history of traits. The earliest parsimony-based phylogenetic methods were grounded in morphological evolution [19], considering how traits transform over time and how these accumulated transformations can be used to infer the evolutionary history of lineages. Even as modern phylogenetics relies largely on sequence data to estimate relationships, the primary motivation for building trees is often to understand how traits, be they morphological, behavioral, molecular, or ecological, evolved.

Given their importance in tracing the evolutionary history of traits, phylogenetic comparative analyses have a key role to play in genotype-to-phenotype mapping across species, a research program that we term '**PhyloG2P**'. At a fundamental level, a phylogenetic perspective is required to determine the direction of evolutionary change (i.e., from which ancestral state to which derived state) as well as the timing of these changes. Ancestral state estimation can also localize the phylogenetic position of trait transitions to distinguish homologous traits (inherited from a common ancestor) from those that have arisen convergently. We expect to find shared genetic mechanisms for homologous traits [20], while such similarities in the case of convergent origins may indicate evolutionary constraints [21]. Phylogenies also provide the opportunity to decompose complex traits, like C4 photosynthesis, into a series of ordered component changes, which can then be studied individually [22]. Comparative analyses are similarly powerful for testing evolutionary relationships among multiple traits. While coordinated evolution among traits is often interpreted as evidence of functional or adaptive significance [16,23,24], a shared genetic basis

(i.e., due to **pleiotropy**) provides a less explored explanation, at least at macroevolutionary scales. Expanding PCMs to explore genetic mechanisms, as we propose, could lead to important insights into the role of genetic architecture in trait evolution and provide evidence complementary to what we already know on this topic from population genetic studies.

New Comparative Methods Allow Genotype-to-Phenotype Mapping in a Phylogenetic Framework

In the past few years, a range of comparative methods have emerged that aim to identify the loci of phenotypic evolution from phylogenomic data (Table 1). These can be roughly divided into those adapted from population genetic approaches and those built from the toolkit of molecular evolution. The former includes phylogenetically informed variants of GWASs, which test for associations between genetic markers and phenotypes of interest while accounting for phylogenetic history (Table 1). As with standard GWASs, the detection of a significant association requires that all or most of the species with similar phenotypes share the genetic variant. These approaches have proved powerful when phenotypic evolution has occurred through parallel fixation of ancestral variation [25,26] or through the movement of the casual variant between lineages (e.g., through introgression) [27,28] (Box 1).

By comparison with GWAS-based approaches, the class of PhyloG2P methods focusing on rates of molecular evolution has received significantly greater attention. This emphasis reflects, in part, their ability to capture a wide array of predicted patterns, from substitution rate variation [29–31] to convergent shifts in amino acid preferences [32]. For example, PhyloAcc [33] is tailored to identify accelerations in noncoding sequences that are highly conserved under a particular phenotype but are accelerated in others, consistent with positive selection or relaxed selective constraint in association with repeated phenotypic transitions. While early molecular-evolution-based approaches focused on discrete traits, new methods are also available for continuously varying traits [34,35]. These have the potential to take advantage of the wide range of comparative models that have been developed to capture the diverse histories shaping continuous phenotypic variation (e.g., stabilizing selection, early bursts, pulsed evolution) [36–38].

Table 1. Example Research Questions and Approaches in PhyloG2P

PhyloG2P question	Approach in concept	Example method
How many loci control macroevolutionary trait variation and what are the effect sizes of these loci?	Genetic markers (e.g., SNPs) that predict trait variation are presumed to be in or linked to the causal genetic regions	PhyloGWAS [25]; Coal-Miner [66]; treeWAS [27]
What is the contribution of interspecific introgression to trait evolution?	Introgressed alleles associated with trait variation will follow genealogies different to the rest of the genome	Coal-Map [28]; Coal-Miner [66]
How do trait transitions affect rates of sequence evolution?	Coding genes or regulatory regions that are functionally associated with a trait may exhibit changes in rates of evolution (e.g., relative rates of synonymous to nonsynonymous substitutions) in concert with trait transitions	TraitRateProp [29]; Coevol [34]; relative-rates method [31]; PhyloAcc [33]
Is trait loss associated with gene degeneration?	Genomic regions required for a particular trait will decay when that trait is lost, leaving a signature of elevated sequence divergence associated with repeated trait losses	Forward genomics [28,35,39]
Is trait evolution linked to changes in gene content?	Traits can evolve through gene duplication or loss, leading to correlated changes in gene content and trait variation at a phylogenetic scale	COMPARE [67]; PAM [40]

Much of the power of PhyloG2P methods lies in repeated (convergent) phenotypic transitions, as these serve as the replicates that provide power to the analysis [30]. Moreover, cases of convergent trait losses seem to provide particularly fertile ground for PhyloG2P because of the distinctive genomic signatures associated with relaxed selection (high substitution rates, inactivating mutations, gene losses) [39–41]. For example, Marcovitz *et al.* [42] scanned ~3400 discrete mammalian phenotypes and ~266 000 conserved noncoding elements (CNEs) [43] and found 496 instances of trait loss associated with loss of CNEs. Although their approach used parsimony and other methods with known biases, the precision of some of the inferred associations is striking. For example, they found one CNE covarying with middle ear traits, and this region resides near BMP7, a gene implicated in middle ear development. In addition to such exciting cases with convergent trait losses, several studies have detected functional genomic variation associated with traits of single lineages, such the accelerated evolution of genes involved in neural function in humans [44]. Thus, while convergent evolution will no doubt be a powerful framework for linking genes and phenotypes [45], it is likely to be not a strict requirement for the PhyloG2P program.

Box 1. Empirical Examples of PhyloG2P

Case Study I: Genetic Basis for Climate Adaptation in Tomatoes

Tomatoes and their wild relatives (*Solanum* sect. *Lycopersicon*) naturally occur along the western coast of South America, from the northern Andes to the Atacama Desert. Pease *et al.* [25] sequenced transcriptomes for 13 tomato species and used PhyloGWAS to identify genetic variants associated with plant traits like fruit color as well as environmental variables. They uncovered several strong candidate loci; for example, photosystem I reaction center subunit (*PSI RCIII*), which was linked to seasonal climate variation (Figure I).

Case Study II: Aging-Related Genes in Primates

Primates show wide variation in maximum lifespan, from less than 10 years in some prosimians and New World Monkeys to 60 years or more in some of the great apes, including humans. Muntane *et al.* [69] harnessed this interspecific variation to search for genes that show higher rates of protein evolution in longer-lived species, suggesting a potential functional relationship between the gene and longevity. They computed root-to-tip dN/dS ratios (ω) for *ca.* 19 000 shared genes and regressed these values against maximum lifespan and other life history traits using **phylogenetic generalized least squares (PGLS)**. The strongest association for lifespan involved STK17B (Figure II), a death-associated protein kinase. Other genes among the top hits belong to pathways related to cardiovascular function and senescence.

Case Study III: Regulatory Evolution Associated with Losses of Flight in Birds

Sackton *et al.* [58] investigated genomic changes correlated with independent losses of flight in birds. Using PhyloAcc [33], they identified *ca* 2300 conserved nonexonic elements (CNEEs) with elevated substitution rates in flightless lineages. These regions were enriched in areas of open chromatin and near genes involved in morphogenesis, suggesting that the accelerations were tied to *cis*-regulatory evolution. Follow-up functional studies of one such region (CNEE mCE967994; Figure III) demonstrated that the sequence from a volant tinamou (*Eudromia elegans*) possessed enhancer activity while the sequence from a flightless rhea did not, consistent with the hypothesized regulatory role.

Figure I. Association between Genetic Variation and Climate in Wild Tomatoes. Allelic variants (represented by the As and Ts) at multiple loci were associated with seasonal climate variation (represented by the sunny and cloudy symbols) across the tomato phylogeny. Adapted from [25].

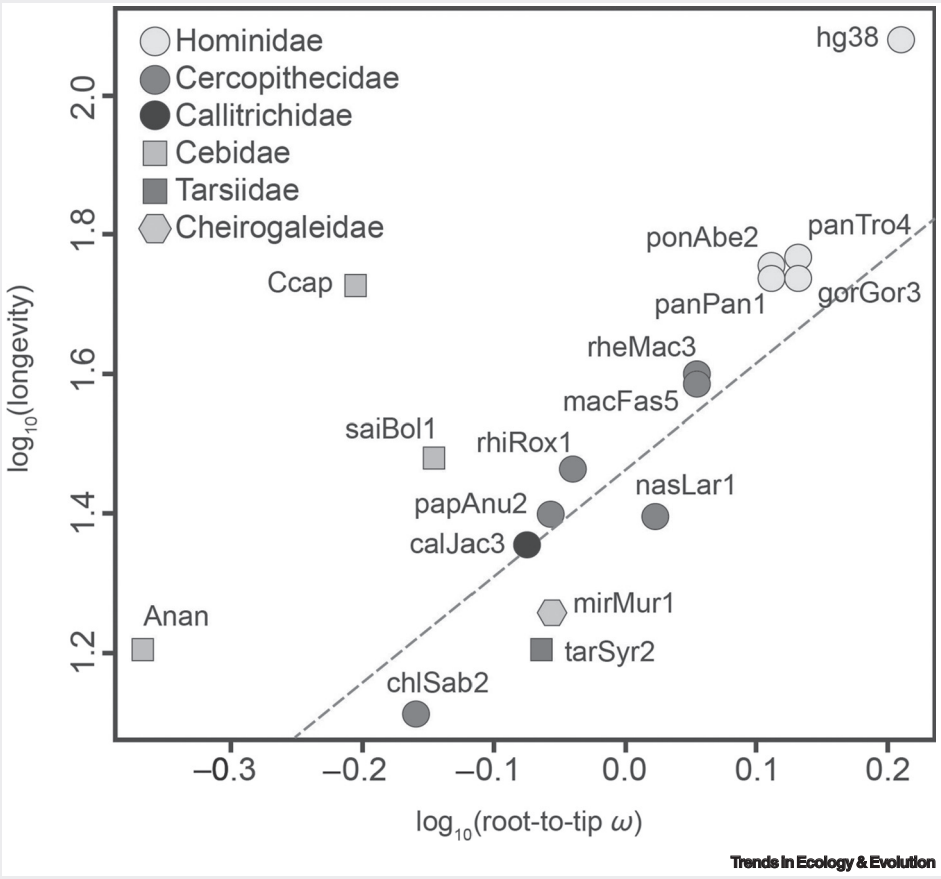

Figure II. Relationship between Rates of Molecular Evolution at the *STK17B* Locus and Longevity. The broken line represents the best fit from the phylogenetic generalized least squares analysis. Each point corresponds to a single species; symbols are grouped by higher taxon (e.g., filled black circles for Callitrichidae). Adapted from [69].

PCMS Can Serve as Tools for Exploring Gene Function

In our view, the applications of comparative methods to genotype–phenotype mapping described above constitute the tip of the iceberg in terms of potential synergies between phylogenetics and genetic studies of trait evolution. With decades of developments since the publication of **independent contrasts** [46], statistical comparative methods are tailored to meet a wide range of analytical challenges, such as high-dimensional data [47,48], nonlinear relationships among variables [49–52], and heterogeneous processes across lineages and timescales [53–55]. However, the vast majority of these innovations have yet to be applied to questions relating genotype to phenotype, particularly in a hypothesis-driven framework.

PhyloG2P can play an important role in generating hypotheses. For example, phylogenetic comparative studies could identify a small number of genes with evolutionary variation in sequence or expression that is associated with evolutionary changes in a trait of interest. These genes could then be examined in greater detail in one or more of the species of interest to experimentally test causal functional hypotheses about the changes (Figure 1). Beyond this, we envision a multitude of scenarios in which statistical comparative methods could be used directly to test causal hypotheses about evolutionary changes in genes and phenotypes. There is growing recognition of the important role that observational data can play in testing

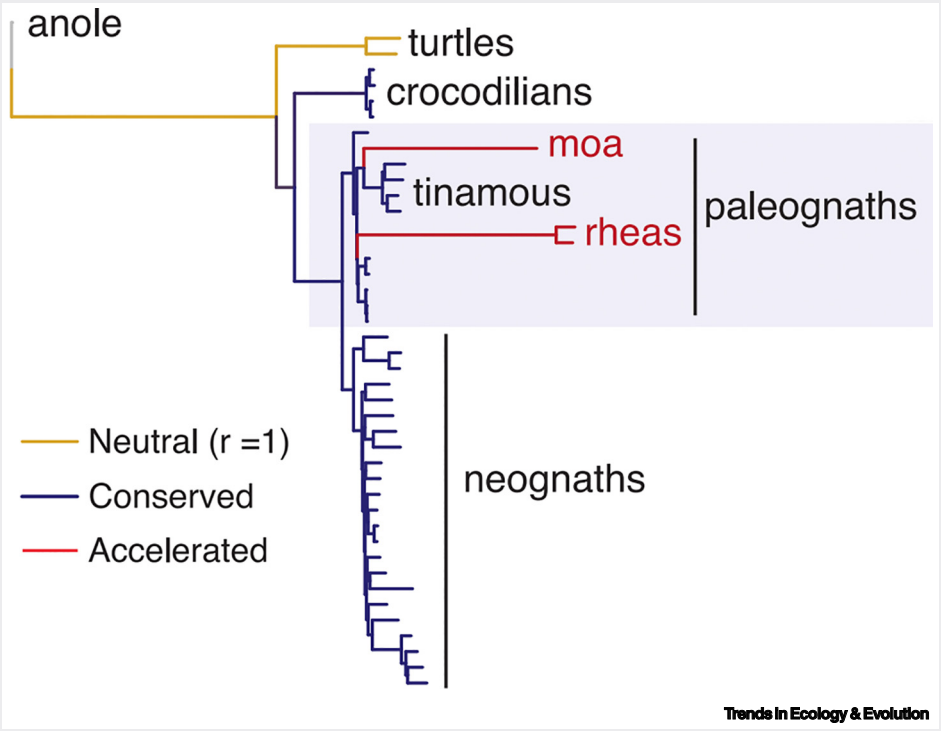

Figure III. Accelerated Regulatory Evolution in Flightless Birds. Branch lengths correspond to the substitution rate at the conserved nonexonic elements mCE967994. Both moas and rheas (two flightless bird lineages; red lines) show elevated rates of substitution in this region compared with volant lineages and non-avian reptiles (blue and yellow lines). Adapted from [58].

causal hypotheses [16,56], such as the link between genome changes and phenotype changes. Hypothesis testing requires making falsifiable predictions, which can then be tested with new data not in hand when the prediction was made. Those new data can be experimental, but they can also be observational [57]. Observational data can also be used to test causal hypotheses through the consideration of mediating variables. For example, if genome-wide exploratory studies, like those described above, implicated a particular *cis*-regulatory element in the evolution of a trait, further comparative methods could be used to test predictions about the evolution of expression of genes under the control of that element that are expected to mediate the phenotype (Figure 2).

Concluding Remarks

Although PCMs are applicable to any biological question involving cross-species comparisons, theoretical and empirical work in the field has historically focused on problems in ecology and morphology as opposed to genetics and development. Comparative genomics has begun to push phylogenetics into these realms, and already the results have supported known loci of phenotypic evolution in addition to highlighting previously unexamined candidate loci. As with any association method applied above or below the species level, validating the functional relationship between genotype and phenotype requires additional downstream experimental approaches (e.g., [58]). We argue that comparative methods are also part of the hypothesis-testing toolkit and can be used to interrogate hypothesized functional relationships (Figure 2).

Outstanding Questions

To what degree will macroevolution involve the same loci or even the same mutations uncovered by the microevolutionary research program? Studies connecting genotypes to phenotypes below the species level have identified genetic hotspots for evolution (i.e., loci or even particular sites that are repeatedly involved in trait variation). The PhyloG2P program has the potential to test how these associations hold across time and across lineages.

At a phylogenetic scale, what are the relative contributions of structural and regulatory changes to phenotypic evolution? Existing methods are aimed at identifying candidate genomic regions for trait variation across species (Table 1), but PCMs could be extended to test functional hypotheses (e.g., connecting genetic changes to molecular phenotypes, such as gene expression, and then to observable phenotypes as in Figure 2).

How does the power to detect genotype–phenotype relationships vary across timescales? GWAS-based approaches have identified strong candidate regions for traits of interest in groups of closely related taxa, but we expect that the power of these methods will decrease at broader timescales. Methods that target genetic signatures other than SNPs (e.g., rates of evolution or changes in gene family size) may be better suited for PhyloG2P of distantly related taxa.

How do interactions among genes evolve across the phylogeny and, in turn, affect phenotypes? Multivariate PCMs have been a central focus for theory and methods development in recent years and can be applied, for example, to estimate phylogenetic correlations among multiple characters. Such comparative approaches have been used to quantify gene coexpression and even to reconstruct changes in regulatory networks over evolutionary history. The next step will be to directly connect the evolution of gene interactions to the evolution of phenotypes at a phylogenetic scale.

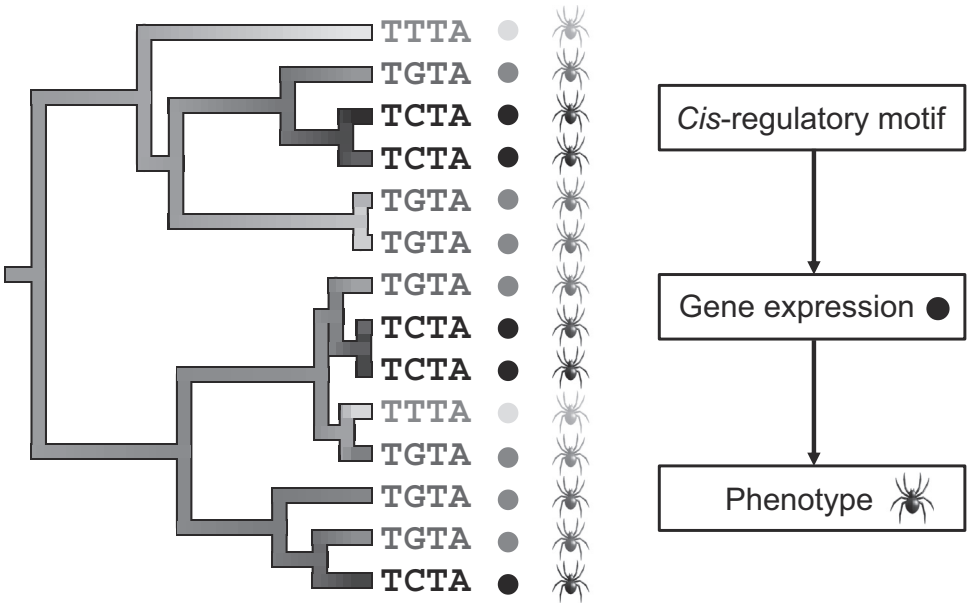

Figure 2. Hypothetical Comparative Analysis Testing the Role of Genetic Variation in Phenotypic Evolution via Regulatory Change. Assuming that variation in this *cis*-regulatory motif has been implicated through a comparative genomic analysis (e.g., [33]), its effect on phenotype could be tested with comparative methods, such as phylogenetic path analyses [68]. The prediction would be that this variation in this motif influences levels of gene expression (indicated by the shading of the circle), which in turn gives rise to variation in the pigment phenotype (the color of the spider). These hypothesized causal relationships are depicted in the flow chart to the right.

In addition to the insights into new traits and new lineages brought by the PhyloG2P program, we anticipate new analytical challenges (see Outstanding Questions). For example, phylogenomic studies have uncovered substantial, albeit unsurprising, variation in gene histories across the genome. The resulting discordance means that gene trees will often fail to mirror overall species relationships, which can lead to incorrect inferences about trait evolution when the **species tree** is equated with the gene tree (Box 2). Just as the field of phylogenetic inference has come to incorporate gene tree variation in estimating species relationships [59], we expect that approaches for PhyloG2P will be expanded to incorporate the probability of hemiplasy (Box 2) into estimated relationships between genotype and phenotype. Other challenges on the horizon include accommodating shifting genome content and genomic reorganization, which complicate alignment-based comparisons across taxa. Nevertheless, these challenges arise from biological processes that permeate timescales, and thus addressing them will open the door to phylogenetic comparative genomic approaches that can be applied seamlessly across clade, species, and population levels.

We envision that ongoing advances in PhyloG2P will tackle persistent yet fundamental questions about phenotypic evolution (see Outstanding Questions). For example, evo–devo studies from the past few decades have put forward the notion that evolution is often predictable at the genetic level; that is, similar phenotypes will evolve by similar mechanisms and genetic changes [60,61]. Comparative methods are ideally suited to address this issue in a statistically rigorous framework and allow us to probe more nuanced questions, such as how and why molecular predictability varies across traits. The expansion of trait databases, such as Morphobank [62], as well as the growing methods for assembling and visualizing large phenomic matrices [63–65], will further our efforts to capture a broader swath of biodiversity in PhyloG2P. We also foresee that the

Box 2. The Challenge of Hemiplasy for PhyloG2P

The most powerful statistical signal for an association between genotype and phenotype comes from replicated originations or reversals. However, a singular origin of a character may appear to be a series of independent events if there is a discordance between the species tree (on which character and molecular changes are typically mapped) and the gene tree for the locus (or loci) that underlie this character. This phenomenon is referred to as hemiplasy [70] to distinguish it from true character convergence, or homoplasy. In the scenario shown on the left in Figure I, the history of the gene for the trait matches the species tree, indicating that there are two origins of the trait, while on the right the gene tree is discordant with the species tree and the trait evolved only once. The frequency of hemiplasy is driven by the same phenomena that generally lead to discordance among gene trees (e.g., hybridization, horizontal gene transfer, gene duplication and loss, **incomplete lineage sorting** [59,71]).

Given the substantial amount of species tree–gene tree discordance that modern phylogenomic studies are revealing (e.g., [25,72]), a critical challenge for phylogenetic studies of the genotype–phenotype map will be to better distinguish hemiplasy from homoplasy. In their PhyloGWAS approach, Pease *et al.* [25] sidestep this issue altogether by focusing only on phenotypic variation associated with ancient segregating polymorphisms. To make use of all of the data, we will need both new theory and new hemiplasy-aware inference procedures. Recently, Guerrero and Hahn [73] made good progress on this front: they derived a measure of the probability that a particular phylogenetic distribution of binary character values is the result of true homoplasy rather than hemiplasy, given the internode distances and rate of substitution. In addition to extending this theory to incorporate sources of gene tree incongruence beyond incomplete lineage sorting, drawing robust conclusions about phenotype–genotype associations is likely to require the relevant evolutionary processes to be explicitly included in the inference model.

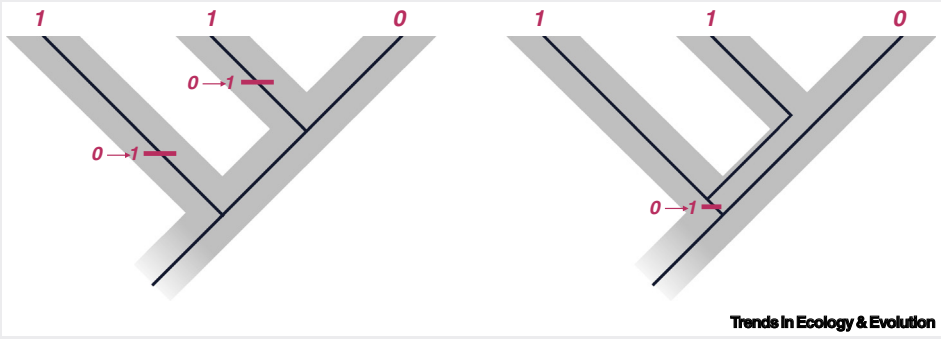

Figure I. Convergence versus Hemiplasy. The two diagrams show the same species tree (gray lines) and distribution of states at the tips (0s and 1s), but the histories of genetic changes and trait evolution differ. The diagram on the left shows an example of convergence, wherein the focal trait (1) arose twice via independent changes (0➔1) in the history of the gene (the black lines). The diagram on the right shows a case of hemiplasy, where the gene tree does not match the species tree and the evolution of the trait occurred once.

PhyloG2P program will bring new avenues for applied phylogenetic research. Many empirical studies in this area have been motivated by the discovery of the genetic basis for complex traits in humans by harnessing variation in genes and phenotypes among related taxa [44]. These studies underscore the fact that every branch of the tree of life carries information about how evolution works. Implementing PhyloG2P approaches will allow us to leverage the power of phylogenetic history and begin to discover new lessons about the evolution of biodiversity.

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