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Are the Eyes Homologous?

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Since the 1990s research in developmental genetics has followed the approach of borrowing pathways described in one context and testing to see if the members of a pathway or genetic regulatory circuit can be found in a new context. This approach has raised questions of how the concept of homology should be used when comparing genetic regulatory circuits. One particularly cautious response has been to claim that gene expression patterns are informative for the understanding of morphological evolution *only* when coupled with a detailed understanding of comparative anatomy and embryology.

This reflects the concern that recruitment can lead to a situation where orthologous genes are expressed in novel contexts during development, thus suggesting that these similarities in gene expression patterns were not derived from a common ancestor with the structure of interest. Defining homology as a property of structures, genetic networks, or genes, rather than viewing homology as a particular way to explain observed similarities, is confusing. Specifying the similarities first and then entertaining hypotheses to explain them (including appealing to common ancestry, i.e., homology) allows us to dispense with tortured discussions of levels of biological organization at which the concept of homology may be applied.

Other chapters in this book address specific questions of gene regulation and metabolism without explicit mention of the connection between networks and the phenotype. One of the challenges, computationally, in understanding gene regulation is finding, capturing, and leveraging the information in better-studied networks. It is standard practice to apply conclusions from well-studied proteins to similar, but less well-understood, proteins. This is done when annotating for

function and even when trying to predict structure (see the cautions in chapter 2 in this volume). This practice of borrowing annotations and setting expectations relies on tacit assumptions about the transitive nature of these attributes once homology has been established. It is my goal in this essay to clarify what hypotheses of homology actually are in the context of borrowing network and gene regulatory information from one (well-described) regulatory circuit to another (less well-understood).

To make the case for homology of regulatory circuits, and using what is known in one context and applying it to another, we will have to examine homology and the emergence of phenotype from regulatory circuits. This is the current challenge in computational biology. As genomes are sequenced, there comes the realization that interpreting the genome sequence is not straightforward. Coding regions are interspersed with noncoding regions, and an individual locus may give rise to multiple gene products. This has stimulated experimental approaches to identify the full spectrum of messenger RNAs (the transcriptome) and their corresponding protein products (the proteome) (RIKEN, 2001). If we now ask about the many modifications of proteins, and the numerous interactions and the detailed biophysics of protein-protein, protein-DNA, protein-RNA, and protein-lipid interactions (see chapter 9 in this volume), we quickly see why sequence-based computational biology hits a snag.

Part of the enthusiasm for moving to descriptions at the network level is the hope (or intuition) that there will be regularities that allow us to offer useful descriptions without losing the emergent biological narrative in a fog of biophysical details. In addition, the increasing availability of transcription profiles and the need to interpret them has encouraged researchers to use known regulatory networks to establish expectations against which profiling experiments can be statistically compared. I will offer an operational definition of homology, watch it at work in a current example of gene regulation (eye development), and endorse hypotheses of gene regulatory homology that push experimental work and set expectations for establishing statistical significance.

HOMOLOGY

Since evolution was championed in the mid-1800s, it has been possible to define homologies as similarities due to shared ancestry (Lankester,

1870; Donoghue, 1992; Patterson, 1987; Patterson, 1988). To understand the use of this concept when thinking about developmental regulatory circuits or pathways, it is worth reflecting on the use of the term “homology.” There is general agreement that attributions of homology are shorthand for the claim that particular similarities are best explained by common ancestry (Abouheif et al., 1997; Bolker and Raff, 1997; de Beer, 1971; Hall, 1995; Roth, 1984; Roth, 1988; Wagner, 1989a; Wagner, 1989b). There is still some confusion that flows from conflating “homology as an explanation for similarity” (as hypothesis) with treating homology as if it were a (discernible) property of individual things.

As more and more developmental pathway information becomes available, comparative work becomes of particular interest. I will try to provide the framework within which concepts of homology can be based in these cases. My goal is to reciprocally illuminate the comparison of regulatory pathways and those explanations that rest on homology. I will use examples from spatiotemporal gene expression patterns in developmental biology because these are the best studied. But I think much of the argument carries easily to gene regulatory circuits or metabolic pathways (see Burian, 1997 for tensions between developmental and genetic descriptions).

Here is an example. The eyespots on the wings of butterflies in the genera *Precis* and *Bicyclus* look very similar. In both species, eyespot foci are established in the larval stage. However, at the pupal stage things look quite different. The pattern of engrailed expression correlates with the development of eyespot rings. *Engrailed* is a transcription factor that is also involved in establishing body segments by activating the secreted protein *hedgehog*. In *Precis*, engrailed expression extends out to the second ring by 24 hours after pupation and then collapses to the center of the ring by 48–72 hours. In *Bicyclus*, it is expressed at the third ring but not in the second. Whereas both butterflies may use the same mechanism to place eyespots, the ways in which they specify the developing rings of the eyespot appear to be different, though the adult pattern appears similar again (Keys et al., 1999). Given the profligate reuse of transcription factors in development, we have a real challenge in applying notions of homology and in borrowing annotations from one situation to the next.

Reactions to complicated (i.e., actual) examples include the claim that homology at one level does not require homology at another, or that

homology means nothing more than shared expression patterns of important regulatory genes during development, or that any assignment of homology must specify a level in order to be meaningful. Although homology may apply to (developmental) mechanisms per se (“process homology”), rather than to their structural end products, there is tension in the possibility that homology at one level of organization may not imply homology at another. For example, nonhomologous wings are said to have evolved from homologous forelimbs. Pterosaurs, bats, and birds share the underlying pattern of homologous forelimb bones of their tetrapod ancestor, but their wings have evolved independently. The problem is that because there is no clear way to assign levels unambiguously, one may conclude, unnecessarily, that gene expression patterns should not be used as a primary criterion of homology.

In addition to rejecting hypotheses of homology using gene expression patterns because they may disagree with each other at varying levels of organization, some critics cite specific errors that have come from using expression patterns (Abouheif et al., 1997; Bolker and Raff, 1997). These include the failure to distinguish between orthology and paralogy,¹ the confusion of analogy (convergence) and homology (noting that gene-swapping experiments do not resolve this question), the failure to notice that orthologous genes can be recruited and expressed in structures whose similarities may not be due to common ancestry. So, for example, the *distal-less* gene (the transcription factor that is the first genetic signal for limb formation to occur in the developing zygote) may be homologous in different animals, but its cis regulation may be convergent in different lineages, so that finding *distal-less* expression in different outgrowths does not, by itself, warrant the claim that the resultant limbs are homologous.

These concerns all seem reasonable, and might chill our enthusiasm for recognizing and borrowing knowledge gleaned from developmental regulatory circuits in different contexts. Must any hypothesis of morphological homology based on gene expression include, at a minimum, a robust phylogeny, a reconstructed evolutionary history of the gene, extensive taxonomic sampling, and a detailed understanding of comparative anatomy and embryology? Or are these requirements unnecessarily cumbersome? To untangle these issues I will return to a definition of homology.

HOMOLOGY: A DEFINITION

The use of the term “homology” implies that a given similarity is a result of common ancestry. This definition has a critical requirement: similarity comes first. There are many cases in which the similarity is cryptic, but this should not fool us into thinking that we are explaining something other than the similarity.

There are some instructive examples of structures that are not at first glance similar, but are more obviously so once the hypothesis of common ancestry is considered seriously, as in studies of insect wing evolution (Kukalova-Peck, 1983) and wing venation patterns (Kukalova-Peck, 1985). But we generally begin with the perception of similarity and then explain the similarities by appealing to a short list of possibilities. Biologists usually consider similarity to be the result of shared ancestry (homology), chance, convergence (homoplasy), or parallelism (including repeated co-optation of the same regulatory genes), or an intricate mix of these. Explanations that posit horizontal transfer are still appealing to homology to explain similarity, even though they relax the requirement for an unbroken shared lineage.

We should not appeal to homology to explain dissimilarity. And, importantly, it is not at all clear what the claim that dissimilar objects are “nonhomologous” would mean. Homology as I have defined it is coherent only when we begin with similarity. Nonhomologous similarity does make sense, however. Claiming that similarity is not due to shared ancestry sends us to the other possibilities (convergence, chance, and biomechanical constraint).

There are other uses of “homology” that we will set aside. There is the unfortunate use of the word to refer to the degree of DNA sequence identity or similarity (e.g., 30% homology). This use does not make particular claims about the origin or process that gives rise to the similarity.

Then there is the interesting phenomenon of serial homology, as in the forelimbs and hind limbs of quadrupeds, the repeated segments of a millipede, or the petals of a flower. A similar situation arises in developmental genetic terms when, for example, the expression of *apterous* in dorsal cells and *engrailed* in posterior cells in both wing and haltere discs has been taken as evidence that these two appendages are built on a “homologous groundplan” (Akam, 1998). Serial homology

does not imply the existence of a common ancestor with just one segment, limb, or other structure; rather, it gives us insight into how a structure develops. Sometimes paralogy is assumed to be “serial homology” at the level of genes. However, paralogy of open reading frames does imply a common ancestor with just one copy.

HOMOLOGY AS HYPOTHESIS

As biologists, when we give ourselves the task to explain similarity, we have a limited list of options:

1. Mistaken perception: the similarity is solely in the eye of the beholder (flightlessness, an outgrowth, the coelom)
2. Shared ancestor had the anatomical structure, gene, regulatory network, behavior, temporal and spatial protein distribution, or other component (homology or horizontal transfer, developmental constraints)
3. Convergence, parallelism (adaptation)
4. Chance (drift, contingency, historical constraints)
5. Physical principles (biomechanics).

These options are not mutually exclusive. The claim that the perception of similarity itself is illusory is an epistemological question (and not unique to biologists), so I will put it aside. Physical constraints have been in vogue as an explanation of similarity periodically since the work of D’Arcy Thompson. Contemporary practitioners who focus on biomechanics (e.g., Mimi Koehl and Steven Vogel) are part of this tradition, as are the recent wave of neostructuralists (Webster and Goodwin, 1996; Depew and Weber, 1996). The clearest examples of this kind of similarity are in chemistry (ice crystals look similar due to the physical processes involved, not shared ancestor relationship between individual water molecules).

Physical and chemical constraints do not play a large part in most biologists’ explanations, so explanations involve appeals to the other three. Much of the discussion of homology as structural, or dependent on the relative position of surrounding parts or on the percent of identical bases or amino acids comes down to questions of the relative merits of attributing overall similarity to common ancestors, not arguments about the definition of homology.

The job of explaining similarities is one of partitioning credit. Take two gene sequences that can be aligned. There will be certain positions where the residues are shared (i.e., the same). As we move along the alignment, we can imagine that some of the shared residues reflect a shared ancestor, whereas others have mutated since the common ancestor and have secondarily returned to the same residue thanks to either drift (there are only four bases possible) or to convergence (the protein works better if a particular residue is coded for at a particular position). Clearly the observation of the similarity depends strongly on the alignment (already an important hypothesis that privileges the idea that shared residues are due to homology). It should be clear that understanding what percent of the identities are due to homology, chance, and convergence may be difficult, but it is at least formally possible. Many biologists take identical residues to indicate common ancestry in combination with stabilizing selection.

Sequence comparison allows us to partition credit, at least in principle. Doing the same thing when we are discussing morphology or gene regulatory circuits is more difficult. This is both because it is much harder to atomize the trait unambiguously and because the explanations are deeply intertwined. This difficulty does not have to block inquiry.

Focusing on convergence is the traditional way to gain insight into the selectionist forces at work. Lineages are assumed to be independent trials in a natural experiment, so convergence suggests similar selection pressures (Losos et al., 1998). Alternatively, attention to the underlying homologies² offers insight into possible origins, and relationships among and constraints on the evolution of forms in the taxa under consideration (see Amundson, 1998 for a discussion of the structuralist tradition). Devotion to chance events has been used to good effect in both understanding the distribution and abundance of lineages and in inferring times of divergence by using background mutation rates of DNA sequences. The importance of contingent events in the history of life is well described by Gould's review of the Burgess shale fossils and his discussion of which lineages got to participate in the Cambrian explosion (Gould, 1990). These three accounts are not mutually exclusive; rather, they are the strands from which evolutionary explanations are braided.³

Can gene circuits and spatial and temporal expression patterns be perceived as similar? Certainly. Are they candidates for hypotheses of

homology? I would say, absolutely yes! Now the question of diagnosis is open and difficult—but the appeals to homology, chance, and convergence as parts of an explanation are *not* especially problematic for developmental genetics (see also Gilbert et al., 1996; Gilbert and Bolker, 2001). Due to changes in developmental timing, it is often a real challenge to identify the equivalent developmental stages across lineages. Correlating equivalent developmental stages in different organisms is much like testing multiple alignment hypotheses in sequence-based comparison, though the criteria for identity are less obvious. However, if we are comparing which regulatory elements are upstream or downstream in a circuit, we can anchor our particular questions to the circuit under consideration, even before we have full resolution of the stage problem.

Can regulatory genes be homologous if the structures they produce are not? Again, I would answer this with an enthusiastic yes. I suspect that what is usually meant by “not homologous” is that the structures produced are not similar (or the part of the structures we are trying to explain are not the similarities). I find it less likely, but formally possible, that someone could convince us that the similarities of the structures are best explained by an appeal to convergence or chance or physical constraint even if the regulatory genes’ similarities were best explained by their sharing a common ancestor (i.e., they are homologous). Are tissues homologous if similarity is cryptic and apparent only at level of genes? We are constantly increasing the number of ways that we can probe and understand a tissue. As should be clear by now, I would prefer to reserve assertions of homology for the actual similarities (the noncryptic gene similarities).

THE EVOLUTION OF THE EYE

The evolution of the eye stood for years as a paradigmatic example of independent evolutionary paths fulfilling the same need. Vertebrates and mollusks have single-lens eyes (though the photoreceptive cells under the lens have opposite orientation), whereas insects have compound eyes. These differences had been taken to imply that the eye evolved (independently) numerous times. We now know that the large morphological differences share a common developmental pathway of elements for optic morphogenesis. The evidence for commonality in these developmental pathways comes from looking at similar proteins

in mammals and flies (the *Pax* proteins) (Gehring, 1999). A particular protein, called *eyeless* for its mutant phenotype in fruit flies, was shown to produce eye structures on wings and legs of flies when ectopically expressed in those locations. It seems reasonable to conclude that it must be near the top of the developmental hierarchy for eye development.

A mutation in a similar protein in mammals (Pax6, the *eyeless* homologue, based on sequence and motif similarities) results in abnormal formations of the eye. The mouse protein, when expressed in unusual locations in the fly, also results in production of ectopic fly eyes. Whether Pax6 recruits native *eyeless*, which then auto-upregulates more *eyeless*, or does the job itself is not known. But in either case, these two proteins have very similar functions. This finding also suggests that either (a) the common ancestor of flies and mice also had working eyes whose development used this protein (i.e., the common ancestor of Pax6 and *eyeless*) or (b) whatever this protein was doing in the common ancestor, it facilitated the evolution of eyes in other lineages (a Pax6-like protein is found in squid and octopus, too).

So are the eyes homologous? If we begin with similarities, we can avoid a fruitless argument. The differences between compound fly eyes and single-lens vertebrate eyes cannot support a hypothesis of homology because they are differences. This allows us to focus on the similarities; bilateral symmetry, positioning on the head, the expression patterns of regulatory genes, the pathway itself (*eyeless*, *twin of eyeless*, *sine oculis*, *eyes absent*, *dachshund* ...). All of these similarities do seem to be homologous; or, more carefully, we would credit those similarities to shared ancestry.

It is relevant to point out that work on the regulation of chick muscle development has shown that homologues of genes involved in mouse eye development (*Dach2*, *Eya2* and *Six1*) are involved in vertebrate somite (muscle) development (Heanue et al., 1999). Again by focusing on the similarities, in this case the regulatory feedback loops, we might appeal to homology while simultaneously avoiding the question of whether eyes are homologous to the segmentally organized mesodermal structures that are the embryonic precursors of skeletal muscle.

Do we need a new word for homologous gene circuits (e.g., true homology, deep homology, homiology), or should we talk about homology at different levels? I have been arguing that attribution of similarity to historical relatedness is an appeal to homology, *whenever* it is made. The additional adjectives (“true” or “deep”) do not add much.

Contingency, homology, selection (functional convergence), and physical constraints are constitutive parts of any explanation for a trait, whether it is a gene sequence, a gene expression pattern, or an adult tissue.

METHOD

While similarity surely results from a mix of explanations, a methodological preference for homology can still be defended. Looking for and highlighting homology when discussing developmental regulation serves us by generating hypotheses that inspire tests in ways that contingency and convergence do not. This does not mean that the hypothesis of homology will be supported by those tests, but we know what to do next in the laboratory.

I would like to contrast the kinds of hypotheses that are generated when we focus on differences attributed to selection rather than on similarities attributed to homology. C. J. Lowe and G. A. Wray studied several homeobox genes and concluded that they were recruited into new roles: “Each of these cases [*orthodenticle*, *distal-less*, *engrailed* expression in brittle stars, sea urchins, and sea stars] represents recruitment (co-option) of a homeobox gene to a new developmental role. . . . Role recruitment implies that the downstream targets are different from those in other phyla.” This assessment—that if the genes were recruited into new roles, their downstream targets would be different—presents a significant experimental challenge. Where to go next? What if, instead, Lowe and Wray had asserted that the upstream and downstream factors were what had been found previously in other organisms? They would then have known which genes (and expression patterns) to hunt for. This suggests that it may be methodologically useful to hypothesize homologies, especially when looking at pathways and developmental circuits, since previously characterized networks provide a list of candidates that might be involved in the new situation.

Most evolutionists recognize that explaining every feature of an organism as an adaptation can become mere storytelling. This is why nonhomologous similarities are of special interest (i.e., distinct clades that share the feature of interest). With multiple clades, if we have ruled out homology, chance, and physical constraint, we can then look to commonalities in the respective environments to suggest that there may have been similar selection regimes. Dispensing with the compar-

ative step can result in an uncritical adaptationism that explains (by an appeal to natural selection) the existence of a trait that is unique or novel in our lineage of interest. Without multiple lineages for comparison (focusing just on the autapomorphy) we are free to assert that the population faced whatever challenges could select for the structures under consideration.

These selectionist accounts are too difficult to challenge and can be produced at will. Flying, for example, has arisen numerous times from flightless ancestors. Should every structure that makes flight possible be treated as a complete novelty in each lineage? Because of the possibilities of finding developmental and structural homologies, there are certain parts of the explanation of flight in these lineages that will be better examined by restricting our inquiry to the three vertebrate clades that had flight (pterosaurs, birds, and bats) as distinct from the flying insects. It should be clear that comparative work is critical, and fortunately the sequencing projects and advances in transcript and protein profiling make comparative work ever easier. And the information that can be gleaned from comparative work (borrowing annotations and candidates justified by hypotheses of homology) should motivate ever more comparative studies.

From a methodological standpoint, then, identifying homologies has salutary effects. First, it demands an actual comparison. Second, in comparing across clades we can easily generate hypotheses. If our trait of interest stands in particular relations to other features in one organism—a given regulatory gene, for example—we can hypothesize that it will also do so in another. We still may not find the targets, but hypotheses of homology can tell us what to test initially.

As we move from the initial wave of genome sequencing to the wonderfully more complicated problems of understanding what proteins do, how they interact, and how they are regulated, we will need principled ways to interpret profiling information, generate network hypotheses, and annotate myriad functions. In that project, homology plays a useful role both in giving a methodological starting point for generating candidate interactions and in reminding us that inference from similarity is difficult. The use of comparative developmental genetics to generate hypotheses of homology should be embraced. Expression patterns and regulatory networks are legitimate foci for hypotheses of homology, because they help us understand the origin and evolution of structure. Finally, attributions of homology should be

sought, solely on methodological grounds, because they offer us specific testable hypotheses.

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NOTES

1. The paralogy and orthology distinction was introduced to distinguish two kinds of homology in proteins (Fitch, 1970). Paralogy is meant to cover those situations when a gene duplication allows related proteins to evolve independently within the same lineage. Orthologues are found in different individuals, and paralogues can be found in the same individual (reviewed in Patterson, 1987).

2. "The importance of the science of Homology rests in its giving us the key-note of the possible amount of difference in plan within any group; it allows us to class under proper heads the most diversified organs; it shows us gradations which would otherwise have been overlooked, and thus aids us in our classification; it explains many monstrosities; it leads to the detection of obscure and hidden parts, or mere vestiges of parts, and shows us the meaning of rudiments. Besides these practical uses, to the naturalist who believes in the gradual modification of organic beings, the science of Homology clears away the mist from such terms as the scheme of nature, ideal types, archetypal patterns or ideas, &c.; for these terms come to express real facts.

The naturalist, thus guided, sees that all homological parts or organs, however much diversified, are modifications of one and the same ancestral organ; in tracing existing gradations he gains a clue in tracing, as far as that is possible, the probable course of modification during a long line of generations. He may feel assured that, whether he follows embryological development, or searches for the merest rudiments, or traces gradations between the most different beings, he is pursuing the same object by different routes, and is tending towards the knowledge of the actual progenitor of the group, as it once grew and lived. Thus the subject of Homology gains largely in interest" Charles Darwin, *On the Various Contrivances by Which British and Foreign Orchids Are Fertilised by Insects*, 2nd ed. (London: John Murray, 1877), pp. 233–234.

3. This insistence on a pluralistic account (including homology, selection, and chance) is not meant to defend claims of percent homologue. A particular similarity either is or is not homologous. The use of "homology" with respect to gene sequences to indicate percent similarity should be avoided. I am only making the uncontroversial claim that any comparison of particular traits in toto will be require an appeal to homology, convergence, and chance.

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URLs FOR RELEVANT SITES

Flybase: The Interactive Fly describes fly proteins and their actions and interactions. <http://flybase.harvard.edu:7081/allied-data/lk/interactive-fly/aimain/1aahome.htm>

The Hennig Society. If your work with homologies brings you to constructing trees, you will want to explore cladistics. <http://www.cladistics.org/education.html>

Kyoto Encyclopedia of Genes and Genomes (KE66) is an effort to capture molecular and cellular biology in terms of the information pathways that consist of interacting proteins. <http://www.genome.ad.jp/kegg/>

Virtual Embryo is a collection of developmental biology tutorials and links. <http://www.ucalgary.ca/UofC/eduweb/virtualembryo>