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How Complexity Originates: The Evolution of Animal Eyes

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Abstract

Learning how complex traits like eyes originate is fundamental for understanding evolution. In this review, we first sketch historical perspectives on trait origins and argue that new technologies afford key new insights. Next, we articulate four open questions about trait origins. To address them, we define a research program to break complex traits into component parts and to study the individual evolutionary histories of those parts. By doing so, we can learn when the parts came together and perhaps understand why they stayed together. We apply this approach to five structural innovations critical for complex eyes and review the history of the parts of each of those innovations. Eyes evolved within animals by tinkering: creating new functional associations between genes that usually originated far earlier. Multiple genes used in eyes today had ancestral roles in stress responses. We hypothesize that photo-oxidative stress had a role in eye origins by increasing the chance that those genes were expressed together in places on animals where light was abundant.

1. INTRODUCTION

How do complex (multipart and functionally integrated) biological traits such as eyes, feathers and flight, metabolic pathways, or flowers originate during evolution? These biological features often appear so functionally integrated and so complicated that imagining the evolutionary paths to such complexity is sometimes difficult. Although structurally and functionally complex systems clearly originated through evolutionary processes, broad questions still remain about which evolutionary processes more commonly lead to innovation and complexity. Here, we use eye evolution as a focus for how to implement a research program to gain understanding of the origin of complex traits. This research program requires first defining the trait in question and then inferring with comparative methods the timing of past evolutionary events, including changes in function. By understanding when different components came together, we can begin to understand how they came together, and by making inferences about possible functions and environmental context, we can begin to understand why those components stayed together. Eye evolution is particularly amenable to such a research program because we can use optics to predict function from morphology, and we can use extensive knowledge about the genetic components of eyes and light sensitivity to predict and test gene functions in a broad range of organisms. This approach leads to a narrative on animal eye evolution that, although still incomplete, is already rich and detailed in many facets. We know that a diversity of eyes evolved using functional components that interact with light. All of these components were used outside of eyes and all were recruited into light-receptive organs during evolution at many different times and in many different combinations. One common theme emerges: Many eye genes had ancestral roles related to stress response. Therefore, evolved responses to light as a stressor may have brought together many of the genes that today function in eyes.

2. PAST AND PRESENT PERSPECTIVES ON ORIGINS

We begin with a sketch of two historical perspectives on trait origins that influence current perceptions of the topic. We have termed these the gradual–morphological perspective and the binary–phylogenetic perspective. Next, we explain these perspectives and their shortcomings and then explain how new information and new technology allow us to enrich our understanding of trait origins compared with the historical perspectives.

2.1. Two Incomplete Perspectives on Trait Origins

The gradual–morphological model provides a typical evolutionary narrative for the origins of complex traits, involving gradual elaboration driven by natural selection (Darwin 1859, Nilsson & Pelger 1994, von Salvini-Plawen & Mayr 1977). When applied to eyes, the model begins with a light-sensitive patch of cells, which evolves to form a deeper and deeper cup and progresses toward an increasingly more efficient lens within the cup. This gradual progression was first imagined by Darwin (1859) when he explained a corollary to natural selection: If complex traits like eyes were produced by natural selection, there should exist a series of functional intermediates between a light-sensitive patch and a complex eye. To highlight these intermediates, Darwin reviewed functional variation in eye complexity in different species. Later, von Salvini-Plawen & Mayr (1977) illustrated several cases in which related species, such as various snails, showed graded variation between eyespots and lens-eyes. Taking the idea one step further, Nilsson & Pelger (1994) quantified the gradual morphological changes probably necessary to evolve from patch to eye and estimated that the progression can occur rapidly in geological time. Variations of

the gradual–morphological model are common in textbooks and in popular books and videos explaining natural selection.

Although these gradual–morphological progressions are logical and provide a powerful and visual way to imagine the stepwise evolution of complexity, they also have at least two shortcomings (Oakley & Pankey 2008). First, the linear series incorrectly implies that evolution always proceeds from simple to complex (Oakley & Pankey 2008). Instead, evolution often results in loss or reduced functionality of structures, including eyes (Porter & Crandall 2003). Second, the source of variation is not addressed. In fact, each gradual step requires natural selection to act upon variation. However, the developmental–genetic basis for how this morphological variation originates was not considered (understandably, given the technological limitations of the time). Further, discrete origins were not considered, except again by assuming that the variation simply arose in the past. For example, the origin of light sensitivity itself was not addressed, nor the origin of the cup structure or of the first lens material. These discrete origins were treated no differently than the gradual elaboration of existing structures. Therefore, although not uninformative, using a gradual series of eyes as a model for how evolution proceeds is incomplete, because it assumes morphological variation without addressing the mechanisms leading to variation. How did light sensitivity originate? How did lenses or eye pigmentation originate? Answering these questions is critical for a complete picture of eye origins and evolution.

A second perspective, which we term binary–phylogenetics, can be useful but makes potentially misleading assumptions. Phylogeneticists often score complex traits as binary (present/absent) to study character distributions in a clade. For example, armed with a phylogenetic tree, an evolutionist might score species as eyed or eyeless, to infer the number and/or timing of gains and losses (e.g., Oakley & Cunningham 2002; **Figure 1**). On the basis of analyses like parsimony or maximum likelihood, phylogeneticists estimate trait history as a series of all-or-none gains and losses. This approach has value—for example, by providing an estimate of when a fully integrated trait might have evolved. However, scoring complex traits as present or absent implicitly assumes that all components of the trait are gained or lost in concert. Even if the separate components of multipart systems have different evolutionary histories, as we argue they usually do, scoring complex traits as binary traits makes it impossible to infer the separate histories of parts. This

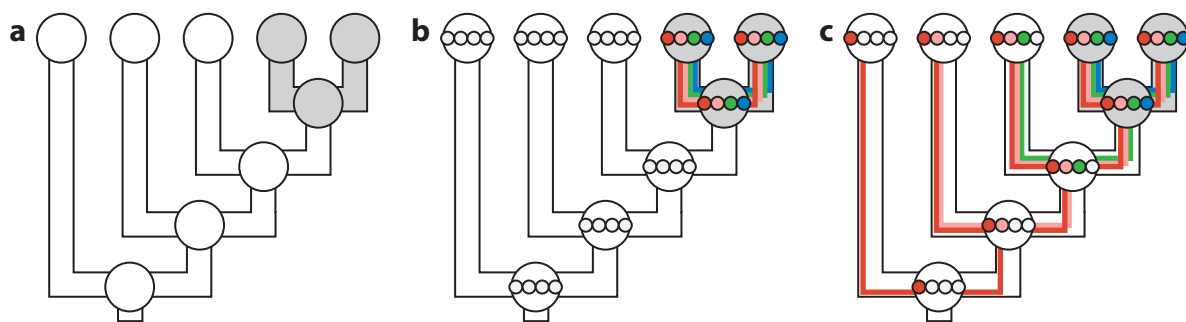


Figure 1

(a) Phylogeneticists sometimes score complex traits like eyes as absent (*white*) or present (*gray*) in different species. This makes the implicit assumption that all components of that trait share the same evolutionary history. (b) However, complex traits comprise many components, as illustrated by four small, colored circles. For eyes, these traits might be lenses, opsin genes, pigments, and ion channels. By only scoring complex traits as present or absent, we force a punctuated mode of evolution, whereby all components are gained and lost together. Under such a model, a complex trait and each of its components is either fully present or fully absent. (c) This panel illustrates a more gradual mode of component evolution, in which one component is added at each of four different ancestral nodes. Explicit consideration of the component histories could allow for inference of this gradual mode of evolution.

approach imposes a punctuated mode of evolution, such that all components of a complex trait originate or become extinct simultaneously (but see Marazzi et al. 2012 for an alternative phylogenetic model). We advocate that studying the history of separate components of multipart traits is a valuable extension to the binary–phylogenetic approach.

2.2. New Information, New Perspectives on Origins

Newfound connections between genotype and phenotype allow new ways to explore the origins of multipart traits. Historically, it was not possible to go beyond the gradual–morphological models because the developmental–genetic basis of trait variation was unknown. Information to extend the binary–phylogenetic perspectives on origins was also missing. Although phylogeneticists historically could score the presence or absence of a trait like an eye by simply looking at a species, knowing the components of those eyes and their separate histories requires more information. Even when molecular components became known for model organisms, extending that knowledge outside of models was not feasible, which made comparative, evolutionary studies intractable. We now know many molecular components of eyes, and we now can obtain extensive information about these components from nonmodel organisms. When these components are proteins, as is often the case, we can trace their individual evolutionary histories. Instead of the all-or-none perspective that is implicit in scoring traits like eyes as present or absent, tracing individual histories of components highlights that some components are ancient and others are new. This understanding leads us to new questions and insights about evolutionary origins of traits like eyes.

3. FOUR OPEN QUESTIONS ON ORIGINS: EYE EVOLUTION AND BEYOND

3.1. What Types of Mutations Are Involved in Origins?

Mutations that became fixed in populations are the primary source of evolutionary change, and various types of mutation may be more commonly associated with trait origins than others. Here, we differentiate the mutational requirements for two modes of trait origin: coduplication and co-option. Coduplication is defined as multiple parts of a trait originating simultaneously. Simultaneous duplication requires large-scale copying of entire genomes or chromosomal blocks, which occurred early in vertebrate history and led to the duplication of phototransduction genes (Nordström et al. 2004). Following such block duplication, each set of duplicates must also diverge in function, which requires other mutations after the duplication event. For coduplication to occur without whole genome duplication (and without many simultaneous, yet independent, mutations), cofunctioning genes could also be located near each other on a chromosome so they can be copied all at once.

Co-option is defined as “the acquisition of new roles by ancestral characters” (True & Carroll 2002, p. 54), yet definitions of co-option are diverse and often conflate pattern and process or structure and function. Given the diverse definitions for the term, a comprehensive survey of the mutational causes of co-option is challenging. For the purpose of this review, we simply point out that co-option often involves regulatory mutations that cause a gene (whether duplicated or not) to be expressed in a new place. Because there is no general relationship between regulatory sequence and spatiotemporal gene expression, inferring the history of co-option can be challenging. Usually, inferring co-option requires comparing gene function with the phylogenetic history of those genes (Plachetzki & Oakley 2007, Serb & Oakley 2005). Therefore, the specific mutational source of co-option may often remain unknown, especially in very ancient comparisons.

3.2. Do Multipart Traits Form Gradually or Abruptly?

The different parts of complex traits like eyes could come together gradually, when they are added sequentially over longer periods of time, or could originate abruptly, with all the parts of a trait coming together in a short period of time (Plachetzki & Oakley 2007). Gradual versus punctuated patterns of origin are two ends of a spectrum, and intermediates are also possible: A particular trait may have had bouts of both gradual and punctuated addition of components before arriving at its current state. Furthermore, some traits may have originated gradually and others abruptly. Armed with increasing knowledge of traits' components and with phylogenetic methods to reconstruct the timing of their origins, we are now in a position to elucidate the origins of eyes and other traits to determine gradual versus punctuated origins, which could lead to a general understanding of the mechanisms underlying the origin of complex traits. Similar ideas were explored in the work of Plachetzki & Oakley (2007), in which they suggested that coduplication of all parts of a trait (punctuated change) could serve as a null model for the origin of multipart systems. The inferred origin(s) of traits can serve as a null expectation for the timing of origin of each part. If parts are older than the trait, those parts may have been co-opted or recruited from a previously existing function into the newly evolved trait. Coduplication serves as a useful null expectation because it can be rejected by any part of a complex trait. The dual phototransduction systems of vertebrate retinas, one used in rods and the other in cones (Hisatomi & Tokunaga 2002, Nordström et al. 2004), may be a prime example of coduplication. In contrast, there are few other examples of coduplication, which is often rejected in favor of co-option (Oakley et al. 2007). One reason that co-option may be much more common than coduplication is that the mutational events required for coduplication may be less common.

3.3. What Originates First: Structure or Function?

How do functional changes relate to structural changes during evolution (see also Ganfornina & Sánchez 1999)? This is an enduring yet underexplored question about trait origins (Darwin 1859, Mayr 1963, Muller & Wagner 1991). One possibility is that structural changes arise first (**Figure 2a**). For example, a gene could duplicate first (a structural change in DNA), followed by a gain in function in one of the new genes. This corresponds to the classic neofunctionalization model of gene evolution (Ohno 1970). Similarly, a cell type, organ, or other structure could furcate (as defined by Oakley et al. 2007) during evolution, followed by a change in function in one of the new structures. This neofunctionalization process would yield a pattern whereby closely related structures have different functions and outgroup structures share a function with one of the ingroup modules (**Figure 2a**). Alternatively, functional changes could evolve first. In this scenario, a biological structure like a gene, cell, or organ could first gain a function, making it multifunctional [a process sometimes termed gene sharing (Piatigorsky 2007)]. Later, the structure could duplicate and subdivide the ancestral functions between the duplicates, in a subfunctionalization or division of labor mode of evolution (Arendt et al. 2009, Darwin 1859, Force et al. 1999). Subfunctionalization could yield a different pattern than neofunctionalization yields, whereby subfunctionalization leads to two closely related modules with different functions and a multifunctional outgroup module (**Figure 2b**).

3.4. What Is the Environmental Context of Origins?

Inferring when and where traits and their components originated could give information about the environmental context of origins. Some broad patterns about origins are already evident

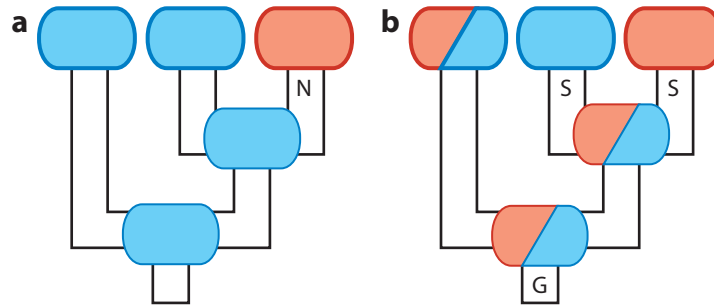


Figure 2

Rounded rectangles represent a generalized biological structure (gene, pathway, organ, etc.). Blue and red colors represent different functions, broadly construed (including spatial, temporal, or contextual differences as well as separate biochemical functions). The functions at the tips of the trees are observed (illustrated with a bolder outline), but functions at the nodes are inferred with phylogenetic techniques. (a) A new structure evolves first, before a new function. Here, two closely related ingroup structures have distinct functions, and the outgroup structure has the same function as one of the ingroup members. In this case, parsimony favors a single change in function leading to the functionally unique ingroup structure. In the gene duplication literature, this is termed neofunctionalization (Force et al. 1999). (b) A new function evolves first, before the structure duplicates. Here, two closely related ingroup structures have nonoverlapping functions, and an outgroup structure performs both functions. With this phylogenetic distribution of structures and functions, a parsimonious explanation is subfunctionalization or division of labor, such that an ancestral structure had two functions that specialized after duplication. In both panels *a* and *b*, other evolutionary histories are possible that could lead to conclusions of the opposite evolutionary process, but these conclusions require more events and are less parsimonious. Abbreviations: G, gain of function; N, neofunctionalization (equals a gain of function); S, subfunctionalization.

from paleontological distributions and phylogenetic studies. For example, many evolutionary novelties that define major taxonomic clades originated in the tropics (Jablonski 1993) and in shallow marine environments (Jablonski 2005). In addition, new traits may tend to originate in lineages that shifted environments, such as transitions between aquatic and terrestrial, marine and freshwater, and benthic and pelagic life histories (e.g., Lindgren et al. 2012). In fact, the origins of image-forming eyes may be correlated with transitions from sedentary to active lifestyles (de Queiroz 1999). These general patterns relate to species-level environmental interactions, but similar ideas can be applied to other levels, like gene or cell type. For example, genes expressed in different organismal locations experience different cellular environments. One logical hypothesis about cellular environments and origins is that light creates a stressful environment for cells, such that the origins of new expression patterns of light-interacting genes may often be responses to light-induced stress. We return to this hypothesis in Sections 5 and 6.

4. A RESEARCH PROGRAM TO INVESTIGATE ORIGINS

4.1. Define the Trait and Its Parts

How can we address unresolved questions about the origins of multipart systems like eyes? The first step is to define the trait in question, which involves enumerating its parts. Here we face the challenge that complex traits like eyes contain many generic genetic components, like basic cellular machinery, which are not especially informative about the evolution of eyes per se. Identifying the parts unique to eyes may sound tempting; however, with this strategy, most (or even all) components would be excluded because they have functions outside of eyes, even if those

components are functionally critical to eyes. One way forward is to identify and explicitly define modules with important functions. For visual systems, approachable modules whose evolutionary histories can be understood include pigment synthesis pathways and phototransduction cascades. We also know of structural components of lenses and corneas whose histories can be traced. These parts are enumerated and established in model organisms, and we can search for similar components in the rapidly growing database of fully sequenced genomes. Furthermore, high-throughput sequencing in nonmodel organisms can produce detailed transcriptomes from which genetic components can be identified by similarity to known genes (Porter et al. 2013, Speiser et al. 2013). After defining the trait, we can better understand when, how, and why complex traits like eyes originated during evolution.

4.2. Estimate When the Trait Originated

Estimating the relative or absolute timing of trait origins can be done using phylogenetic methods to compare the distribution of presence/absence of traits with phylogenetic history (**Figure 1a**). For example, if two species share a trait, we might infer that their common ancestor also had that trait and thus the trait originated earlier. To understand the history of animal eyes and their components specifically, major animal clades become a focus. We see that many light-interaction components are well characterized in protostomes like flies and deuterostomes like vertebrates, indicating an origin of the trait at or before bilaterians. Many traits are present in bilaterians and cnidarians, implying an origin at or before Eumetazoa, and many traits are also present in sponges or even choanoflagellates, implying an origin before animals. This core logic for determining relative timing of a trait compared with a phylogenetic tree is based on parsimony, and the enterprise of understanding the evolutionary history of traits, often termed ancestral state reconstruction or character mapping, has developed a rich array of statistical techniques (Cunningham et al. 1998).

We can also estimate the absolute timing of trait origins when character mapping is performed on a time-calibrated phylogeny (Alexandrou et al. 2013). Estimating character histories and the absolute timing of evolutionary events is not trivial. Phylogenetics has an extensive literature on the challenges involved in character mapping, including limitations of character evolution models (e.g., Cunningham et al. 1998) and issues of accurately estimating divergence times using relaxed molecular clock models and fossil calibrations (e.g., Ho et al. 2005). Despite these challenges, estimating when a particular trait first evolved serves as an initial point of comparison for the evolutionary histories of the parts that compose the trait under investigation. Although this initial estimate is a starting point, one quickly realizes a major challenge: Different components of a trait invariably have different histories. So instead of an all-or-none tracing of traits on a phylogeny, the individual histories of those parts and how they came to function together must be the focus. Therefore, the critical next step is to understand those separate histories.

4.3. Determine When the Components Originated and Became Functionally Associated

Once a trait and target suite of parts is identified—such as the genes used to make a pigment or a lens—the next step is to determine when the parts themselves originated. Unfortunately, similar genetic structures do not always imply similar functions. A full understanding of the history of complex traits also requires estimating the history of function. To understand trait origins, we must consider several aspects of function. First, a gene's biochemical function is always of critical importance. Second, the molecules with which a gene interacts are critical to function. Third, the site and timing of gene expression has critical implications for function. Finally, a particular

gene is of interest because of how it contributes to an organismal function. All of these functions change over evolutionary time, and because we do not have direct ways to test the function of genes from long-extinct ancestors, we must rely on comparative analyses of function in living organisms. Because comparative analyses of function rely on sound experimental demonstrations across organisms at different levels of function, understanding the evolutionary origins of complex traits requires a diverse suite of information from genetics, biochemistry, physiology, development, behavior, and phylogenetics. We next summarize the state of this information relating to the evolution of light-sensing systems in animals.

5. LIGHT-INTERACTION GENES AND THEIR EVOLUTIONARY ORIGINS

A recent synthesis of eye evolution by Nilsson (2009, 2013) departs in multiple ways from the traditional gradual–morphological model described in Section 2.1 and provides new opportunities to understand the evolutionary origins of eyes. First, by making use of knowledge about how morphological structures interact with light, Nilsson’s synthesis explicitly considers function by calculating the amount of light required to perform different light-mediated behaviors. In earlier gradual–morphological models, functional considerations rarely went beyond the idealized notion that more intricate optical structures could be functionally better and could evolve by natural selection. Second, Nilsson’s recent synthesis incorporates a more punctuated perspective than the gradual–morphological model by enumerating at least four structural innovations leading to four classes of photoreception that underlie different organismal behaviors. After originating light-sensing mechanisms, organisms with nondirectional photoreception (Class 1) are able to sense changes in light intensity. After originating screening mechanisms such as light-absorbing pigments adjacent to photoreceptors, organisms gain directional photoreception (Class 2). After more finely dividing the visual field by adding a curved array of shielded photoreceptors, organisms may gain low-resolution spatial vision (Class 3) by adding specializations to the membranes of their photoreceptor cells that enhance the capture of photons. Finally, after evolving a focusing apparatus, like a lens, organisms may evolve high-resolution vision (Class 4). We hasten to add that, although simple photoresponses may be achieved without nervous systems (Jékely 2010, Nordström et al. 2003, Rivera et al. 2012), complex eyes require rather elaborate nervous systems (e.g., Randel et al. 2014). Although we could apply a similar approach to neural circuits, we restrict this review to the optical components of eyes.

Nilsson’s synthesis defines critical innovations whose multipart evolutionary histories can be studied: phototransduction cascades, screening apparatuses, membrane elaborations, and focusing apparatuses. To these four, we add another innovation and hypothesize that a visual cycle—a specialized pathway for regenerating chromophores of visual pigments—may often be critical for vision that provides fine spatial and/or temporal resolution. Many of these innovations fit well into the component-based approach we promote here because their genetic parts are characterized, allowing researchers to separately trace the origins of each of those parts. Next, we discuss what is known about each of these innovations, including definitions of each trait and its parts, estimates of each trait’s time of origin, and estimates of evolutionary histories and origins of the individual parts.

5.1. Light Detection: Origins of Photosensitivity

The most basic light-sensitivity function is a nondirectional light sense. The simple detection of light is immediately useful for several organismal functions, including telling day from night, setting daily or seasonal rhythms, or determining depth in the water. Nondirectional light sensors

Table 1 Four different phototransduction cascades

Main model	G protein α subunit	Intermediary enzyme	Mechanism	Ion channel
Flies (Hardie 2001, Montell 1999)	G- α -q	Phospholipase C	Mechanical (Hardie & Franze 2012)	TRP
Vertebrates	G- α -t	Phosphodiesterase	cGMP hydrolysis	CNG
Scallops (Kojima et al. 1997)	G- α -o	Guanylate cyclase	cGMP increase	K ⁺ channels
Box jellyfish (Koyanagi et al. 2008)	G- α -s	Adenylyl cyclase	cAMP increase	CNG? (Plachetzki et al. 2010)

Abbreviations: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CNG, cyclic nucleotide-gated; K, potassium; TRP, transient receptor potential.

are often found dispersed in the skin of many animals (Ramirez et al. 2011). The structural innovation required for light sensitivity is the molecular machinery for detecting light. Across all of life, there exist only a handful of different molecular mechanisms that mediate biological responses to light; these mechanisms include Type II opsins (animals only), Type I opsins (e.g., halorhodopsin, bacteriorhodopsin, channelrhodopsins of bacteria, and many eukaryotes), lite-1 (nematodes and flies), phototropin (plants), neochrome (ferns and green algae), phytochrome (plants, fungi, bacteria), cryptochrome (plants and animals), light-oxygen-voltage-sensing proteins (bacteria, plants, fungi), and a photoactivated adenylyl cyclase (euglenoids) (Björn 2007, 2015; Krauss et al. 2009; Ntefidou et al. 2003; Spudich et al. 2000). Although the component-based approach advocated here could be used to understand the origins of any of these molecular mechanisms of light sensitivity, here we focus on opsin-based phototransduction cascades because many components are well-studied and they form the keystone functional modules of almost all animal eyes. We argue later that Type II and Type I opsins are not homologous and that Type II opsins originated within animals, at or before the common ancestor of eumetazoans. However, other components of phototransduction are older, suggesting that opsin-based light sensitivity originated when the sensor in an older signal transduction pathway became sensitive to light.

5.1.1. Define the trait: opsin-based phototransduction. On the basis of studies primarily in model species of flies and mammals, we have a good understanding of many parts of opsin-based phototransduction and their functional interactions. An important take-home message is that there is not a single, canonical phototransduction cascade; rather, there are at least four dramatically different ones (**Table 1**). Opsins are G protein-coupled receptors (GPCRs) that bind a light-reactive chromophore (usually retinal). Collectively, an opsin/chromophore complex is termed rhodopsin. When a photon strikes the chromophore, it changes from *cis*- to *trans*-, causing a concomitant change in the opsin protein. The opsin shape change exposes sections of the protein that activate signal transduction cascades leading to nervous impulses in the photoreceptor cells that house opsin. The nonopsin components of phototransduction are the components of GPCR pathways, including heterotrimeric G proteins, intermediary enzymes, and ion channels. In addition to opsins from very divergent subfamilies, the nonopsin components vary and comprise different cascades.


5.1.2. Estimate when opsin-based phototransduction originated. Estimating the origin of a trait involves comparing the phenotypes and phylogenetic histories of species. The trait of phototransduction can be conceived as a molecular phenotype, but it also manifests as physiological

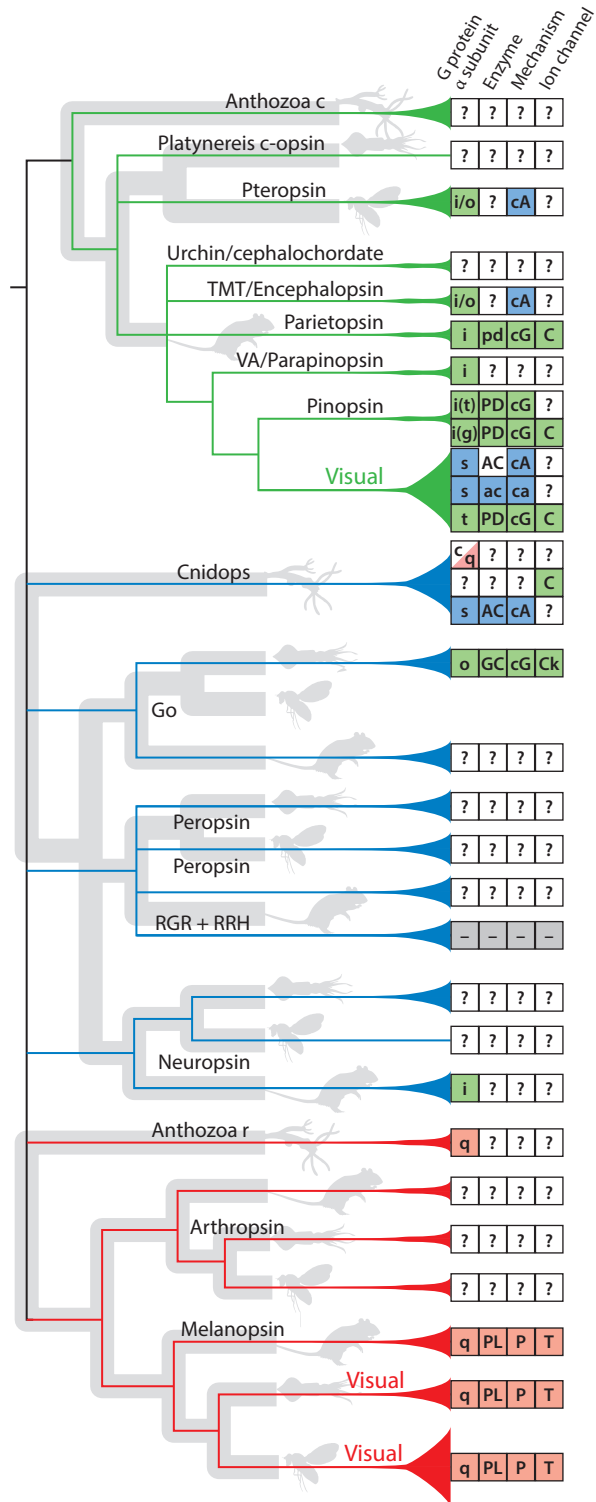
phenotypes that can be scored as present or absent and compared with a phylogeny. Physiologically, phototransduction results in a change in a cell's membrane potential that can be measured using electrical recordings from single cells. Even in the absence of single-cell recordings, electroretinograms and microspectrophotometry may suggest opsin-based phototransduction. Comparing physiological phenotypes with phylogenetic relationships of animals indicates that phototransduction is ancient, because both bilaterian animals and some nonbilaterian animals have the trait (Brown & Wiesel 1959, Granit 1941). This relative estimate for the timing of photoreceptor cell origins provides a framework for studying the components of these cells, especially the genes involved in opsin-based phototransduction. Did the components originate at the same time as the cells? If not, which components are new and which are old? What changes allowed the separate parts to function together? Separately addressing the evolutionary histories of the components can begin to answer these questions.

5.1.3. Determine when the components of opsin-based phototransduction originated. We now have a strong consensus that opsins originated within animals and not earlier. Since the 1980s we have known that fly (a protostome) and cow (a deuterostome) opsins are homologous and therefore originated at or before the first bilaterian animals (**Figure 3**). Only recently has clear evidence that Type II opsins exist outside bilaterian animals emerged; this evidence indicates a pre-eumetazoan origin of opsins (Koyanagi et al. 2008, Plachetzki et al. 2007, Suga et al. 2008). Furthermore, the absence of opsin in the genome sequence of the sponge *Amphimedon queenslandica*, the choanoflagellate *Monosiga brevicollis*, and multiple fungi, including *Saccharomyces cerevisiae*, has suggested Type II opsins might have originated within animals (Plachetzki et al. 2007).

Figure 3

The evolution of opsins and phototransduction. A phylogeny of opsin genes is shown with green, blue, and red branches. Phylogenies of species in gray illustrate paralogous opsins in Cnidaria (hydra silhouette), Lophotrochozoa (squid silhouette), Ecdysozoa (fly silhouette), and Deuterostomia (mouse silhouette). The relationships shown are based mainly on Hering & Mayer (2014), and the paralogous relationships implied—c-opsins (*green* branches), r-opsins (*red* branches), and type 4 opsins (*blue* branches)—are based on considerations from other analyses (Feuda et al. 2012, 2014). We exclude ctenophore opsins from this summary because of uncertainty in the animal phylogeny and because they fall close to known major groups of opsins (Feuda et al. 2014, Hering & Mayer 2014). At the right is a summary of functional experiments on phototransduction, focusing on cases in which particular opsin genes are functionally linked to a G protein α subunit, an intermediary enzyme, a cellular mechanism, and/or an ion channel. We colored components' boxes on the basis of their general association with Gi/o (*green*), Gq (*red*), or Gs (*blue*) α subunits. The letters o, t, g, i, s, q, and c refer to different G protein α subunits, in which t is transducin and g is gustducin. The letters o and i are colored green because they are in one gene family; c is a cnidarian-specific G protein (Mason et al. 2012). Lophotrochozoa photoisomerases (retinochromes) are known but highly diverged, making reliable phylogenetic placement difficult, so they are excluded from this figure. We detail opsin groups and functional experiments from top to bottom of the figure, along with functional evidence and references, in **Supplemental Table 1** (follow the **Supplemental Material link** from the Annual Reviews home page at <http://www.annualreviews.org>). Abbreviations: ac, adenylyl cyclase decrease; AC, adenylyl cyclase increase; C, cyclic nucleotide-gated (CNG) channel; ca, cyclic adenosine monophosphate (AMP) decrease; cA, cyclic AMP increase; cG, cyclic guanosine monophosphate (GMP); Ck, a potassium channel with properties similar to CNG; GC, guanylate cyclase; P, phosphatidylinositol 4,5-bisphosphate; pd, phosphodiesterase (PDE) that lowers cyclic GMP; PD, PDE that increases cyclic GMP; PL, phospholipase C. Gene names originally derived from abbreviations include the following: RGR, retinal G protein receptor; RRH, retinal-pigment-epithelium rhodopsin homolog; T, transient receptor potential; TMT, teleost multiple tissue; VA, vertebrate ancient. Dashes represent isomerases that presumably do not initiate a G protein-coupled receptors cascade.

 **Supplemental Material**



Even though some Type II opsin-like sequences exist outside of animals, no evidence that they are functional opsins has been found. This lack of evidence is consistent with our assertion that opsins originated within animals. One intriguing candidate was a Type II opsin-like sequence in the chytrid fungus *Allomyces macrogynus* (Heintzen 2012). This sequence was a particularly intriguing result in light of an earlier study by Saranak & Foster (1997), which interrupted retinal synthesis in *A. reticulatus* to show that phototactic behavior of zoospores depends on retinal. Because opsins (Type I and Type II) are the only known retinylidene proteins (Björn 2007, Spudich et al. 2000), the use of retinal in phototaxis indicated that *A. reticulatus* very likely uses opsin to detect light. Recent experiments on phototactic zoospores of a third closely related species (*Blastocladiella emersonii*) has indicated that light sensitivity is not due to a Type II-like opsin but rather to a fusion gene that includes a Type I opsin (Avelar et al. 2014). Because most chytrid Type II-like opsins lack the critical lysine residue present in all known opsins and because phototactic behavior can be ascribed to a Type I opsin, no convincing evidence remains for Type II opsins outside of animals. Therefore, we maintain that Type II opsins originated near the common ancestor of eumetazoan animals (Plachetzki et al. 2007).

Some researchers still suggest that Type I and Type II opsins are homologous; because Type I opsins are present in bacteria, this points to a very ancient origin of opsins. Mackin et al. (2014) recently resurrected the homology hypothesis, claiming that structural similarities and a lack of functional constraint indicate homology. They further speculate that Type I opsins evolved from Type II opsins through an ancient horizontal transfer event that led to erasure of all historical signal of homology, except for primary structural features (Mackin et al. 2014). Although that hypothesis is challenging to test scientifically, a number of facts instead indicate nonhomology and therefore convergent origins of Type I and Type II opsins. First, no amino acid similarity beyond a random expectation of similarity has been found (Spudich et al. 2000). Second, crystal structures of Type I and Type II opsins are known, and structural comparisons show strong differences in protein structure (reviewed in Spudich et al. 2000). Third, only Type II opsins interact with G proteins. Fourth, Type I opsins show a signal of origin by domain duplication, but Type II opsins show no such signal (Larusso et al. 2008). Fifth, Type I and Type II opsins often use different retinal chromophores (reviewed in Spudich et al. 2000). This evidence indicates that the similarities between Type I and Type II opsins evolved convergently, consistent with our assertion that the Type II opsins used in most eyes originated within animals.

Even though opsins originated in animals, other phototransduction components predate animals. Phototransduction cascades are GPCR cascades, and whereas opsins originated within animals from non-light-sensitive receptors, other components of phototransduction have more ancient origins. Therefore, the origin of the first animal phototransduction cascade probably evolved when a GPCR became light sensitive, perhaps by evolving to bind a chromophore as all extant opsins do today. The additional diversity of phototransduction cascades evolved later, again from existing components. Here, downstream parts—including arrestins, G proteins, intermediary enzymes, and ion channels—probably were used in other GPCR cascades before their functional association with opsin. If so, their ancient histories indicate that duplicated opsins diversified by co-opting existing downstream components of other GPCR pathways to form multiple phototransduction cascades, probably caused by mutations in opsin that activated different G proteins (Oakley & Pankey 2008, Plachetzki & Oakley 2007, Plachetzki et al. 2007).

Phototransduction components that predate phototransduction itself include at least the following: arrestins, G protein α subunits, and cyclic nucleotide-gated (CNG) and transient receptor potential (TRP) ion channels. Arrestins function in signal transduction by interacting with GPCRs like opsin to regulate receptor activity (reviewed in DeWire et al. 2007). Functionally characterized arrestins are present in deuterostomes (Nakagawa et al. 2002) and protostomes

(Gomez et al. 2011, Mayeenuddin & Mitchell 2003), and sequences are known from sponges and choanoflagellates (Speiser et al. 2014b). Core arrestin domains are present in fungi in pH sensors (Herranz et al. 2005). Opsins activate heterotrimeric G proteins, which also predate animals, as they are known from fungi and plants (Ullah et al. 2001). Even the different G protein α subunit genes that help define different phototransduction cascades (G- α -s, G- α -t, G- α -o, and G- α -q) originated by duplication prior to metazoans (Suga et al. 1999). CNG ion channels are involved in a variety of signaling cascades and may be the ancestral ion channel in phototransduction (Plachetzki et al. 2010). If so, signaling cascades involving TRP probably were co-opted somewhat later (Plachetzki et al. 2010), although still early in animal evolution. TRP ion channels form an ancient—and structurally and functionally diverse—superfamily. The TRP ion channels involved in phototransduction are from the TRP-C subfamily, which itself predates animals (reviewed in Venkatachalam & Montell 2007).

5.2. Screening Pigments: Multiple Origins of Directional Photoreception

By combining screening pigments and photoreceptors to evolve eyespot structures, organisms gain the function of directional photoreception, which is useful for tasks such as phototaxis and the detection of motion (Nilsson 2013). Eyespots can be quite simple morphologically, yet even single photoreceptors may provide directional photoreception to mobile organisms if they are screened by pigments appropriately (Jékely et al. 2008, Nordström et al. 2003). In more complex visual organs, screening pigments help preserve the contrast of images through the absorption of off-axis photons and may contribute to dynamic range control. Therefore, screening pigments not only aid visual function in animals that lack image-forming eyes but also retain their utility if additional optical refinements arise. The evolution of screening pigments—especially their synthesis—can be subjected to a component-based study because many of the genes responsible for generating pigments are deeply conserved and many have been well characterized in model species (Kronforst et al. 2012, Sugumaran 2002, Takeuchi et al. 2005, Wittkopp & Beldade 2009, Ziegler 2003).

5.2.1. Define the trait: screening pigments. Here, we focus on the evolutionary histories of the three types of pigment most commonly used by metazoans to screen the photoreceptors of their eyes and eyespots: melanins, pterins, and ommochromes (Vopalensky & Kozmik 2009). Melanins, synthesized from the amino acid tyrosine, include the yellow to red-brown pheomelanins and the brown to black eumelanins (Borovansky & Riley 2011, d'Ischia et al. 2013). Pterins (also termed pteridines) are synthesized from purines, such as guanosine triphosphate (GTP), and range in color from yellow to orange to red (Hurst 1980). Ommochromes, which tend to be yellow, red, brown, or black, are derived from the amino acid tryptophan (Linzen 1974, Ryall & Howells 1974). Certain organisms screen their photoreceptors in other ways, but these methods of screening tend to be either too generalized in form or too rare to be studied through a comparative, component-based molecular approach (Blevins & Johnsen 2004, Mohamed et al. 2007, Ullrich-Lueter et al. 2011). Researchers characterize pigments by their solubility and absorption spectra and verify their identities with techniques like high-performance liquid chromatography and mass spectroscopy (e.g., Speiser et al. 2014a). These techniques are reliable because readily available standards can be compared with naturally occurring pigments (or their degradation products) (e.g., Porcar et al. 1996).

5.2.2. Estimate when screening pigments originated in separate lineages. Although the evolutionary origins of melanin, pterin, and ommochrome pigment synthesis are clearly ancient, we know little about when particular pigments became associated with particular visual organs (but

see Vopalensky & Kozmik 2009). To estimate when screening pigments were co-opted within lineages as components of particular visual systems, we need to know more about the specific taxonomic distributions of pigments and to build phylogenies with sampling strategies appropriate for learning when, where, and how many times certain types of screening pigments became functionally associated with photoreception. Yet, we already know that melanins, pterins, and ommochromes are widespread taxonomically and that all three types of pigment tend to be used by organisms for a variety of tasks. Melanins (e.g., Wittkopp et al. 2003), pterins (Watt 1967), and ommochromes (Asano & Ito 1955, Nijhout 1997) all benefit organisms by creating color patterns useful for camouflage and signaling (Ruxton et al. 2004). Melanins and pterins also may help prevent oxidative damage to organisms by absorbing UV radiation and scavenging free radicals (reviewed in McGraw et al. 2005). Because they are so phylogenetically widespread, these roles are generally accepted as ancestral. Melanins, pterins, and ommochromes were likely each co-opted separately from these ancestral roles by different lineages of animals to act as screening pigments for their eyespots or eyes. For example, melanin-based screening pigments have been identified in certain cnidarians, turbellarian flatworms, nematodes, polychaetes, molluscs, nonvertebrate chordates, and vertebrates (reviewed in Vopalensky & Kozmik 2009). Pterins are associated with the eyes of certain arthropods (Ziegler 1961) and annelids (Viscontini et al. 1970), and ommochromes are expressed by the compound eyes of certain arthropods (Butenandt 1959) and the camera eyes of cephalopod mollusks (Butenandt et al. 1967). Placing these data on pigment types in photoreceptors in an explicitly phylogenetic comparative context will yield more specific hypotheses about when screening pigments became associated with other components in different photoreceptors.

5.2.3. Determine when the genetic components of pigment synthesis originated. The synthesis pathways for melanins, pterins, and ommochromes are deeply conserved: In most cases, the genes necessary for producing screening pigments originated prior to the appearance of animals, making them much older than any eyespots or eyes. For example, the vast majority of melanin-expressing organisms synthesize melanins using the enzyme tyrosinase (TYR) (Borovansky & Riley 2011, d'Ischia et al. 2013). Given evidence that TYR helps produce melanin in fungi (Bernan et al. 1985) and that this enzyme can produce melanin from tyrosine without the involvement of other enzymes, it appears that TYR has a deep evolutionary history as a producer of melanin (Esposito et al. 2012, Takeuchi et al. 2005). The single exception to this pattern are arthropods, which produce melanin through a synthesis pathway in which phenoloxidase assumes the functional role of TYR (Sugumaran 2002). It also appears that the common ancestor of Metazoa had the capacity to produce both pterins and ommochromes. Pterin synthesis in metazoans involves the conversion of the purine GTP to H₄biopterin (Esposito et al. 2012, Ziegler 1961), and three different enzymes involved in this process also contribute to the synthesis of H₄biopterin in the fungus *Mortierella alpine* (Wang et al. 2011). Likewise, the genetic components of the ommochrome synthesis pathway are deeply conserved among metazoans (Takeuchi et al. 2005) and beyond [e.g., some are found in yeast (Wogulis et al. 2008)].

5.3. Membrane Elaborations: Enhanced Sensitivity for Vision in Low Light

Another critical step in the evolution of eyes is the elaboration of the membranes of photoreceptor cells. When the membranes of photoreceptor cells are elaborated—for example, by invaginations that lead to stacking—the probability that the cell will capture a photon increases because more rhodopsin molecules can be packed in the increased surface area of the cell. Therefore, membrane elaboration increases the efficiency of photoreceptors, allowing for visual organs that are able to

operate at lower levels of light. The increased efficiency of photon capture may be required for eyes that allow directional light sensitivity and high performance vision because those eyes split a field of view into fine subdivisions and a finite number of photons pass through any given field. When and how did membrane elaborations of photoreceptors evolve?

5.3.1. Define the trait: membrane elaborations. The lure of a simple two-category classification for photoreceptor cells based on membrane elaborations has both inspired biologists and led to controversies. Eakin pioneered electron microscopy techniques, which remain the best way to characterize photoreceptor morphology, and he proposed a two-category classification (Eakin 1965). In Eakin's classification, photoreceptor cells evolved increased surface area either by elaborating a cilium or adding numerous cilia (ciliary) or by adding numerous invaginations (rhabdomeric) to the cell membrane. von Salvini-Plawen & Mayr (1977) suggested two additional categories, but few biologists follow their lead today. The advent of molecular data reinvigorated Eakin's classification because ciliary receptors tend to use hyperpolarizing phototransduction and a particular clade of opsins, whereas rhabdomeric receptors tend to use depolarizing, TRP-based phototransduction and another clade of opsins (Arendt 2003). We now know that exceptions to morphological classifications of photoreceptor cell types (Eakin 1979) are commonplace and that there are no reliable relationships between phototransduction pathways and cells types (Porter et al. 2012).

5.3.2. Determine when membrane elaborations originated. Membrane elaborations in photoreceptor cells include microvilli and cilia, which also have evolutionary histories older than photoreceptors. Microvilli are comprised of cross-linked actin filaments and are present not only in animals but also in choanoflagellates (Sebé-Pedrós et al. 2013). Furthermore, microvilli are structurally related to filopodia, which have an even more widespread phylogenetic distribution (Sebé-Pedrós et al. 2013). Given their varied function and broad phylogenetic distribution, microvilli very likely evolved before phototransduction in a different functional context. Cilia, and structurally related organelles like flagella, have a microtubule-based cytoskeleton and are present in the cells of most eukaryotes (Carvalho-Santos et al. 2011, Jékely & Arendt 2006). Interestingly, the cAMP (cyclic adenosine monophosphate) and cGMP (cyclic guanosine monophosphate) signaling mechanisms used in photoreceptor cells are also present and associated with cilia in most eukaryotes; this presence suggests an ancestral role of cyclic nucleotide signaling in sensory cilia (Johnson & Leroux 2010, Satir & Christensen 2007). Even though cilia were lost secondarily in several lineages, like plants and most fungi, they play a dominant role in animal sensory structures. Similar to microvilli, cilia have varied function and a broad phylogenetic distribution indicating that they too evolved before phototransduction.

5.3.3. Determine when the components of membrane elaborations originated. A component-based approach very similar to what we outline for eyes has been published for both microvilli (Sebé-Pedrós et al. 2013) and cilia (Carvalho-Santos et al. 2011, Jékely & Arendt 2006). The components of these organelles originated much earlier than animals and much earlier than their use in photoreceptors. Because microvilli, cilia, and their components originated long before animals, the key information for the evolution of photoreceptors and eyes is when the organelles became functionally associated with other photoreceptive components. Here, we still have much to learn.

5.4. Image-Formation Mechanisms: Multiple Transitions to High-Resolution Vision

Image-formation (focusing) mechanisms, such as lenses or mirrors, improve the resolution of eyes by restricting the angular regions of space from which individual photoreceptors gather photons (Land & Nilsson 2012). Thus, by adding a focusing mechanism to a collection of pigmented photoreceptors, an animal is able to gather finer-grained spatial information from its environment. As an additional benefit, focusing mechanisms help alleviate trade-offs between resolution and sensitivity (Land & Nilsson 2012): The sensitivity of a pigment-cup eye is proportional to the cross-sectional areas of its photoreceptors (a matter of microns), but the sensitivity of an eye with a lens is proportional to the cross-sectional area of the lens (a matter of millimeters or centimeters) (Nilsson 2013). The origins of focusing mechanisms may be relatively simple from a molecular perspective. The evolution of an imaging lens, for example, may begin with the expression of any water-soluble protein resistant to light-induced damage or self-aggregation; as long as such a protolens has a refractive index higher than the surrounding medium, it helps improve both the resolution and sensitivity of an eye (Land & Nilsson 2012). With these predictions in mind, it is not surprising that focusing mechanisms evolved multiple times in animals through the co-option of a wide range of molecular components.

5.4.1. Define the trait: focusing structures. The eyes of most animals form images using light-refracting structures such as lenses and/or corneas, and other eyes may use mirrors to focus light. Biological lenses are relatively thick structures that lie below an animal's epithelium or cuticle. Compared with lenses, corneas are relatively thin structures that are formed from modified regions of the outermost layer of an animal's body. Aquatic organisms generally use lenses as focusing structures because lenses tend to provide more refractive power than corneas. Terrestrial animals, such as vertebrates and spiders, tend to use their corneas for image formation—a workable option because corneas provide more focusing power in air than in water (Land 2012). The vast majority of biological lenses and corneas are composed of proteins (Piatigorsky 2007), but several distantly related lineages of animals have eyes with focusing structures made of minerals such as calcium carbonate (CaCO_3) (e.g., Speiser et al. 2011). As an alternative to lenses or corneas, certain animals use mirrors to form images by reflection instead of refraction (Land 2000).

5.4.2. Estimate when focusing mechanisms originated in separate lineages. Although there is some disagreement about the number of times that image-forming eyes (i.e., eyes with focusing mechanisms) evolved in metazoans, authors generally list more than a dozen separate occurrences (de Queiroz 1999, Land & Fernald 1992, von Salvini-Plawen & Mayr 1977). Many of these eyes are superficially similar, but phylogenetic and structural analyses indicate that their image-forming capabilities evolved separately. For example, camera-type eyes with proteinaceous lenses are found in cubozoan cnidarians, cephalopod mollusks, and vertebrates. The proteins that compose the lenses of these eyes are nonhomologous, supporting separate instances of the evolution of spatial vision (Piatigorsky 2007). A phylogenetic perspective offers further evidence that camera eyes with lenses have evolved separately in different lineages. Cubozoans, for example, are in a derived position within Cnidaria (Kayal et al. 2013), and most other cnidarians lack lensed eyes. Similar arguments may be applied to other eyes as well, allowing researchers to determine when and how many times certain focusing mechanisms evolved. Given what appear to be limited phylogenetic distributions, mineral-based lenses and image-forming mirrors possibly represent relatively recent appearances of spatial vision among animals.

5.4.3. Determine when the genetic components of focusing structures originated. Although we can take a similar component-based approach to studying the origins of corneas, mineral-based lenses, and image-forming mirrors, here we focus on biological lenses, which tend to derive refractive power from expressing high concentrations of water-soluble proteins termed crystallins (Piatigorsky 2007). Crystallins evolved separately in different lineages of animals, and they often originated from proteins expressed broadly outside of eyes with ancestral roles in stress responses (Piatigorsky 2007). For example, the α -crystallins expressed in the lenses of vertebrates are small heat shock proteins (Ingolia & Craig 1982) that are up-regulated in response to stress in a broad range of tissues outside of eyes (Dubin et al. 1989, Klemenzen et al. 1991). Similarly, the diverse S-crystallins that provide focusing power in the separately evolved camera eyes of cephalopods are derived from glutathione-S-transferase (Tomarev & Piatigorsky 1996), a stress-response protein [and, perhaps not coincidentally, also a member of the pterin pigment-synthesis pathway (Kim et al. 2006)]. As a final example, the Ω -crystallins of cephalopods (Chiou 1988, Zinovieva et al. 1993) and scallops (Carosa et al. 2002) are aldehyde dehydrogenases, representing two separate cases in which a third class of stress-response enzymes was co-opted as a lens protein. Thus, it appears that the molecular components required to produce lenses in animals tend to have origins that greatly precede those of the lenses themselves. As a counterexample, lenses in the adult eyes of the cubozoan cnidarian *Tripedalia cystophora* express cnidarian-specific proteins known as J-crystallins (Tomarev & Piatigorsky 1996). Here is a case, intriguing in its rarity, in which the timing of the origin of new genes matches closely with the appearance of a new focusing structure.

5.5. Visual Cycles: Origins of High-Performance Vision?

Opsins bind retinal, a derivative of vitamin A that undergoes a *cis*-to-*trans* isomerization when it absorbs a photon (Porter et al. 2012, Wald 1968). For retinal to be reused by an opsin for light detection, it must be converted back to its *cis* form (Marmor & Martin 1978). Some animals use specialized enzymatic pathways, termed visual or retinoid cycles, to convert *trans*-retinal to *cis*-retinal. Following previous authors, we hypothesize that visual cycles evolved multiple times in Metazoa (Albalat 2012, Kusakabe et al. 2009, Wang et al. 2010). We hypothesize that visual cycles coevolve with image-forming eyes that provide fine spatial and temporal resolution. High-performance eyes require large amounts of *cis*-retinal to be supplied at rapid rates because fine spatial resolution requires many photoreceptors and fine temporal resolution requires photoreceptors that are highly sensitive to light (Nilsson 2013). Alternately, visual cycles may evolve as mechanisms for fine-tuning the sensitivities of photoreceptors that operate in variable light environments. For example, a visual cycle could tune the sensitivities of photoreceptors by supplying large amounts of *cis*-retinal when light levels are low and relatively small amounts of *cis*-retinal when light levels are high.

5.5.1. Define the trait: visual cycles. Visual cycles are multistep, enzymatic pathways that convert *trans*-retinal to *cis*-retinal for the use of opsins expressed by photoreceptor cells (Lamb & Pugh 2004, Wang et al. 2012). Here, we distinguish visual cycles from photoreconversion (also termed photoregeneration), a phenomenon in certain bistable visual pigments in which *trans*-retinal remains bound to an opsin and is converted back to *cis*-retinal when it absorbs a photon of an appropriate wavelength. As in our inquiries into the molecular components of phototransduction and pigment synthesis, characterizing the components of visual cycles and studying their distributions and modes of origin will help us learn how and why visual cycles have evolved in different lineages. For example, we can test whether visual cycles and high-performance eyes tend

to coevolve, perhaps due to the latter's need for large amounts of *cis*-retinal. Following past reports (e.g., Albalat 2012), we can also ask if the visual cycles of animals employ lineage-specific genes with evolutionary histories that are shallow relative to those of other genetic components of photosensitivity and eyes.

5.5.2. Estimate when and how many times visual cycles evolved. Lineages of animals differ in the molecular mechanisms of the visual cycles that they use to convert *trans*-retinal to *cis*-retinal. Specifically, recent discoveries reveal that the visual cycles of vertebrates (Lamb & Pugh 2004), cephalopod mollusks (Hara-Nishimura et al. 1990), and fruit flies (Wang et al. 2010) differ in fundamental ways. The Gt-coupled opsins of vertebrates, for example, release retinal once the photopigment absorbs a photon. The reconversion of *trans*-retinal to its *cis*- form subsequently involves a multistep, intercellular process that includes a specialized form of opsin termed retinal G protein receptor (RGR) (Shen et al. 1994). Cephalopod mollusks use an opsin closely related to RGR, termed retinochrome, for their intracellular visual cycle; however, the other components of this pathway differ from those of vertebrates (Hara-Nishimura et al. 1990). Until recently, it was thought that a visual cycle was absent in arthropods because the Gq-coupled opsins expressed in their eyes are bistable and thus capable of photoreconversion. We now know that *Drosophila* has a distinct, multistep visual cycle and that the components of this cycle are required for normal visual performance (Wang et al. 2012). A gap in our current knowledge is whether visual cycles are present in the low-resolution eyes or eyespots found in many animals.

5.5.3. Estimate when the molecular components of visual cycles originated. Aside from their use of related opsins as photoisomerases, the visual cycles of vertebrates, cephalopods, and arthropods employ dissimilar genetic components. The evolutionary origins of these components tend to be recent relative to the origins of the molecular components of opsin-based phototransduction and pigment synthesis. For example, the visual cycle of vertebrates likely originated in the common ancestor of jawed and jawless fish. Two genes critical to the vertebrate visual cycle are present and capable of aiding in the visual cycle of lampreys (*Petromyzon marinus*) but are either absent or incapable of appropriate enzymatic activity in nonvertebrate chordates (Poliakov et al. 2012). Like vertebrates, cephalopods employ lineage-specific components in their visual cycle. Specifically, cephalopods use the retinal-binding protein RALBP to transport retinal between rhodopsin and retinochrome (Ozaki et al. 1987, Terakita et al. 1989). The phylogenetic distribution of RALBP outside of cephalopods remains largely unexplored, but evidence that a visual cycle based on RALBP and retinochrome may also be present in the eyes of other mollusks has been found (Katagiri et al. 2001). Despite employing Gq-coupled opsins that are bistable, the eyes of arthropods also show evidence of separately evolved visual cycles. Recently, Wang et al. (2012) compiled evidence that *Drosophila melanogaster* has an enzymatic visual cycle that functions separately from the de novo synthesis of retinal. Enzymes involved in *D. melanogaster*'s visual cycle that are necessary for normal visual function include a pigment-cell-enriched dehydrogenase (Wang et al. 2010) and a retinol dehydrogenase (Wang et al. 2012).

6. SYNTHESIS

The history of eyes is a history of tinkering with existing components. Although eye-specific genes exist in a few particular animal clades, most gene families expressed in eyes contain genes that function outside of eyes and have evolutionary origins that predate animals. Therefore, the genes of today's eyes had other uses before they formed new functional associations. Genes of eyes combined forces at different times, in different clades, and in different combinations to detect,

absorb, or focus light. We notice that many of these gene families have ancestral roles in stress responses, indicating possible mechanisms that influenced co-option. One example is the opsin gene family: Opsin genes are related to melatonin receptors (Feuda et al. 2012, Plachetzki et al. 2010), and melatonin breaks down in light and may have originated as an antioxidant (Tan et al. 2010). Additionally, pigments are often used to protect cells from light. Genes produce proteins that synthesize melanin and pterin pigments, which absorb potentially harmful photons and reduce tissue damage by acting as antioxidants (McGraw et al. 2005). Different genes for lens proteins are also stress enzymes. For example, α B-crystallin/small heat shock protein (sHSP) protects mitochondrial function in vertebrate eyes against oxidative stress (McGreal et al. 2012). Because light causes photo-oxidative stress and DNA damage, protective responses are mounted in cells exposed to much light. We speculate that during evolutionary history multiple genes that now interact for visual function originated in stress responses to light.

Our study of eye evolution has inspired a research program that breaks complex traits into component parts to understand the timing and mechanism of their origins. This approach may be applied to most any biological trait and, when applied broadly, allows insights into fundamental evolutionary questions. Do interacting parts originate gradually or abruptly? What types of mutation more commonly lead to trait origins? Which changes first during evolution, structure or function? What are the environmental contexts of trait origins? The answers to these questions will enrich our understanding of the evolutionary process and continue to provide clear, scientific explanations for how biological complexity originates.

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