The eye as a replicating and diverging, modular developmental unit

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Sparked by new discoveries in developmental genetics, few topics have generated as much debate as eye evolution. This is somewhat surprising because the central controversy is not unique to eyes, but is a general theme of developmental genetics: evolutionarily conserved genes are deployed during the development of highly divergent morphological features. In the case of eyes, this paradox has engendered opposing camps entrenched in what has been termed a 'scientific war'. One camp highlights conserved genetic features, concluding that eyes stem from an ancestral prototype. The opposing camp emphasizes variation, arguing that some eyes must have recruited the same genes after separate morphological origins. Here, I blur the line between these camps and suggest that eyes have often evolved by replication, perhaps through the ectopic expression of a conserved, modular regulatory cascade to produce serially homologous structures that often diverged during evolution. Therefore, morphologically diverse eyes could stem from a single ancestral prototype, yet also result from multiple morphological origins.

The enigma of eye evolution, that shared 'building blocks' underlie diverse and seemingly convergent morphologies, is not unique to eyes: instead, it is an emerging generality of the evolution of development [1,2]. For example, although classically considered evolutionarily independent, segmentation in arthropods and chordates share some genetic machinery [3,4]. In addition, morphologically distinct limbs and appendages, such as those of vertebrates, insects and echinoderms, also share similar patterns of gene expression [5]. In spite of this potential generality, the finding of such a pattern in eyes has prompted a polarized, often acrimonious debate between those arguing for the common ancestry of all eyes [6,7] and those promoting recruitment hypotheses of similar genes into eyes with separate morphological origins [8–10]. What is it about eye evolution that elicits such passionate debate?

A strong possibility is the sheer magnitude of the dichotomy between morphological disparity and genetic conservation. 'Eyes' are fantastically varied and have been described as a 'riotous display of diversity' [11]. This diversity makes even definition difficult. For the purpose of this discussion, I use a rather liberal definition for the minimum requirements for an eye and agree that eyes can range from single photosensitive cells with shading pigments [12] to more complicated and familiar image-forming organs, such as vertebrate lens eyes and arthropod compound eyes. More exotic morphologies have also evolved, including parabolic mirrors, corner reflectors and lens arrays [13] (Figure 1). Coupled with varied morphology are uncanny similarities in developmental genetics. Analysis of at least ten genes suggests conserved function for eye development across phyla [14]. Even the way in which cells are patterned in the eye shows interphyletic similarity: differentiation of *Drosophila* eyes progresses in a wave, which relies on several genes, including *hedgehog* (*hh*) [15,16]. Ahead of the wave are disorganized, undifferentiated cells. Behind the wave are precisely arrayed cells, which comprise the multiple facets (ommatidia) of the compound eye. Interestingly, eye differentiation in zebrafish also progresses in a similar wave that relies on the vertebrate homologue to *hh*, *Sonic hedgehog* (*Shh*) [17]. How can such similar developmental genetic processes underlie such widely divergent morphologies?
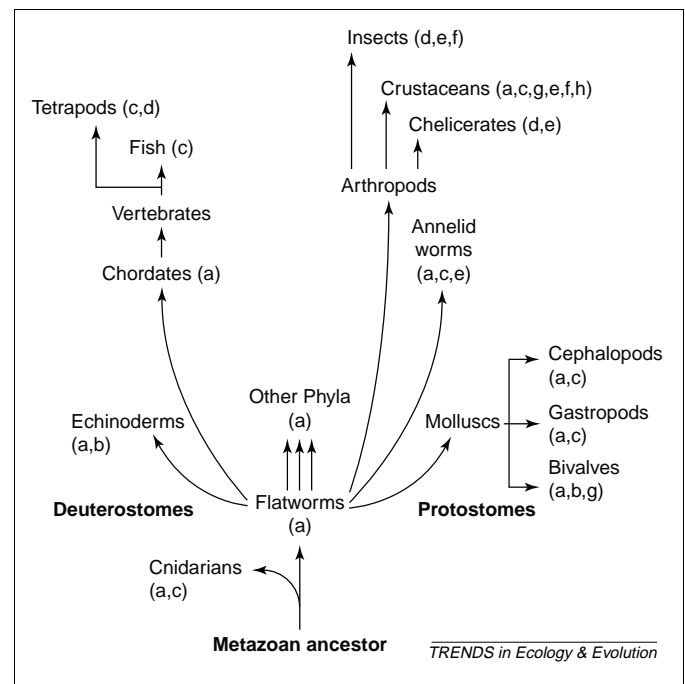

Figure 1. Phylogenetic distribution of the eight major types of eye. Letters in parentheses indicate which eye type(s) occur in a particular group: **(a)** pit eyes; **(b)** basic compound eyes; **(c)** aquatic lens eyes; **(d)** corneal lens eyes; **(e)** apposition compound eyes; **(f)** refracting superposition compound eyes; **(g)** single chambered eyes that utilize concave mirrors; and **(h)** reflecting superposition eyes. Redrawn, with permission, from [13].

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A 'scientific war' to resolve the paradox

Attempts to answer how a conserved process can govern widely divergent phenotypes 'have sparked a scientific war over the evolutionary origins of the eye' [14]. Some researchers have focused on the conservation of developmental genetic mechanisms and conclude that all eyes must have a common evolutionary origin. One explicit evolutionary model suggests that a common metazoan ancestor had a prototypic eye that already used the conserved genetic building blocks [7,18,19]. The prototypic eye evolved into the spectrum of eyes that exist today, perhaps via the addition of new genes to a conserved developmental program. By contrast, others have concentrated on the variation of eyes, suggesting that the widely divergent phenotypes cannot be the product of a single evolutionary origin. Instead, they argue that some eyes have separate morphological origins and have recruited or co-opted common developmental genes [8,9].

My current theory is that replication and divergence, largely ignored in previous discussions of eye evolution, have important implications for the 'war'. Here, I point out that replication was probably a common occurrence during eye evolution, and go on to discuss three possible fates of replicated structures: differentiation, loss and maintenance. Each fate has been documented in eye evolution. Finally, I discuss implications of replication and divergence for the debate about eye evolution. The two seemingly opposing viewpoints can be reconciled, perhaps providing a truce in this 'scientific war'. Furthermore, replication and divergence are a central concept in molecular evolution and developmental evolution, enabling eye evolution to be considered in a more general theoretical construction.

Eye replication during evolution

The structural replication of eyes is probably common during evolution. For example, developmental evidence suggests that stemmata (the larval eyes of insects) arose by modification of compound eye facets [20]. In some insects, the stemmata are small compound eyes and, in *Drosophila*, the early development of the larval eye, called Bolwig's organ, closely resembles the early development of compound eye facets [21]. In addition, serially repeated eyes occur on segments of some polychaetes [22] and many compound eyes occur on tentacles of sabellid fan worms and along the mantle edge of ark clams [23]. The ark clam *Barbatia cancellara* has ~300 compound eyes in addition to ~2000 simple cup eyes [23]. Many spiders have eight similar eyes and many crustaceans have median eyes as well as lateral compound eyes [24]. The well known Cambrian fossil *Opabinia* had five apparently similar eyes, indicating that multiplicity of eyes is not a new phenomenon. Many organisms have multiple photoreceptors and many of those eyes might have evolved by replication (Figure 2).

There are at least two mechanisms that could lead to eye replication. In the laboratory, driving the expression of any one of a few different genes in an abnormal location sets in motion a complex regulatory cascade leading to the development of an eye. For example, induction of ectopic expression of *eyeless* is sufficient to produce compound eyes on the legs, wings and antennae of *Drosophila* [18]. Altered expression of other genes, including *dachshund*, *eyes absent* and *teashirt*, can also induce ectopic eyes [14]. Furthermore, experimental eye induction is not restricted to *Drosophila* and has been demonstrated in vertebrates, such as the frog *Xenopus* [25]. Presumably, similar changes could occur during evolution, perhaps by addition of novel regulatory elements to one of the multiple genes capable of inducing ectopic eye development. Modular regulatory regions, such as those that determine tissue-specific expression of *eyeless* and other genes, could be added to genes during evolution to drive expression in new tissues.
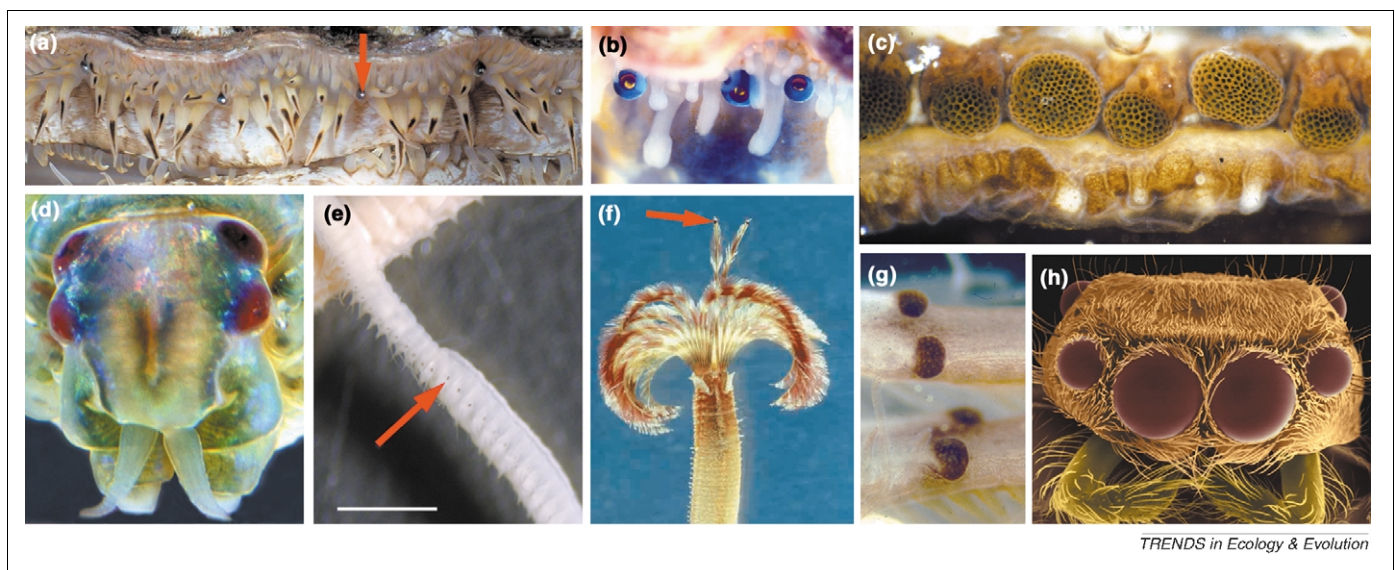
Figure 2. Many organisms have multiple photoreceptors that probably arose by replication. **(a,b)** Simple eyes on the mantle edge of the scallop *Pecten*; **(c)** Multiple compound eyes of the ark clam *Barbatia*; **(d)** Anterior head of a *Nereis* annelid worm with four eyes; **(e)** Stolons of the annelid worm *Haplosyllis spongicola* with pairs of parapodial eyespots; **(f,g)** Sabellid fanworms (*Sabella* is shown) contain multiple eyes on their radioles; **(h)** Many spiders have eight eyes, including this (artificially coloured) jumping spider, *Plexippus paykulli*. All images used with permission from: (a,d) R. Lord; (b,c,g) D-E. Nilsson; (e) from [43]; (f) D. Fiege; (h) Dennis Kunkel Microscopy, Inc.

The origin of new regulatory regions theoretically can occur by chance rather easily [26].

A second mechanism for the structural replication of eyes could be quantitative effects on a patterning process. In other words, replication can be caused by a periodic processing phenomenon, whereby one process generates an array of structures. The facets of compound eye are a prime example, where a similar process patterns individual cells of each different facet. Re-recruiting the process in different evolutionary lineages or in different parts of the organism can generate replicated structures. Perhaps stemmata originated in this way. In these cases, the structure is duplicated in a morphological sense, but each individual structure is also the product of the same wave-generating process.

Fates of duplicated eyes

Regardless of the mechanism, once a replicated eye originates, three fates are possible: differentiation, loss or maintenance. Eye differentiation can occur rapidly in evolution according to a model devised by Nilsson and Pelger [27]. They suggested that lens eyes could evolve from simple eyes through a series of small steps in fewer than half a million generations, merely an instant in geological terms for most organisms. Another form of differentiation is reduction and there are many cases of eye reduction during evolution, a well known example being the vertebrate parietal (also called pineal) eye. Although present in many fish, reptiles and amphibians, the parietal eye probably lost photoreceptive function during the evolution of birds and mammals [28,29], in spite of the retaining of the gene encoding the visual pigment opsin [30]. Although one might expect replicated modular structures to be constrained to evolve in concert because they share many genes, vertebrae, heterodont teeth, limbs, butterfly eyespots and insect segments provide clear examples that variable differentiation of replicated modules often occur [31]. In addition to differentiation, complete loss of eyes is also common: numerous cave and deep-sea organisms have lost eyes independently and rapidly, the blind cavefish *Astyanax* being a familiar example. Finally, some examples of maintenance (without divergence) of duplicated eyes have already been mentioned (e.g. segmental eyes of polychaetes, mantle eyes of ark clams and tentacle eyes of sabellid polychaetes). Other examples might include paired lateral eyes, such as those of vertebrates, which, interestingly, develop by splitting a single eye field during ontogeny and which might be homologous to the single frontal eye of urochordates [32]. The similarity of eyes to each other within individuals indicates that those eyes were maintained after putative replication events.

Implications of replication and divergence of eyes

So far, I have discussed plausible mechanisms for eye replication and have argued that replication, along with divergence, loss and maintenance, is common in evolution. I now present some of the implications of my theory of eye evolution.

Interestingly, eye replication in evolution is consistent with both hypotheses discussed above, which many consider diametrically opposed. First, replication is consistent with a recruitment model of evolution, in which the same genes are co-opted into morphologically new eyes [9]. For example, consider a simple case of duplication where an ancestor has one eye and a descendant has two. Although the second eye can be considered either paralogous (i.e. resulting from duplication rather than speciation) or serially homologous to the first eye, there is no strict homologue of the second eye in the ancestor. In other words, the second eye is a new morphological feature in the descendent. Yet, if the second eye duplicated by either of the mechanisms discussed above, then it develops through the same process as the first eye. In short, a new eye (one that was not present in its immediate ancestor) evolved and uses the same genes as an older eye, consistent with a co-option hypothesis of eye evolution. Morphological differentiation, loss, or maintenance might occur subsequently.

Replication is consistent with the co-option model by providing one possible mechanism. However, other mechanisms for co-option are also possible and are not mutually exclusive. For example, Davidson [2] proposed that some elements of eye evolution are conserved and some are co-opted. Namely, he distinguishes processes of terminal cell differentiation (e.g. the direct regulation by *eyeless* of eye structural genes [33]) from processes of upstream pattern formation (e.g. the control that *eyeless* has over early morphogenetic processes, as demonstrated by ectopic eye induction). He argues that terminal cell differentiation processes are conserved and can easily be co-opted into different upstream patterning processes. In other words, the specific function of regulating eye structural genes is a conserved function of some regulatory genes, such as *eyeless*, which might facilitate independent co-option of the upstream, morphogenetic functions in different taxa.

Besides consistency with co-option, evolution by replication is also consistent with the single origin hypothesis of eyes. Based on the finding of highly conserved developmental genetic features, Gehring and co-workers have argued that all eyes can be traced in an unbroken lineage to a common ancestral prototype [6,7,34]. To illustrate how replication is consistent with this model, an analogy with multi-gene families is instructive. I have suggested here that, similar to genes, eyes can replicate with subsequent loss or divergence. In both cases, multiple rounds of replication and divergence or loss can create a complex relationship between the replicated entities and the phylogeny of the species [35]. In spite of potentially complex histories, members of a gene family can be traced to a single common ancestral gene. Similarly, replicated and diverged eyes might form an 'eye family' of diverse morphological types that could be traced to a single ancestral structure (Figure 3).

I further note that replication and divergence is consistent with proposed mechanisms for the morphological divergence of eyes. First, Gehring and Ikeo [7] suggested an 'intercalary evolution' model, whereby some new developmental genetic processes are added to conserved ones, resulting in morphological change. Here, replication could serve as an impetus for such intercalation: eyes originating at new sites on the organism would be under new selective constraints and adding new genes that act during
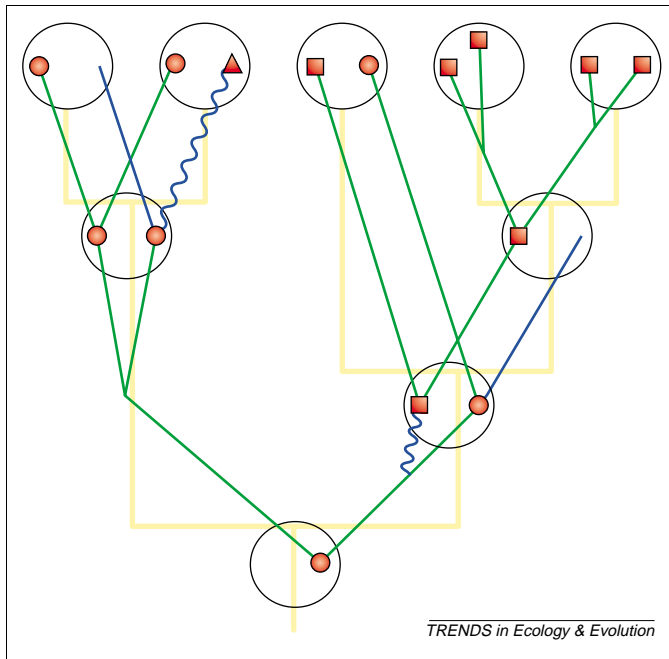
Figure 3. A hypothetical example of eye replication and divergence during evolution. Eye replication coupled with divergence (blue wavy line), maintenance (green line) or loss (straight blue line) can produce a complex relationship between eye evolutionary history (green and blue lines) and the phylogenetic history of the organisms (yellow). All the eyes (red shapes) can be traced back to a common ancestor, yet many are also the result of new morphological origins by duplication events.

development could mold different adaptations. Second, models of morphological reduction and subsequent elaboration have been proposed to explain evolutionary transitions between complex morphological types of eye. For example, lateral eyes in the ancestor of myriapod arthropods might have been reduced to simple eyes, which were later elaborated into distinctive compound eyes in one group, the Scutigeromorphs [36]. Here again, replication and divergence could play a role if selective constraints are lowered on a replicated complex eye, which is reduced during evolution and later elaborated independently. This idea is similar to the classic hypothesis of gene duplication evolution, whereby a redundant gene is free from selective constraints until a new function arises [37].

A final implication for the importance of replication in eye evolution is conceptual, allowing consideration within broader contexts. For example, duplication and divergence is a central concept in the evolution of body form [38,39] and molecular evolution [40]. Duplicative changes in modules ('discrete subunits of the whole' [38]) such as genes or structures could generally facilitate morphological divergence. Arthropods are a prime example, because body segments have duplicated and specialized into numerous different forms. I suggest that eyes represent one such morphological module and replication probably has facilitated diversification whilst deploying many of the same conserved genes. A similar idea was proposed by Minelli [41,42], who argued that body appendages, which express similar genes in morphologically and phylogenetically distinct instances such as vertebrate limbs and echinoderm rays, can be considered duplicates of the main body axis.

Conclusion

The structural replication of eyes in evolution, with subsequent divergence, loss, or maintenance, is a ubiquitous phenomenon that deserves more attention. Furthermore, divergence or loss can be rapid and instances of maintenance are well known, leading to important implications for the debate about eye evolution. For example, replication and divergence might facilitate morphological change and provide a mechanism for co-option of similar genes into morphologically new eyes. As Raff stated, 'reinvention of whole modular assemblages is far less likely than duplication and divergence of existing modules' [38]. At the same time, a common ancestry of many morphologically diverse eyes can be reconciled by replication.

Does the consideration of replication solve the paradox of eye evolution and mark a ceasefire in the 'scientific war' over common ancestry and multiple origins of eyes? Certainly not, because replication does not exclude other possible modes of eye evolution, such as Davidson's co-option model or parallel evolution (independent origins from homologous precursors). Therefore, even if replication and divergence occurs quite commonly during evolution, some eyes might still have separate origins. Although it does not end the 'war', noticing the prevalence and potential of replication and divergence points us toward new lines of research into the importance of replication relative to other potential factors in eye evolution.

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