Eye ancestry: **Old genes for new eyes**

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The vast differences between vertebrate and arthropod eyes suggest that the recently discovered homologous master control genes for eye development had another function before eyes evolved in the early Cambrian.

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Current Biology 1996, Vol 6 No 1:39–42

 ISSN 0960-9822

A biological enigma has been brought to light by new genetical data that seem to contradict established views of eye evolution. The eyes of vertebrates and insects are fundamentally different, from the organ level down to the molecular mechanisms underlying photoreceptor cell function. For this reason, eyes have served as textbook examples of functional convergence or parallelism. In apparent disagreement with this view, it has recently been demonstrated [1] that homologous master control genes initiate eye development in vertebrates and insects. The genetics of eye formation thus suggest that vertebrate and insect eyes are homologous, yet it seems impossible to trace the eyes themselves back to a common ancestor. How can these apparently incompatible facts be understood? To begin to address this problem, we have to ask when eyes evolved and when the common master control genes originated.

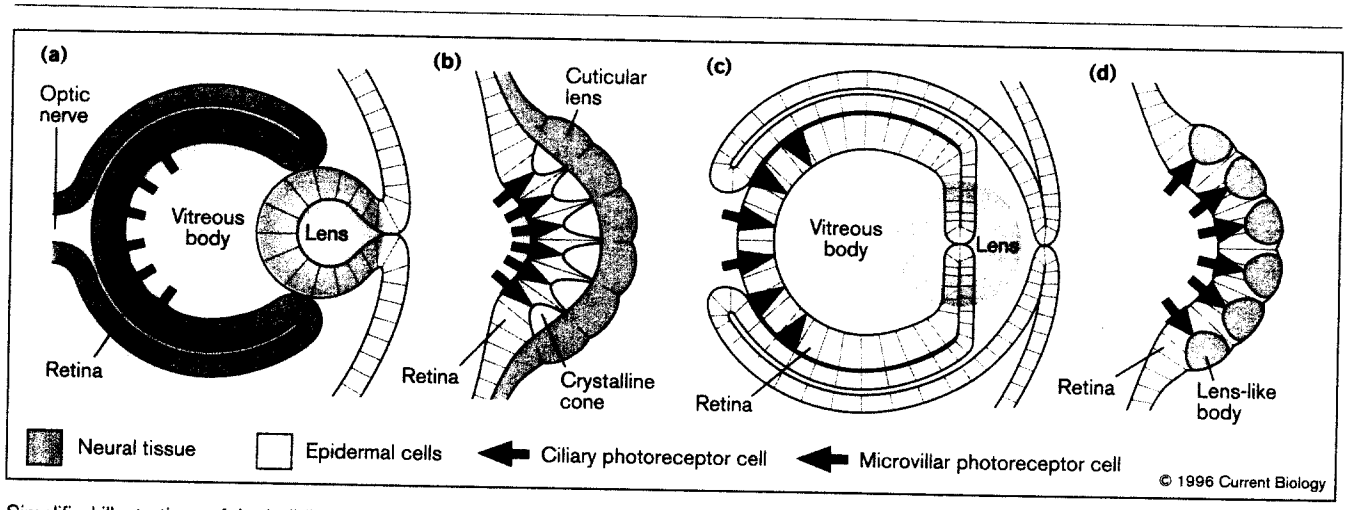
In mammals, the *Pax-6* gene is essential for the initiation of eye development in the embryo [1]. Heterozygous *Pax-6* mutants develop small or defective eyes, and homozygous mutants have no eyes at all. Last year, Walter Gehring and co-workers [1] made the surprising discovery that a gene known as *eyeless*, which is important for eye development in the fruitfly *Drosophila*, is a homologue of the mammalian *Pax-6* gene. Even more remarkably, they went on to find that eye development can be induced at virtually any place on the *Drosophila* body by targeted expression of its *Pax-6* homologue [2]. These results suggest that *Pax-6* is a master control gene for eye development in both vertebrates and insects. *Pax-6* encodes a transcription factor which is believed to activate other genes in the cascade that leads to the development of an eye. Genes with a clear sequence homology to *Pax-6* have also been found in squid, flatworms, nemerteans, nematodes and ascidians, indicating its general occurrence in at least the triploblastic phyla ([1,3,4] and Walter Gehring, personal communication). Furthermore, another *Drosophila* eye control gene, *sine oculis*, has been found to have a vertebrate homologue expressed in the developing eye [5]. If these conserved genes turn out to have the same roles in triggering eye development in all phyla, it is certainly tempting to believe that the eyes also share a common origin [1,5–7].

To give a balanced view of the role of the *Pax-6* gene, I should say that it is expressed several times both before and after the start of eye development [1]. In vertebrates, *Pax-6* takes part in the early formation of the neural tube, the eye and the olfactory epithelium. Later on, it is also expressed in several parts of the brain and again in both the neural and epidermal parts of the developing eye. In *Drosophila*, the *Pax-6* homologue is expressed both in the embryonic nervous system and in the imaginal disk that gives rise to the eye, but the median ocelli, which contain photoreceptor cells of the same type as those in the compound eye, seem to develop without *Pax-6* involvement. The nematode *Caenorhabditis elegans* has no eyes, and in this species *Pax-6* genes take part in patterning the head region, and are also essential for the development of a sense organ in the tail [3,4].

For an assessment of the potential homology between eyes of animals from different phyla, useful indicators are the eye's ontogenetic origin, the way photoreceptor cells are constructed, and the molecular machinery responsible for light detection. Eyes of some sort occur in most animal phyla, but their construction and ontogeny vary enormously (Fig. 1) [8]. One distinction is between eyes with photoreceptor cells that differentiate from the central nervous system, and those with photoreceptor cells that differentiate from the epidermis. The vertebrate eye is of the former kind, and cephalopod and arthropod eyes are of the latter. The different optical types of eye — simple *versus* compound — also, of course, require fundamentally different developmental programs. Even eyes of the same type often show fundamental differences, such as the retina being inverse (photoreceptors facing the back of the eye) in vertebrates and everse (photoreceptors facing the front of the eye) in cephalopods.

The tissues and materials that have been recruited to build retinas and lenses vary from one phylum to another. The building materials are not, however, fundamentally unique to eyes: the proteins that make up the lens are different in vertebrates and cephalopods, but in both cases they are identical, or very similar, to proteins with other functions in these animals [9]. It thus seems that eyes have evolved numerous times, in each case using whatever tissues and materials that were at hand. The positioning of eyes on the body is also highly variable [8,10].

Figure 1



Simplified illustrations of the building-plans of four types of eye: **(a)** a vertebrate eye; **(b)** an arthropod compound eye; **(c)** a cephalopod lens-eye; **(d)** a compound eye in polychaete tube-worms and arcoid clams. All are paired cephalic eyes, except those in polychaete tube-worms and arcoid clams, where large numbers of the eyes are spread on the feeding tentacles and along the mantle edge respectively. The examples given here are just some of the fundamentally different building plans for eyes that exist in animals.

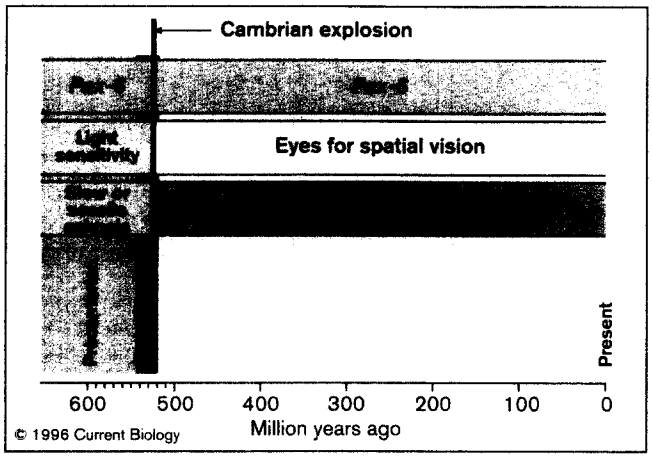
Median and lateral cephalic eyes are by far the most common, but a list of eyes at unusual locations can be made, which is both long and surprising. Eyes or groups of photoreceptor cells are found on several body segments and the rear end of some polychaete worms; on the feeding tentacles of tube-building polychaetes; all over the dorsal surface of chitons; on the mantle edge of several different groups of clams; on the tip of starfish arms; and on the genitals of butterflies [11]. One should perhaps not be too surprised at this diversity, because it is now clear that even the most advanced and impressive eyes, which gave Charles Darwin his famous cold shudder, can potentially evolve in a very short time [12].

Photoreceptor cells are of two basic types in the animal kingdom: those with cilia and those with microvilli [8]. In both cases, the desired effect is a large membrane area for the visual pigment molecules. The microvillar type dominates in invertebrates, whereas all vertebrate photoreceptors are ciliary. But this distinction is not unique to photoreceptor cells, as cilia and microvilli are standard organelles of eukaryotic cells — for example, chemoreceptor cells also come in microvillar or ciliary varieties [13]. A common feature of all eyes is use of a vitamin-A-based visual pigment, the major constituent of which is the opsin protein with its seven transmembrane helices. Opsins of all animals are probably homologous, and when activated they all couple to a trimeric, GTP-binding G protein [14,15]. But this does not suggest eye homology, because G-coupled receptor proteins, homologous to opsins, are known to function in many physiological processes — for example, in synaptic transmission, in the immune system, in chemoreception and as hormone receptors.

The important point here is that neither the G-protein nor the type of receptor molecule is unique to vision. Even bacteria have light-sensitive receptor proteins — bacteriorhodopsin and halorhodopsin — that have the seven transmembrane helices that are characteristic of the G-coupled receptor family. The visual transduction cascade following the G-protein in photoreceptors is not principally different from the signalling pathway in other G-protein systems. But different second messengers transmit the signal downstream of the G protein in different species: vertebrate photoreceptors use cyclic GMP, whereas insect photoreceptors use inositol trisphosphate [15]. The end result of light detection is a membrane depolarization in most invertebrates, insects included, but a hyperpolarization in vertebrates.

It thus seems that, at all levels of organization in the visual system, there is either more than one functional solution, or the single solution is shared with functions other than vision. There are thus no unique prerequisites for vision, except, of course, for the use of vitamin-A-related chromophores in the visual pigment, but then again, this is also found in bacteria. For most functional parts of the eye, there are alternative but equivalent solutions seen in different animals. As no improvement would occur by changing between equally good alternatives, it is likely that the particular solutions seen in a given species are the original ones. This makes a very strong case against any type of general eye homology. It is more likely that eyes evolved independently numerous times [8], and even photoreceptor cells may have evolved more than once from the molecularly similar chemoreceptors. At present, it is particularly fashionable to compare vertebrate and insect eyes [1,5–7]. But such a comparison is discouraging, because at

Figure 2



A plausible chronology for animal locomotory abilities, visual function and the occurrence of master control genes (here *Pax-6*). The need for fast locomotion and vision are likely to have originated during the Cambrian explosion, whereas master control genes in general would have been needed much earlier. Bilaterally symmetric animals with prominent eyes appear suddenly in the fossil record from the Cambrian explosion (which lasted less than 10 million years [16]).

important levels — optical design, ontogenetic origin, structural type and orientation of photoreceptor cells, transduction cascade and response polarity — there is not a single match between vertebrate and insect eyes. There can thus be no doubt, despite the use of homologous master control genes, that the eyes of these two animal groups evolved independently.

To get a useful answer one has to ask the right question, and at this stage it is appropriate to ask when the different eyes originated. Most modern phyla can be traced back to the Cambrian explosion, 530–520 million years ago (Fig. 2) [16]. The fauna that appeared during the Cambrian explosion included a wealth of bilaterally symmetric and mobile animals with well developed eyes [17]. The Precambrian fauna must have contained the ancestors to the mobile and visually guided species of the Cambrian, but Precambrian fossils show no evidence of fast-moving bilateral animals, or animals with distinguishable eyes. This suggests that visually guided fast locomotion was the key invention of the Cambrian explosion.

The slow moving, sessile or microscopic species of the Precambrian period would have had little use for eyes, although light sensitivity must have been useful, and photoreceptor cells of various designs probably existed long before the Cambrian explosion. The sudden appearance of eyes thus happened together with the appearance of modern animal phyla. As *Pax-6* homologues are widely represented in the phyla that came into existence during the Cambrian explosion, these genes must have already existed 530 million years ago. But a long sequence of nucleotides does not suddenly evolve by chance in a short time. *Pax-6* genes certainly existed before the Cambrian explosion, because Precambrian animals, regardless of their body plan, must also have needed master control genes to orchestrate their development. It is therefore likely that *Pax-6* genes significantly pre-dated the appearance of eyes in the early Cambrian.

A similar argument can be extended to other master control genes, such as those determining embryonic polarity and body segmentation [18–22]. Today, these genes are important in bilaterally-symmetric and segmented animals, but there must have been precursors of these genes that guided body development before bilateral symmetry and segmentation evolved. These master control genes would thus be much older than many of the structures they control in modern animals. On the nature of the previous role of *Pax-6* genes we can only speculate. The expression patterns in the various phyla suggest an ancestral role in determining nervous or sensory cell fate in parts of the ectodermal tissue. One would expect that, when a simple nervous system became more elaborate, and new sensory organs were acquired, the ancient *Pax-6* genes gradually changed their role to include new targets which were functionally related to, or physically near, older targets. Thus, even if master control genes are homologous across much of the animal kingdom, they may have been similarly recruited in different phyla to trigger the development of later and independent acquisitions. Hence, these may be old genes for new eyes.

Acknowledgements

I thank Eric Warrant for helpful comments on the manuscript. Funded by the Swedish Natural Science Research Council, grant 01742-310.

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