On the other hand, at 160 sites (2.2% of the disease-associated sites), the mouse sequence was the same as the human disease-associated sequence. Moreover, in 23 of these, there is documentation of a cause-and-effect relationship between the mutation and disease in humans (Mouse Genome Sequencing Consortium, 2002). This unexpected finding is important because it implies that the harmfulness of a mutation can depend on the biochemical context in which it occurs. A mutation that causes disease in humans may not have been harmful in the ancestor of the mouse because of other changes occurring in the rodent lineage that served to buffer the mutation's effects.

As with any new genome sequence, the initial report of the mouse genome (Mouse Genome Sequencing Consortium, 2002), together with companion papers (Dermitzakis et al, 2002; The FANTOM Consortium and the RIKEN Genome Exploration Research Group Phase I and II Team, 2002; Wade et al, 2002), only scratches the surface of the information made available to biologists through sequencing of the mouse genome. Comparison of human and mouse genomes is certain to yield important new insights in the near future as well as provide a rich source of testable hypotheses for experimental biologists working in both rodent and primate systems. ∎

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Evolutionary Genetics

Rose-colored goggles

Karen L Carleton and Thomas D Kocher

Evolutionary biologists are fascinated by how so many species of cichlid fishes have evolved in the Great Lakes of East Africa. It seems likely that visual cues played a key role in this explosive speciation process. In a recent paper, Terai et al (2002) provide compelling evidence from one of these amazing species flocks that selection is acting on a key vision gene, suggesting that for cichlids 'seeing is evolving'.

The mechanisms of speciation are difficult to unravel in the simplest systems. When hundreds of species arise quickly, within a small geographic area, the task becomes daunting. There are no more extreme examples than the Great Lakes Tanganyika, Malawi and Victoria, which each harbor hundreds of recently evolved cichlid species (Kornfield and Smith, 2000; Danley and Kocher, 2001).

Pre-mating isolation (where females will only mate with males of their own species) is key to the evolution and maintenance of so many cichlid species. Males display species-specific bright color patterns that differ between the most closely related taxa. Both in the laboratory and the field, females choose males based on these color patterns (Seehausen et al, 1997). Therefore, in their new study, Terai et al (2002) set out to examine a gene determining visual sensitivity in a broad array of cichlids from Lake Victoria.

Much is known about how visual sensitivity is controlled. The retina contains several types of cones. Each cone type has a unique visual pigment, which absorbs light in a different part of the spectrum (Figure 1). Each visual pigment is comprised of an opsin protein, wrapped around a vitamin-A-derived chromophore. The opsin genes fall into four broad spectral classes that arose early in vertebrate evolution. In cichlids, these include very short-wavelength sensitive opsins (SWS1), short-wavelength sensitive opsins (SWS2), medium-wavelength sensitive opsins (RH2) and long-wavelength sensitive opsins (LWS) (Carleton and Kocher, 2001).

A cone's visual pigment can be tuned to maximally absorb different wavelengths of light in three ways (Bowmaker, 1995): (1) opsin genes from different spectral classes can be expressed, causing large shifts of 35–100 nm (Bowmaker, 1995; Carleton and Kocher, 2001), (2) the chromophore (or mixture of chromophores) used can differ in fish, shifting all the visual pigments simultaneously (with large shifts of 30–60 nm in the LWS pigments and small shifts of 5–10 nm in the SWS pigments, Harosi, 1994); or (3)
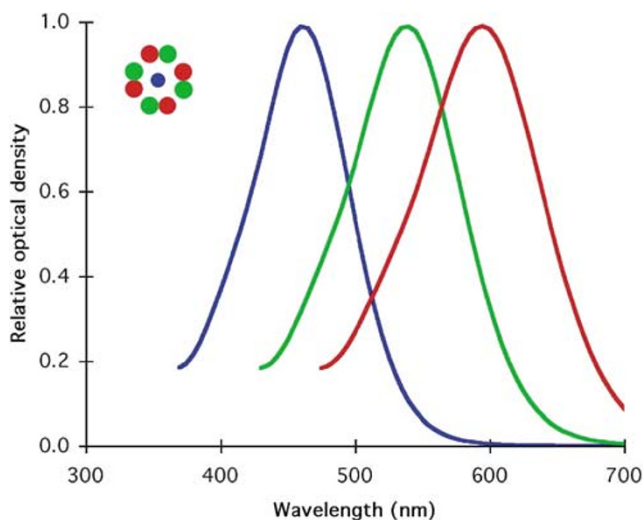

Figure 1 Visual pigment absorption spectra based on the microspectrophotometry of the Lake Victorian cichlid *Haplochromis pyrrhocephalus* (van der Meer and Bowmaker, 1995). The single cones (blue) contain a pigment with peak sensitivity at 462 nm, while the double cones contain pigments with peak sensitivity at 539 (green) and 595 (red) nm. The 595 nm pigment is coded for by the LWS opsin gene. The inset shows the square retinal mosaic typical of cichlids where single cones are surrounded by double cone pairs.

the amino-acid sequence of a particular opsin gene can differ, shifting the absorption by 3–15 nm for changes at each key site (Yokoyama, 2000).

There is no evidence that Lake Victoria cichlids differ in the opsin genes they express. Lake Victoria cichlids are known to use differing chromophore mixtures (van der Meer and Bowmaker, 1995). However, the new study of Terai *et al* (2002) is one of the first to examine the variability of opsin gene sequences and how they differ among species and populations.

The researchers found 14 alleles of an LWS opsin gene in 40 individuals in 14 species from 13 localities in the Lake Victoria/Lake Nabugabo region, far more than observed for any other nuclear or mitochondrial gene in Victorian cichlids. They confirmed the unusual diversity of the LWS gene among Lake Victoria cichlids by sequencing the most highly variable LWS exon in 184 Victoria/Nabugabo individuals from 17 species, as well as 80 haplochromine species from the surrounding East African lakes and rivers.

Terai *et al* (2002) provide strong evidence that selection is acting to modify the spectral sensitivity of the LWS gene. Although most of the LWS sequence variation should not modify visual pigment absorption, they identify two sites known to change visual pigment sensitivities. In the Victoria cichlids, site 177 changes from alanine, A, to serine, S (A177S), which should cause a 7 nm shift to longer wavelengths (Yokoyama, 2000). Site 282 varies from alanine to threonine, T (A282T), a change that is likely to cause a large 15 nm red shift similar to that documented for A282S (Yokoyama, 2000). There is also a third site in the retinal binding pocket (131) that varies in amino-acid polarity (S131A). This site differs in LWS fish opsins with different peak absorptions (Register *et al*, 1994) and could cause a shift of a few nanometers.

If we consider variation at just these three amino acids, there are four functionally unique alleles in the Victoria cichlids (characterized by the amino acids at sites 131, 177 and 282: SAA, SAT, SST, AST). These alleles likely have corresponding peak sensitivities with approximate shifts of 0, 15, 22 and 25 nm. Taken with previous microspectrophotometry studies (van der Meer and Bowmaker, 1995), these results clearly suggest that long-wavelength peak sensitivity varies among Lake Victoria cichlid species. To confirm that these alleles actually confer different visual sensitivities, the absorption spectra of the expressed opsin proteins will have to be measured. Regardless, these results certainly raise the possibility that long-wavelength sensitivity could be important in female mate choice and ultimately speciation.

The visual system has many tasks and is subject to various selection pressures. In addition to choosing mates, vision is critical for finding food and avoiding predators (Endler, 1992). Since water transmission varies at different locations within Lake Victoria (Seehausen *et al*, 1997), it will be important to correlate visual sensitivity to the photic environment as well as the feeding strategies of fish at each location. To examine how the visual system is adapting, the full suite of cichlid opsin genes, and their patterns of expression, needs to be examined. The other cone opsin genes may also vary, shifting the entire visual system to longer wavelengths. Alternatively, the LWS gene may be unique in its variability.

If visual sensitivity is important in driving speciation, we would predict differences in visual sensitivity among sister species. These differences should be correlated with changes in male color patterns, as males adapt their mating signals to the visual sensitivities of choosy females. However, we must consider that genes controlling visual sensitivity are not the same as genes controlling female preference. There is considerable neural processing of the visual signals in the brain, which may guide behaviors such as mate preference. Behavioral studies are needed to test whether differences in visual sensitivity are necessary or sufficient to ensure differences in female preference.

To understand how selection is shaping the cichlid visual system will require exploring these many factors. Only then can we consider the cichlid view of the world, and the effects of different shades of rose-colored goggles. This perspective will help determine whether genes important in driving the speciation of these amazing fishes have finally been identified. ∎

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