

The Evolution of Primate Color Vision

Analyses of primate visual pigments show that our color vision evolved in an unusual way and that the brain is more adaptable than generally thought

By Gerald H. Jacobs and Jeremy Nathans

KEY CONCEPTS

- The color vision of humans and some other primates differs from that of nonprimate mammals.
- It is called trichromacy, because it depends on three types of light-activated pigments in the retina of the eye.
- Analyses of the genes for those pigments give clues to how trichromacy evolved from the color vision of nonprimate mammals, which have only two kinds of photopigments.
- The authors created trichromatic mice by inserting a human pigment gene into the mouse genome. The experiment revealed unexpected plasticity in the mammalian brain.

—The Editors

To our eyes, the world is arrayed in a seemingly infinite splendor of hues, from the sunny orange of a marigold flower to the gunmetal gray of an automobile chassis, from the buoyant blue of a midwinter sky to the sparkling green of an emerald. It is remarkable, then, that for most human beings any color can be reproduced by mixing together just three fixed wavelengths of light at certain intensities. This property of human vision, called trichromacy, arises because the retina—the layer of nerve cells in the eye that captures light and transmits visual information to the brain—uses only three types of light-absorbing pigments for color vision. One consequence of trichromacy is that computer and television displays can mix red, green and blue pixels to generate what we perceive as a full spectrum of color.

Although trichromacy is common among primates, it is not universal in the animal kingdom. Almost all nonprimate mammals are dichromats, with color vision based on just two kinds of visual pigments. A few nocturnal mammals have only one pigment. Some birds, fish and reptiles have four visual pigments and can detect ultraviolet light invisible to humans. It seems, then, that primate trichromacy is unusual. How did it evolve? Building on decades of study, recent investigations into the genetics, molecular biology and neurophysiology of primate color vision have yielded some unexpected answers as well as surprising findings about the flexibility of the primate brain.

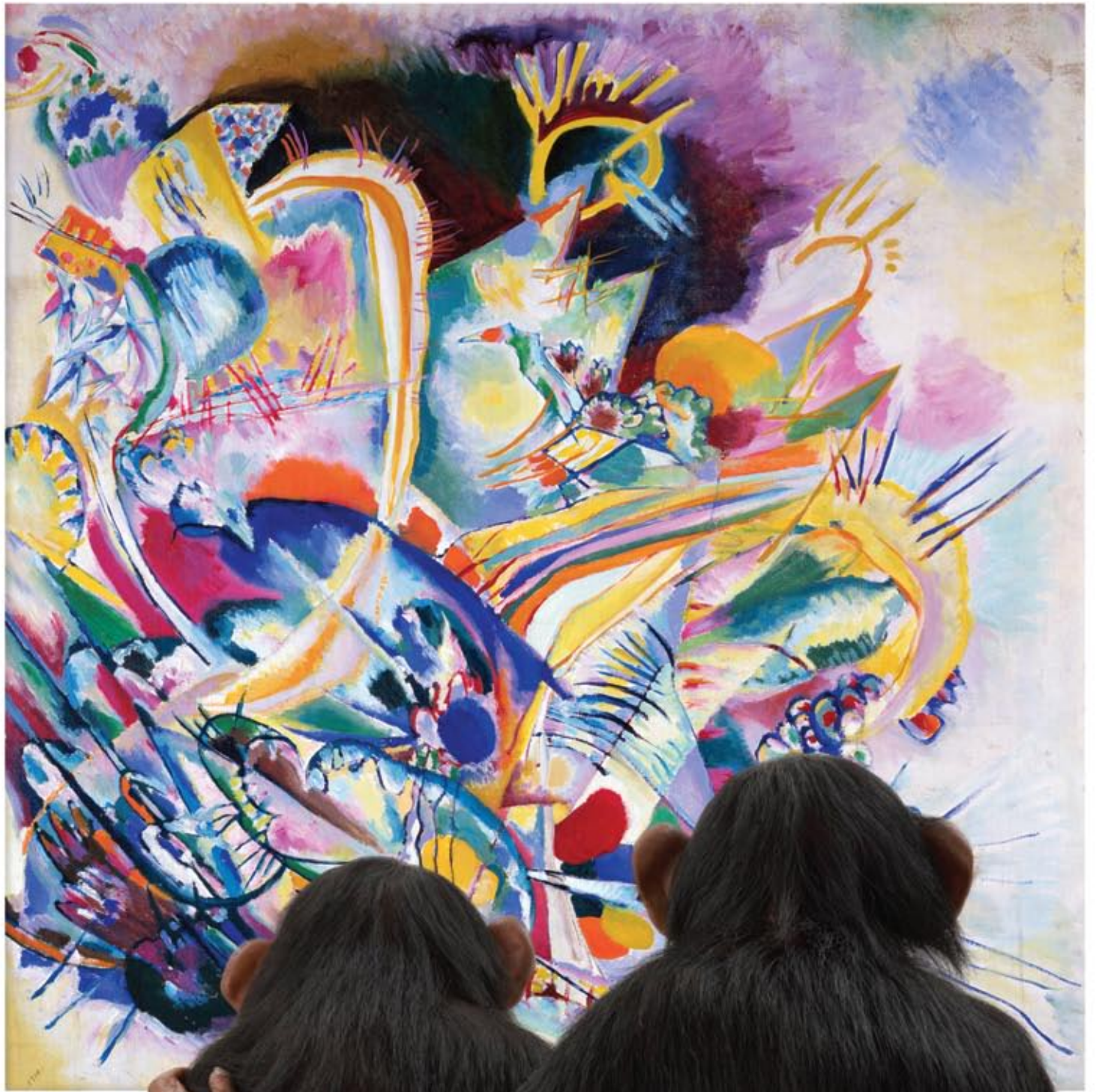
Pigments and Their Past

The spectral sensitivities of the three visual pigments responsible for human color vision were first measured more than 50 years ago and are now known with great precision. Each absorbs light from a particular region of the spectrum and is characterized by the wavelength it absorbs most efficiently. The short-wavelength (S) pigment absorbs light maximally at wavelengths of about 430 nanometers (a nanometer is one billionth of a meter), the medium-wavelength (M) pigment maximally absorbs light at approximately 530 nanometers, and the long-wavelength (L) pigment absorbs light maximally at 560 nanometers. (For context, wavelengths of 470, 520 and 580 nanometers correspond to hues that the typical human perceives as blue, green and yellow, respectively.)

These pigments, each consisting of a protein complexed with a light-absorbing compound derived from vitamin A, sit in the membranes of cone cells: photoreceptive nerve cells in the retina named for their tapering shape. When a pigment absorbs light, it triggers a cascade of molecular events that leads to the excitation of the cone cell. This excitation, in turn, activates other retinal neurons that ultimately convey

► **CHIMPANZEES, like humans, can distinguish among colors that other mammals cannot see. What observers see in a Kandinsky reflects the properties of the paints, the nature of the illumination, and the color vision system of the viewers.**

GEORFFREY CLEMENTS Corbis (painting); BOB ELSDALE Corbis (chimps); LUCY READING-IKKANDA (photo/illustration)



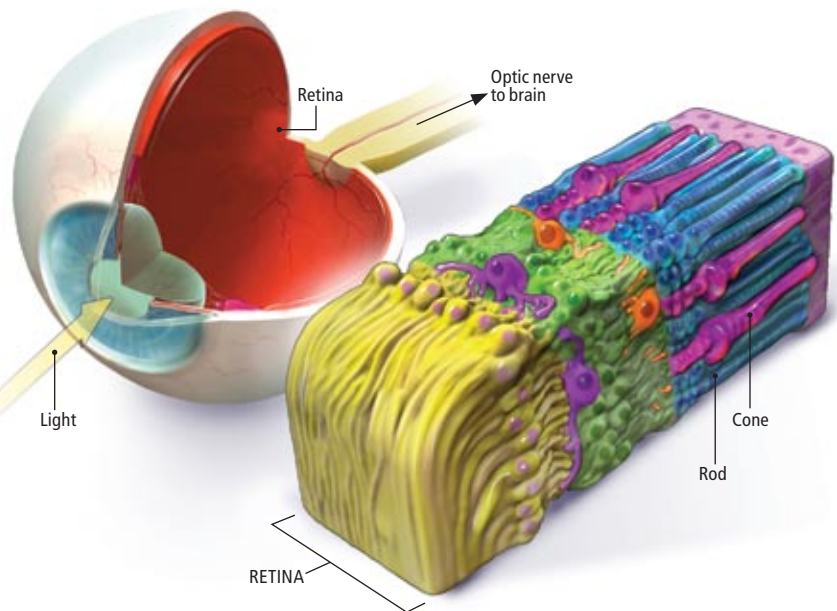
a signal along the optic nerve to the brain.

Although the absorption spectra of the cone pigments have long been known, it was not until the 1980s that one of us (Nathans) identified the genes for the human pigments and, from the DNA sequences of those genes, determined the sequence of amino acids that constitutes each pigment protein. The gene sequences revealed that the M and L pigments are almost identical. Subsequent experiments showed that the difference in spectral sensitivity between them derives from substitutions in just three of the 364 amino acids from which each is built.

Experiments also showed that the M- and L-pigment genes sit next to each other on the X chromosome, one of the two sex chromosomes. (Men have one X and one Y, whereas women have two Xs.) This location came as no surprise, because a common anomaly in human color perception, red-green color blindness, had long been known to occur more often in men than in women and to be inherited in a pattern indicating that the responsible genes reside on the X chromosome. The S-pigment gene, in contrast, is located on chromosome 7, and its sequence shows that the encoded S pigment is related only distantly to the M and L pigments.

By the mid-1990s comparisons of these three pigment genes with those of other animals had provided substantial information about their history. Almost all vertebrates have genes with sequences that are very similar to that of the human S pigment, implying that some version of a shorter-wavelength pigment is an ancient element of color vision. Relatives of the two longer-wavelength pigments (M and L) are also widespread among vertebrates and likely to be quite ancient. But among mammals, the presence of both M- and L-like pigments has been seen only in a subset of primate species—a sign that this feature probably evolved more recently.

Most nonprimate mammals have only one longer-wavelength pigment, which is similar to the longer-wavelength primate pigments. The gene for the longer-wavelength mammalian pigment is also located on the X chromosome. Those features raised the possibility, then, that the two longer-wavelength primate pigment genes first arose in the early primate lineage in this way: a longer-wavelength mammalian pigment gene was duplicated on a single X chromosome, after which mutations in either or both copies of the X-linked ancestral gene produced two quite similar pigments with different ranges of spectral sensitivity—the M and L pigments.



▲ **RETINA**, a layer of nerve cells at the back of the eye, transmits visual information to the brain via the optic nerve. Color vision depends on cones: tapered sensory cells that contain light-activated pigments. Other light-sensitive cells called rods function in dim light and do not usually participate in color vision. The rods and cones, known collectively as photoreceptors, sit behind other cell types that support vision.

[THE AUTHORS]

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A known mechanism for gene duplications of this type occurs during the formation of eggs and sperm. As cells that give rise to eggs and sperm divide, pairs of chromosomes often swap parts in a process called recombination, and occasionally an unequal exchange of genetic material leads to the production of a chromosome that possesses extra copies of one or more genes. Useful mutations subsequently introduced in those duplicate genes can then be maintained by natural selection. That is, by aiding survival, helpful mutations get passed down to future generations and spread within the population.

In the case of primate color vision, trichromacy based on the “new” M and L pigments (along with the S pigment) presumably conferred a selective advantage over dichromats in some environments. The colors of ripe fruit, for example, frequently contrast with the surrounding foliage, but dichromats are less able to see such contrast because they have low sensitivity to color differences in the red, yellow and green regions of the visual spectrum. An improved ability to identify edible fruit would likely aid the survival of individuals harboring the mutations that confer trichromacy and lead to the spread of those mutant genes in the population.

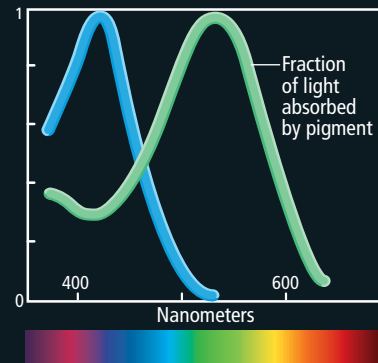
The mechanisms outlined earlier—gene duplication followed by mutation leading to DNA sequence divergence—would seem to be a reasonable explanation for the evolution of the pri-

[BASICS]

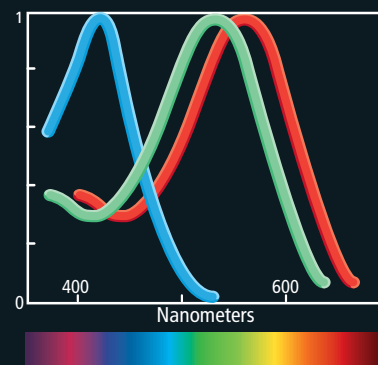
Two Kinds of Mammalian Color Vision

Most mammals are dichromats; their color vision comes from just two kinds of visual pigments (*top panel*): one that absorbs short-wavelength light maximally (*blue curve*) and one that is more sensitive to longer wavelengths (*green curve*). But humans and some other primates have trichromatic color vision (*lower panel*). They see more colors because they use three pigment types: a short-wavelength pigment (*blue curve*) and two kinds of longer-wavelength pigments (*green and red curves*).

DICHROMATIC •



TRICHROMATIC •



mate M- and L-pigment genes because that series of events is known to have occurred in other gene families. Consider, for example, the genes encoding the hemoglobins, proteins that carry oxygen in the blood. The genes for fetal hemoglobin, which is produced beginning in the second month in utero, and the genes for adult hemoglobin seem to have originated as duplicates of a single ancestral gene that then mutated into variants with differing affinities for oxygen. Likewise, immunoglobulins, the proteins that mediate the antibody response of the immune system, come in a great variety and arose from duplication of a single, ancestral gene.

Two Roads to Trichromacy

The real story of the evolution of primate trichromacy, however, turns out to be both more complicated and more interesting. A critical clue came from the discovery that two different genetic mechanisms for trichromatic vision seem to operate in primates: one in the Old World primates (the group that evolved in sub-Saharan Africa and Asia and that includes gibbons, chimpanzees, gorillas and humans) and another in the New World primates (species from Central and South America such as marmosets, tamarins and squirrel monkeys).

Humans and other Old World primates carry both M- and L-pigment genes on each of their X chromosomes and have trichromatic vision. But in testing the color vision of New World primates over the past several decades, one of us (Jacobs) discovered that trichromacy occurs only in a subset of females. All of the New World males and roughly a third of the New World females examined showed the lack of sensitivity to color differences in the middle-to-long wavelengths that is typical of dichromats. Trichromacy was not universal among primates after all.

To explain this curious pattern, several investigators studied the number and arrangement of cone pigment genes in these New World monkeys. Most species turned out to have one short-wavelength pigment gene (presumably located on a nonsex chromosome) and only *one* longer-wavelength gene, located on the X chromosome. In other words, their genetic endowment of visual pigments was comparable to that of the dichromatic mammals. How, then, could *any* of them be trichromats?

The answer is that the gene pool of New World primates includes several variants, or alleles, of the X-linked pigment gene—different versions with slightly modified sequences of

DNA. Allelic variation occurs in many genes, but the small differences in DNA sequence between alleles hardly ever translate to functional differences. In New World primates, however, the various X-linked pigment alleles give rise to pigments having different spectral sensitivities. Typical New World primate species such as squirrel monkeys, for example, have three alleles of the X-linked cone pigment gene in their gene pool: one coding for a protein similar to the human M pigment, a second coding for a protein similar to the human L pigment, and a third coding for a pigment with light-absorption properties roughly midway between the first two.

Having two X chromosomes, a female squirrel monkey—and only a female—might inherit two different longer-wavelength alleles (one on each X chromosome), thereby acquiring trichromacy. About a third of all females, however, will

EVOLUTIONARY ADVANTAGE?

The colors of ripe fruit frequently contrast with surrounding foliage, and trichromats can discern such contrasts better than dichromats do. The improved ability to identify ripe fruit is one way trichromatic vision could have aided survival, leading to the spread of the genes for trichromacy in primate populations.



Two Designs for Primate Vision

The genetic basis of trichromacy in Old World and New World primates differs. In both, a gene encoding a short-wavelength pigment (blue) sits on a nonsex chromosome. The Old World primates also have two longer-wavelength pigment genes (red and green) on each X chromosome. Hence, males (with one X) as well as females (with two Xs) have three pigment genes and are trichromats.

New World primates have three variants ("alleles") of a longer-wavelength X-linked pigment gene in their gene pool (red, yellow and green), but any given X carries just one of these alleles. Consequently, only females having dissimilar pigment alleles on their two Xs are trichromats.

		Short-wavelength pigment gene	+	Longer-wavelength pigment gene(s)	=	Type of color vision
OLD WORLD PRIMATES	Male			2 pigment genes per X chromosome 		Trichromatic
	Female					Trichromatic
NEW WORLD PRIMATES	Male			1 pigment allele per X chromosome 		Dichromatic
	Female					If both X chromosomes have same pigment allele: Dichromatic If X chromosomes have different pigment alleles: Trichromatic



OLD WORLD PRIMATES evolved in Africa and Asia over millions of years and today include great apes (humans, orangutans, gorillas, bonobos and chimpanzees), as well as gibbons, langurs, macaques and mandrills. The Old World primate lineage became isolated from that of the New World—Central and South America—when the African and South American continents became fully separated about 40 million years ago.



◀ MANDRILL

inherit the same pigment allele on both their X chromosomes and end up as dichromats, like the unlucky males. One can think of New World primate trichromacy as the poor man's—or, more accurately, the poor woman's—version of the ubiquitous trichromacy that Old World primates enjoy [see box above].

The disparity in color vision between the New and Old World primates provides a window onto the evolution of color vision in both groups. The two primate lineages began to diverge about 150 million years ago, with the progressive separation of the African and South American continents; their genetic isolation appears to have been complete by about 40 million years ago. One might suspect that the two mechanisms of trichromacy evolved independently, after the New and Old World primate lineages separated. Both groups could have started out as dichromats, with the standard mammalian complement of one shorter-wavelength pigment and one longer-wavelength pigment. The longer-wavelength pigment gene in the Old World primates could have undergone the gene duplication followed by sequence divergence that we discussed earlier. In New World primates the longer-wavelength pigment gene could have simply undergone sequence divergence, with successive mutations creating various longer-wavelength pigment alleles that persisted in the population.

Yet comparison of the amino acid sequences of the X-linked visual pigments suggests another scenario. Across both Old and New World primates, all M pigments share one set of three ami-

no acids that confer a maximum spectral sensitivity at 530 nanometers, and all L pigments share a second set of three amino acids that confers a maximum spectral sensitivity at 560 nanometers. From studies of the absorption spectra of other longer-wavelength pigments, we know that sequence changes in a variety of other amino acids can shift the maximal sensitivity of this family of pigments to longer or shorter wavelengths. It seems unlikely, then, that New and Old World primates converged independently on identical sets of amino acids to shift the sensitivities of their longer-wavelength pigments.

Instead it makes more sense to think that allelic variation like that in today's New World primates was the primitive condition, present in the common ancestor of both groups, and that its appearance was the first step in the path to trichromacy for both [see box on opposite page]. The various pigment alleles probably arose by successive rounds of mutation in the mammalian longer-wavelength pigment gene some time before the Old and New World primate lineages became isolated. (We suppose that the intermediate-wavelength pigment was part of this primitive complement because its amino acid sequence contains a subset of the three sequence changes that distinguish L from M pigments and because its absorption spectrum is partway between the two.) Then, after the two primate groups became separated, a rare error in recombination occurred in a female of the Old World lineage that happened to be carrying two different alleles of the longer-wavelength pigment

gene. This rare event placed an M allele alongside an L allele on a single X chromosome, thereby allowing trichromacy to extend to males as well as all females.

That genetic innovation granted such a strong selective advantage to its carriers that X chromosomes having only one longer-wavelength pigment gene were ultimately lost from the gene pool of Old World primates. Among the geographically and genetically separate New World primates, the primitive system of three longer-wavelength alleles persisted.

The Role of Randomness

Another surprising implication of our findings in New and Old World primates concerns the role of randomness in trichromacy. We are not referring here to the random genetic mutations that at the outset gave rise to the complement of pigment genes that confer trichromacy. Biologists have generally found that once a beneficial trait has evolved by this chance mechanism, it typically becomes “hardwired”: that is, cellular processes that do not stray from a predetermined blueprint meticulously orchestrate the development of the trait in each individual. Yet it seems that for primate color vision, random events in each organism and even in each developing cone cell play a large—indeed, an essential—role.

To explain how randomness helps to produce trichromacy, we must first review how cone cells transmit information about color to the brain. It turns out that having three pigment types, while necessary for trichromatic vision, is just an initial condition. Neural processing of the signals generated by the various photoreceptors is the next step. This step is critical because individual cone cells cannot convey specific information about wavelength. Excitation of each photoreceptor can be triggered by a range of different wavelengths, but the cone cannot signal what particular wavelengths within that band it has absorbed. For example, it could produce the same size signal whether it is hit by 100 photons of a wavelength it absorbs well or by 1,000 photons of a wavelength it absorbs poorly. To distinguish among colors, the visual system must compare the responses of neighboring cones having different pigment types.

For such comparisons to work optimally, each cone cell must contain just one type of pigment, and cones making different pigments must lie close to one another in a kind of mosaic. In fact, in the primate retina each cone cell does contain only a single type of visual pigment, and

different cone types are arranged in the requisite mosaic. Yet every cone cell in a trichromat harbors genes for all three pigments. Exactly how a cone cell “decides” to express just one pigment gene is not entirely clear.

Cells switch on, or express, their genes by way of transcription factors: dedicated DNA binding proteins that attach near a regulatory region called a promoter, thereby triggering a series of events leading to synthesis of the protein encoded by the gene. For the short-wavelength photoreceptors, it appears that during fetal development transcription factors activate the gene for the S pigment. Some unknown process also inhibits expression of the genes for the longer-wavelength pigments in these cells.

But an additional mechanism governs pigment gene expression in the longer-wavelength cones in New World primates, and this mechanism involves an inherently random process. In female New World primates that have different pigment alleles on their two X chromosomes, which allele any given cone cell expresses depends on a molecular coin toss known as X-inactivation. In this process, each female cell randomly disables one of its two X chromo-



WHITE-BELLIED spider monkey ▲

NEW WORLD MONKEYS

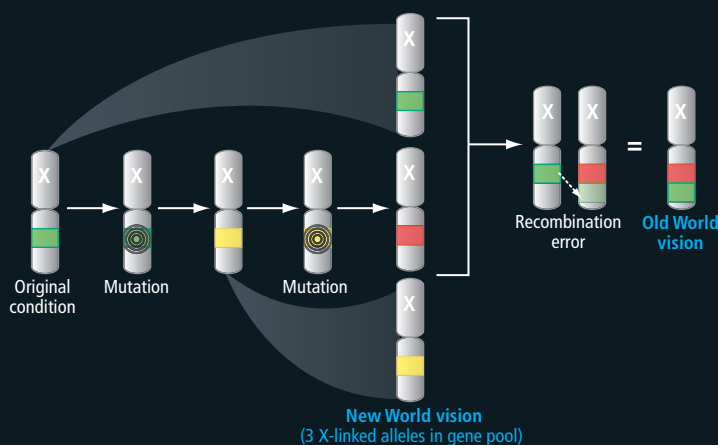
occupy Central and South America and tend to be smaller than their Old World cousins. They include such species as marmosets, tamarins, squirrel monkeys, spider monkeys and capuchins.



[FINDINGS]

How Primate Trichromacy Evolved

Comparison of the genetic basis of color vision in New World and Old World primates indicates the key evolutionary steps that led to trichromatic color vision in some female New World monkeys and in both genders of Old World primates.



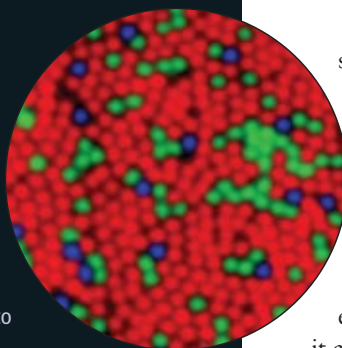
In a common ancestor of both Old and New World primates, an ancestral X-linked longer-wavelength pigment gene (*green at far left*) underwent successive mutations, yielding three longer-wavelength pigment alleles in the gene pool (*green, yellow and red*); these changes persist in modern New World primates. After the Old World and New World primate lineages became isolated

from each other, an error in recombination—the process in which chromosomes swap parts during formation of eggs and sperm—in an Old World primate female placed two different alleles together on the same X chromosome (*far right*). Because this condition gave a selective advantage to males as well as all females, it became the norm in present-day Old World primates.

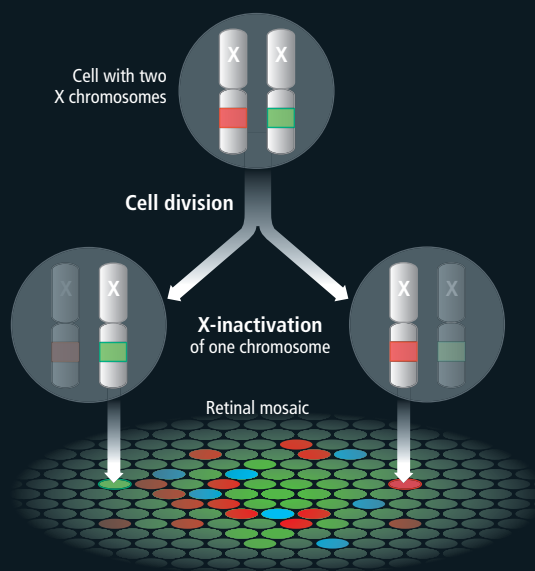
[SURPRISING DISCOVERIES]

Randomness in the Retina

Each individual cone cell contains genes for all three color pigments but selects only one of the three to activate and shuts down the other two. The process that controls selection of the short-wavelength pigment gene is not known in detail. But the mechanisms that determine selection of one of the two longer-wavelength pigment genes appear to be random, and the local distribution of longer-wavelength cone types in the retina appears to be random as well (*computer rendition at upper right*).

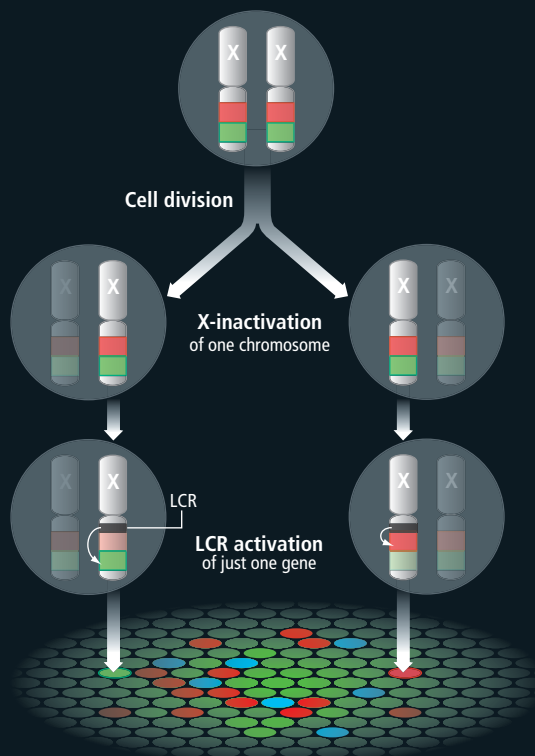


NEW WORLD COIN TOSS



◀ In New World primates the selection of a longer-wavelength pigment gene is accomplished by X-inactivation, a process in which a female cell randomly disables one of its two X chromosomes early in embryonic development. If the female has different pigment alleles on her X chromosomes, inactivation of one of the Xs in each cell will produce a mosaic of longer-wavelength cone types.

OLD WORLD SERENDIPITY



◀ Old World primates have two kinds of longer-wavelength pigment genes on a single X chromosome, so a second step is necessary to narrow pigment types to one per cone cell. X-inactivation takes one X chromosome out of play in female cells. Then, in cells of both genders, a gene regulator called the locus control region (LCR) interacts at random with just one of the longer-wavelength pigment genes, switching only that gene on—again creating a random mosaic of cone types.

some early in development. X-inactivation ensures that just one pigment allele will be expressed (that is, one type of pigment will be made) in any longer-wavelength cone cell. Because the process is random—half of all cells express genes encoded by one X chromosome, and the other half express genes encoded by the second X chromosome—it also ensures that the longer-wavelength cones in New World primate females will be intermingled across the surface of the retina in a mosaic that permits trichromacy.

X-inactivation occurs in all mammals and is essential for species survival. Without it, female cells would use both X chromosomes to produce proteins, causing the sexes to differ in the amounts of proteins made and thus impairing development in one or both of the genders. But because Old World primates have both M- and L-pigment genes on *each* X chromosome, X-inactivation alone does not narrow expression to just one pigment gene per cone cell in those animals. Another mechanism must be operating as well.

Research by Nathans suggests that which of the two X-linked pigment genes an Old World primate cone cell expresses is determined by a nearby DNA sequence known as the locus control region. The choice is probably made during development when in each cone cell the locus control region interacts with one and only one of the two adjacent pigment gene promoters—that of either the M or the L pigment, but not both—and switches on that gene. The particulars of the interaction have not yet been characterized in detail, but current evidence suggests that this choice may be random.

If this pairing of the locus control region and a promoter is indeed determining pigment gene expression in cone cells and if it is in fact random, then the distribution of M and L cones within any small region of the Old World primate retina should be random as well. Studies by David Williams of the University of Rochester and his colleagues show that within the technical limits of current methods for mapping cone cell distribution, this prediction holds.

The Accidental Colorist

Studies examining the underpinnings of primate color vision also imply that certain retinal and brain mechanisms involved in longer-wavelength color vision may be highly plastic. Although dedicated circuits exist for comparing

visual information from the S cones with the combined signal from the longer-wavelength cones, the brain and retina seem to be more improvisational in comparing signals from M cones with those from L cones. In particular, the visual system seems to learn the identity of these cones by experience alone—that is, by monitoring the cones' responses to visual stimuli.

What is more, it appears that the principal neural pathway that conveys responses from these longer-wavelength cones may not even be specifically dedicated to color vision. Rather the ability to extract information about hue from the L and M cones may be a happy accident made possible by an ancient neural apparatus for high-resolution *spatial* vision, which evolved to detect the boundaries of objects and their distance from the viewer. John Mollon of the University of Cambridge points out that in primates high-resolution spatial vision is mediated by the longer-wavelength cones and involves the same kind of neural processing that longer-wavelength color vision does—that is, a comparison of the excitation of one L or M cone with the average excitation of a large number of its L and M neighbors. No separate circuitry has yet been found for longer-wavelength color vision, and perhaps none is required. In this view, trichromatic color vision can be considered a hobby of the preexisting spatial vision system.

GENETICALLY ENGINEERED MOUSE has learned to approach the one panel in three that is a different color from the others, revealing that it can see shades of orange that normal mice, as dichromats, would not be able to distinguish from blue. The mouse gained this ability because it possesses a human longer-wavelength visual pigment gene in addition to its two native pigment genes. The experiment demonstrates the remarkable plasticity of the mammalian brain, because the mouse can use its new pigment without having nerve cells specifically wired for interpreting its signals.



The suggestion of neural plasticity in color vision led us to an intriguing question. We imagine that the first step in the evolution of primate trichromacy was emergence in an early female ancestor to all present-day primates of a second longer-wavelength X-linked allele. Could the ancestral primate brain have improvised enough to “use” the new pigment right away, without also evolving new neural circuitry? Could acquiring a third type of pigment be enough in itself to add another dimension to color vision?

It occurred to us that we might test this idea if we could re-create that initial step in the evolution of primate trichromacy in a dichromatic mammal such as a laboratory mouse. We began this experiment by genetically engineering a mouse X chromosome so that it encoded a human L pigment instead of a mouse M pigment, thereby introducing allelic variation of the kind we believe may have occurred millions of years ago in dichromatic primates. We then demonstrated that the resulting line of mice expressed the human gene in their cone cells and that the human L pigment transmitted light signals with an efficiency comparable to that of the mouse M pigment. In addition, the mice expressing the human L pigment were, as expected, sensitive to a broader range of wavelengths than ordinary mice were.

But for our purposes, the key question was: Could female mice having two different X chromosome pigment genes use the retinal mosaic of M and L cones produced by X-inactivation not only to sense but to make discriminations within this broader range of wavelengths? The short and remarkable answer is that they can.

In laboratory tests, we were able to train females having both M and L pigments to discriminate among green, yellow, orange and red panels that, to ordinary mice, look exactly the same. Along with the new L pigment, these mice apparently acquired an added dimension of sensory experience, implying that the mammalian brain has the innate ability to extract information from novel and qualitatively different types of visual input.

This finding has implications for the evolution of sensory systems in general, because it suggests that changes at the “front end” of the system—in the genes for sensory receptors—can drive the evolution of the entire system. With respect to primate trichromacy, the mouse experiment also suggests that the very first primate with two different longer-wavelength pigments saw a world of color no primate had ever seen before. ■

SUPER COLOR VISION?



Some women have four types of visual pigments instead of three. The fourth pigment resulted from a mutation in one of the longer-wavelength X-linked pigment genes and is known to shift the spectral sensitivity of the retina. Whether this shift actually creates the ability to perceive a broader range of hues is under active investigation. Thus far color vision testing has not produced consistent evidence for tetrachromatic vision, and humans who have this ability—if they exist—would not necessarily be aware of their visual anomaly.

MORE TO EXPLORE

The Evolution and Physiology of Human Color Vision: Insights from Molecular Genetic Studies of Visual Pigments. J. Nathans in *Neuron*, Vol. 24, No.2, pages 299–312; October 1999.

Genetically Engineered Mice with an Additional Class of Cone Photoreceptors: Implications for the Evolution of Color Vision.

P. M. Smallwood et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 100, No. 20, pages 11706–11711; September 30, 2003.

Emergence of Novel Color Vision in Mice Engineered to Express a Human Cone Pigment. G. H. Jacobs, G. A. Williams, H. Cahill and J. Nathans in *Science*, Vol. 315, pages 1723–1725; March 23, 2007.

Primate Color Vision: A Comparative Perspective.

G. H. Jacobs in *Visual Neuroscience*, Vol. 25, Nos. 5–6, pages 619–633; September 2008.