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Genetic Modification Enables Mice to See New Colors

Researchers at the University of California, Santa Barbara, and at The Johns Hopkins University School of Medicine have demonstrated that a particular genetic modification enables mice to acquire new color vision. Their findings, which could have implications for understanding the evolution of color vision and other sensory systems in mammals, will be published in the March 23 issue of the journal Science.

Gerald Jacobs, research professor in the Department of Psychology and the Neuroscience Research Institute at UCSB, and Jeremy Nathans, M.D. professor of molecular biology and genetics at The Johns Hopkins University School of Medicine and a Howard Hughes Medical Institute researcher, are the article's lead authors. The other researchers were Gary A. Williams, a postdoctoral researcher at UCSB, and Hugh Cahill, a graduate student at The Johns Hopkins University School of Medicine.

The study builds on earlier research of Jacobs and his colleagues that has centered on issues related to the biology and evolution of color vision among the primates.

A news release issued by the Howard Hughes Medical Institute explains the study's findings in detail. The text follows:

Genetic Studies Endow Mice with New Color Vision

Although mice, like most mammals, typically view the world with a limited color palette -- similar to what some people with red-green color blindness see -- scientists have now transformed their vision by introducing a single human gene into a mouse chromosome. The human gene codes for a light sensor that mice do not normally possess, and its insertion allowed the mice to distinguish colors as never before.

In a study published in the March 23, 2007, issue of the journal Science, Howard Hughes Medical Institute researchers at Johns Hopkins, together with researchers at the University of California, Santa Barbara, demonstrated in a series of cleverly designed color vision tests that the genetic modification allows mice to see and distinguish among a broader spectrum of light waves. The experiments were designed to determine whether the brains of the genetically altered mice could efficiently process sensory information from the new photoreceptors in their eyes. Among mammals, this more complex type of color vision has only been observed in primates, and therefore the brains of mice did not need to evolve to make these discriminations.

The new abilities of the genetically engineered mice indicate that the mammalian brain possesses a flexibility that permits a nearly instantaneous upgrade in the complexity of color vision, say the study's senior authors, Gerald Jacobs and Jeremy Nathans.

The evolution of color vision has been a topic of intensive study for more than three decades. The new research is the most definitive yet in shedding light on the first steps that led to the emergence of trichromacy -- the variety of color vision found today in most primates, including humans.

"What we are looking at in these mice is the same evolutionary event that happened in one of the distant ancestors of all primates and that led ultimately to the trichromatic color vision that we now enjoy," said Nathans.

Trichromacy is dependent on three types of photoreceptor cells in the retina that preferentially absorb lights at different wavelengths. These are known as cone cells and each type contains a particular kind of light-absorbing sensor protein. Short-wavelength-sensitive (S) cone cells are most sensitive to blue lights, medium-wavelength-sensitive (M) cone cells are most sensitive to green lights, and long-wavelength-sensitive (L) cones are most sensitive to red lights. When light strikes the retina and activates the cone cells, the brain compares the responses of the S,

M, and L photoreceptors, and it is the brain's assessment of their relative levels of activation that we perceive as color.

Most mammals, including mice, are dichromats, possessing only S and M cone pigments.

As a consequence, they can distinguish only a fraction of the wavelengths that can be distinguished by humans.

John Mollon at the University of Cambridge has suggested that the evolution of trichromacy could have permitted primates to discriminate between unripe fruit, which is typically green, and ripe red -- and orange -- colored fruits. Reciprocally, the colors of ripened fruits may have coevolved with primate trichromacy, since animals that could recognize and eat the ripe fruit would have assisted plants by spreading their seeds.

Nathans, a Howard Hughes Medical Institute researcher at Johns Hopkins, worked out the structure of the human S, M, and L pigments and the genetic basis of human color vision variation beginning in the 1980s. At the same time, Jacobs, at UCSB, deciphered the distinctive genetic mechanism that gives rise to trichromatic color vision in New World (South American) primates. Together, their work has suggested that the type of trichromatic color vision that New World monkeys possess may also be the evolutionary precursor to the form found among Old World (African) primates, including humans.

In 2003, Nathans and Jacobs, together with Markus Meister at Harvard University, reported their initial studies on genetically engineered mice carrying the L receptor gene in place of the M receptor gene. Because these genes are carried on the X-chromosome, they are subject to a process known as X-chromosome inactivation. In mammals, every cell in females has two X-chromosomes, while every cell in males has a single X-chromosome.

X-inactivation occurs only in females and results in the silencing of most of the genes on one of the X-chromosomes in each cell.

Because different cells choose to silence either one or the other of the X-chromosomes, female mice engineered to have one copy each of the M and L receptor genes express the M receptor in some cone cells and the L receptor in other cone cells.

These two different types of cones are intermingled with one another across the surface of the retina.

This X-inactivation-based mechanism for producing M and L receptors in different cone cells is the same as the one that Jacobs had identified earlier in New World primates.

For the current study, the team selected mice that possessed roughly equal ratios of M and L cone cells, and compared their vision to that of normal mice.

Jacobs's group at UCSB developed behavioral tests to determine whether the female mice could discriminate among colored lights by comparing the relative activation of the M and L cone cells. The researchers conducted tens of thousands of tests in which two different wavelengths or intensities of light were displayed on three test panels. Mice received a drop of soymilk as a reward when they correctly identified which panel differed from the other two. The genetically altered mice demonstrated their new visual ability by choosing the correct panel in 80 percent of the trials.

By contrast, normal mice only chose correctly one third of the time, the score that one would obtain by guessing randomly among the three panels.

According to the scientists, their findings have implications not just for the evolution of color vision, but for the evolution of sensory systems in general. Previous experiments with the visual, olfactory (smell), and gustatory (taste) systems, have suggested that introducing a new sensory receptor can alter an animal's behavior and nerve activity.

"Our observation that the mouse brain can use this information to make spectral discriminations implies that alterations in receptor genes might be of immediate selective value not only because they expand the range or types of stimuli that can be detected but also because they permit a plastic nervous system to discriminate between new and existing stimuli," they wrote in the Science paper. "Additional genetic changes that refine the downstream neural circuitry to more efficiently extract sensory information could then follow over many generations."

About UC Santa Barbara

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of faculty, students, and staff is characterized by a culture of interdisciplinary collaboration that is responsive to the needs of our multicultural and global society. All of this takes place within a living and learning environment like no other, as we draw inspiration from the beauty and resources of our extraordinary location at the edge of the Pacific Ocean.