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## Photoreceptor Gene Mutation Discovered

HHMI researchers have discovered the cause of enhanced S-cone syndrome (ESCS), a disorder that makes those affected sensitive to blue light and susceptible to developing night blindness at an early age.

A research team led by Val C. Sheffield, an HHMI investigator at the University of Iowa College of Medicine, discovered that 94 percent of DNA samples from ESCS-affected individuals showed mutations in *NR2E3*, a photoreceptor gene that is also known as *PNR* (photoreceptor-specific nuclear receptor).

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The research team, which included lead author Neena B. Haider, an HHMI-supported graduate student in Sheffield's lab, Samuel G. Jacobson at the Scheie Eye Institute at the University of Pennsylvania, Edwin M. Stone from the department of ophthalmology at Iowa, and other collaborators, published its findings in the February 2000 issue of the journal *Nature Genetics*.

Photoreceptors are specialized light-sensitive nerve cells that line the retina. Humans have two types of photoreceptors, called rods and cones. Rods mediate black and white vision and are used mainly at night. During the day, however, humans depend on cones for color vision. Cones come in three types red, green, and blue that are sensitive to different wavelengths of light.

ESCS is a rare degenerative disease of the retina. Patients with ESCS suffer from night blindness and increased sensitivity to blue light. These observations led researchers to speculate that ESCS is caused by mistakes early in photoreceptor development that cause an overabundance of blue cones relative to the number of red and green cones.

Sheffield's lab, which focuses on identifying genes that cause human hereditary diseases, especially hereditary blindness, discovered the ESCS mutations while studying another retinal disorder called Bardet Biedl syndrome (BB).

While sequencing different regions of the genome associated with BB they located a gene called *PNR*. The gene seemed an interesting candidate for BB because it was expressed in the eye, but Sheffield and his colleagues could not find any *PNR* mutations in patients with BB. They did, however, think *PNR* a good candidate for other eye diseases, so they screened nearly 400 DNA samples from people with other eye disorders, and found two samples that possibly contained a *PNR* mutation.

"Interestingly, these patients had ESCS," recalls Sheffield. "Now we had a hypothesis that mutations in this gene cause this specific syndrome."

To increase their sample size, they tested 35 ESCS-affected individuals from 29 families, obtaining samples from collaborators. "Lo and behold we found that nearly every sample had a mutation," remarks Sheffield.

Sheffield and his colleagues also found that the expression of *NR2E3* is specific to the nuclear layer of the retina, which is lined by the nuclei of photoreceptors.

"A lot of interesting biology comes out of rare diseases and rare mutations," says Sheffield. "I think the main interest in this paper will be the insight that it might bring to understanding the signaling pathways that determine cell type in the embryonic retina." Right now, researchers do not know how precursor photoreceptors reach their ultimate cell type.

"ESCS is interesting in what it might imply for how photoreceptor pattern and fate gets set up in the eye," says Contance Cepko, an HHMI investigator at Harvard Medical School, who authored an accompanying *News and Views* article in *Nature Genetics*. "The discovery of any mutation that affects that process is important."

Discovering the molecular signals that determine why one cell becomes a rod or a cone, and how cone cells become blue-, green- or red-sensitive are important questions in the study of eye development. "This disease may provide some answers to these questions," says Sheffield. "Now we've found a mutation and a gene that would indicate that *NR2E3* is one of the signaling genes in retinal development."

As in most scientific discoveries, the findings of this paper now create more questions than answers. If signaling mistakes in the expression of *NR2E3* are the cause of ESCS, how might this happen? One hypothesis is that cone cells become blue by default unless they receive a signal to become red or green. Another hypothesis is that *NR2E3* mutations alter a photoreceptor's fate, causing cells that would normally develop as rods to become cones instead.

To find out what is really happening in ESCS patients, says Cepko, researchers might have to await an animal model of the disorder.