

# Fighting blindness: Scientists bring a key protein into focus

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have discovered how a protein called  $\alpha 2\delta 4$  establishes proper vision. Their research helps explain why mutations in the gene encoding  $\alpha 2\delta 4$  lead to retinal dystrophy, a disease characterized by defective color vision and night blindness.

To study how this protein supports vision, the researchers modeled retinal dystrophy in mice. Like humans, mice lacking  $\alpha 2\delta 4$  succumbed to the disease and their vision was compromised.

"Much of our work is driven by desire to understand what goes awry in a range of blinding conditions," explained TSRI Professor Kirill A. Martemyanov, senior author of the new study. "Now we have found a molecule that plays a key role in allowing photoreceptors to plug into the [neural circuit](#) and transmit the light signals they receive to the brain."

The study was published online recently in the journal *Neuron*.

## A Secret Ingredient for Vision

Our vision depends on two types of photoreceptors in the light-sensitive layer of eye called the retina. Rods photoreceptors detect photons at the lowest levels of light and support night vision, and [cone photoreceptors](#) sense bright light and discriminate between colors. Both rods and cones must wire into a neural circuit of the retina to send information to the

brain.

Martemyanov and his colleagues are studying the neural connections that make vision possible. In a previous study, the researchers identified a novel cell-adhesion protein called ELFN1 that rods use for making contacts with their partners, called bipolar neurons. However, how ELFN1 accomplishes the task of photoreceptor wiring was not clear.

In the new study, experiments spearheaded by TSRI Research Associate Yuchen Wang of the Martemyanov laboratory showed that this connectivity requires  $\alpha 2\delta 4$  to join a structure, called a higher order macromolecular complex, with ELFN1 and other proteins called calcium channels. These calcium channels trigger the release of the chemical messenger glutamate, which photoreceptors use for communicating with bipolar neurons.

In short, Wang explained, without both  $\alpha 2\delta 4$  and the other [calcium channels](#) in the macromolecular complex, rods cannot connect to the neural circuit. "We found that  $\alpha 2\delta 4$  is essential for organizing the presynaptic compartment of [rod photoreceptors](#)," he said.

Strikingly, eliminating the corresponding gene for  $\alpha 2\delta 4$  in a mouse model interrupted the transmission of light signals from photoreceptors to the brain without affecting the ability to detect light. "It's like you are trying to make a phone call—and your phone is fully functional—but you are not heard because there is no signal," Martemyanov said.

**Cones seemed to handle the lack of  $\alpha 2\delta 4$  only slightly better.**

Without the  $\alpha 2\delta 4$ , mice failed to see under dim light conditions and could not navigate a maze in low light due to their dysfunctional rods.

Their cones were affected too, but they could still send some weak signals through to the brain.

"Their dim-light vision was completely abolished," said Martemyanov. "And the signal from the cones could barely make it." Wang said the researchers are doing more research now to account for this difference between rods and cones.

## **A Potential Way to Keep Eyes Healthy**

Going forward, Martemyanov and his team plan to study whether manipulating  $\alpha 2\delta 4$  could help photoreceptors transmit their signals and maintain connectivity to stay functional longer in models of age-related vision loss, a major blinding condition in humans.

"If we can entice dying photoreceptors to augment their communication with the retina circuitry and preserve the connections they make, we can likely delay the loss of vision in degenerative conditions like age-related macular degeneration," Martemyanov said.

The researchers also think that wiring factors such as  $\alpha 2\delta 4$  and ELFN1 could also help researchers address a current challenge in using stem cells to correct vision loss.

Martemyanov explained that current efforts of many laboratories are currently directed towards replacing dead photoreceptor cells with stem cell-derived rods and cones as a strategy to restore vision; however, integrating the new [photoreceptors](#) into the retina circuit has been a challenge. The new study suggests that  $\alpha 2\delta 4$  may be the secret ingredient for getting these new cells to properly wire into the neural circuit.

Provided by The Scripps Research Institute

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