Mutated gene in zebrafish sheds light on blindness in humans

24 March 2009

Adult zebrafish are about one inch in length and recognized by many as a popular aquarium species. Credit: Charles Badland, Program in Neuroscience, Florida State University

Among zebrafish, the eyes have it. Inside them is a mosaic of light-sensitive cells whose structure and functions are nearly identical to those of humans. There, biologists at The Florida State University discovered a gene mutation that determines if the cells develop as rods (the photoreceptors responsible for dim-light vision) or as cones (the photoreceptors needed for color vision).

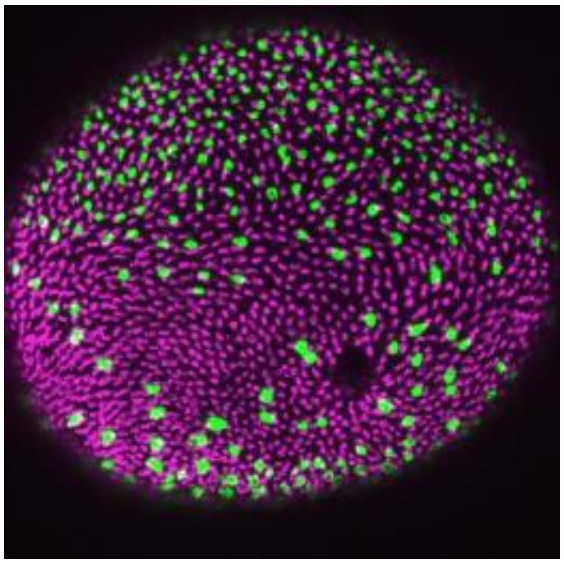
Described in a paper published in the Proceedings of the National Academy of Sciences (PNAS), the landmark study of retinal development in zebrafish larvae and the genetic switch it has identified should shed new light on the molecular mechanisms underlying that development and, consequently, provide needed insight on inherited retinal diseases in humans.

From FSU's Department of Biological Science and Program in Neuroscience, doctoral candidate Karen Alvarez-Delfin (first author of the PNAS paper), postdoctoral fellow Ann Morris (second author), and Associate Professor James M. Fadool are the first scientists to identify the crucial function of a previously known gene called "tbx2b." The researchers have named the newfound allele (a different form of a gene) "lor" -- for "lots-of-rods" -- because the mutation results in too many rods and fewer ultraviolet cones than in the normal eye.

"Our goal is to generate animal models of inherited diseases of the eye and retina to understand the progression of disease and find more effective treatments for blindness," said Fadool, faculty advisor to Alvarez-Delfin and principal investigator for Morris's ongoing research. "We are excited about the mutation that Karen has identified because it is one of the few mutations in this clinically critical pathway that is responsible for cells developing into one photoreceptor subtype rather than another."

"What is striking in this case is that the photoreceptor cell changes we observed in the retinas of zebrafish are opposite to the changes identified in Enhanced S-cone syndrome (ESCS), an inherited human retinal dystrophy in which the rods express genes usually only found in cones, eventually leading to blindness," Alvarez-Delfin said. "Equally surprising is that this study and others from our lab show that while alterations in photoreceptor development in the human and mouse eyes lead to retinal degeneration and blindness, they don't in zebrafish. Therefore, the work from our Florida State lab and with our collaborators at the University of Pennsylvania, Vanderbilt University and the University of Louisville should provide a model for better understanding the differences in outcomes between mammals and fish, and why the human mutation leads to degenerative disease."

Morris calls the zebrafish an ideal genetic model for studies of development and disease. The common aquarium species are vertebrates, like humans. Their retinal organization and cell types are similar to those in humans. Zebrafish mature rapidly, and lay many eggs. The embryos are transparent, and they develop externally, unlike mammals, which develop in utero.



This fireworks display is actually a microscope image of a zebrafish retina immunolabeled for ultraviolet cones (magenta) and rods (green). The image shows the regular pattern of the cones and the scattered pattern of the rods typical of a normal fish. The labeling was performed by Karen Alverez-Delfin, doctoral candidate at Florida State University. Credit: Florida State Associate Professor James Fadool and Alverez-Delfin

"This lets us study developmental processes such as the formation of tissues and organs in living animals," she said.

"From a developmental biology perspective, our research will help us unravel the competing signals necessary for generating the different photoreceptor cell types in their appropriate numbers and arrangement," Morris said. "The highly specialized nature of rods and cones may make them particularly vulnerable to inherited diseases and environmental damage in humans. Understanding the genetic processes of photoreceptor development could lead to clinical treatments for the millions of people affected by photoreceptor cell dystrophies such as retinitis pigmentosa and macular degeneration."

The mosaic arrangement of photoreceptors in fish was first described more than 100 years ago, but the J. Fadool laboratory at Florida State was the first to successfully take advantage of the pattern to identify mutations affecting photoreceptor development and degeneration.

"Imagine a tile mosaic," Fadool said. "That is the kind of geometric pattern formed by the rod and cone photoreceptors in the zebrafish retina. This mosaic is similar to the pattern of a checkerboard but with four colors rather than two alternating in a square pattern. The red-, green-, blue-, and ultraviolet-sensitive cones are always arranged in a precise repeating pattern. Human retinas have a photoreceptor mosaic, too, but here the term is used loosely, because while the arrangement of the different photoreceptors is nonrandom, they don't form the geometric pattern observed in zebrafish.

"So how do we ask a fish if it has photoreceptor defects?" he asked.

Fadool explained that because the mosaic pattern of zebrafish photoreceptors is so precise, mutations causing subtle alterations are easier to uncover than in retinas with a "messier" arrangement.

"Just as we can easily recognize a checkerboard mistakenly manufactured with some of the squares changed from black to red or with all-black squares, by using fluorescent labeling and fluorescence microscopes we can see similar changes in the pattern of the zebrafish photoreceptor mosaic," he said. "Karen showed that within the mosaic of the lots-of-rod fish, the position on the checkerboard normally occupied by a UV cone is replaced with a rod. The identity of the mutated gene is then discovered using a combination of classical genetics and genomic resources."

More information: To access the PNAS paper ("tbx2b is required for ultraviolet photoreceptor cell specification during zebrafish retinal development"), visit the journal's Web site at www.pnas.org/content/106/6.toc .

Source: Florida State University