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Long-suspected cause of blindness from eye disease disproved

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Vision scientists long have thought that lack of very long chain fatty acids in photoreceptor cells caused blindness in children with Stargardt type 3 retinal degeneration, an incurable eye disease. But researchers at the University of Utah's John A. Moran Eye Center have shown in a new study that lack of these fatty acids does not cause blindness, meaning that the search for the mechanism that robs sight from children with the disease must start anew.

Researchers led by David Krizaj, Ph.D., associate professor of ophthalmology and visual sciences at the Moran Eye Center, bred mice that lacked fatty acids in their photoreceptor cells and to their surprise found that the mice's eyesight was normal. "There was no defect in their daytime or nighttime vision," Krizaj says. "The lack of very long chain fatty acids does not appear to compromise vision in itself."

The research was published March 11, 2013, in *PNAS* online. Peter Barabas, Ph.D., a postdoctoral fellow at the Moran Eye Center, is first author on the study.

Stargardt disease is a form of macular degeneration that strikes about one in 10,000 children between the ages of 6 and 20. There is no treatment for the disease, although there is evidence that nutrition supplements and protecting eyes from UV rays might be beneficial in slowing the progression of blindness.

There are three types of Stargardt disease caused by three different gene

mutations. (Paul Bernstein, M.D., Ph.D., professor of ophthalmology and visual sciences and a co-author in the *PNAS* study, discovered one of the mutations in a Utah family.) Type 3, a rare dominant form of Stargardt disease, is caused by a mutation in ELOVL4, a gene that encodes an enzyme that helps to make fatty acids obtained through our diet into forms that can be incorporated into cell membranes. The mutation displaces the enzyme from its location in an intracellular organelle called endoplasmic reticulum into the cell cytosol, which blocks the synthesizing of very long chain fatty acids in photoreceptor cells. But proving that the lack of these fatty acids actually causes blindness has been difficult to show in experiments, because mice in which the ELOVL4 was knocked out did not survive.

Krizaj and his colleagues overcame that problem by engineering mouse models that lacked ELOVL4 only in their photoreceptor cells, allowing the mice to survive but with the fatty acids in those cells reduced up to 90 percent. This allowed them to test directly whether loss of very long chain fatty acids replicates vision loss observed in children with Stargardt's disease. As they report in the journal, electrophysiological and behavioral testing of daytime and night vision in genetically engineered mice showed that sight was not affected despite the dramatic reduction in very long chain fatty acids in photoreceptor cells.

Researchers now must look for a different cause of Stargardt type 3. "If it's not the loss of fatty acids causing the disease, then we'll have to find other strategies to help these kids," Krizaj says.

One possibility, according to Krizaj, is that mutated proteins, escaping from the endoplasmic reticulum are aggregating in the cytoplasm causing large deposits consisting of mutated and normal proteins, which is "almost like causing photoreceptor cell death by blocking intracellular traffic and clogging the cells' drains."