

Researchers find new genetic cause of blinding eye disease

August 9 2011

Combining the expertise of several different labs, University of Iowa researchers have found a new genetic cause of the blinding eye disease retinitis pigmentosa (RP) and, in the process, discovered an entirely new version of the message that codes for the affected protein.

The study, which was published online Aug. 8 in the [Proceedings of the National Academy of Sciences](#) (PNAS) Early Edition, suggests that the mutation may be a significant cause of RP in people of Jewish descent. The findings also lay the groundwork for developing prevention and treatment for this form of RP using a combination of [genetic testing](#), [gene therapy](#) and cell replacement approaches.

Using the latest DNA sequencing techniques to analyze the protein-coding regions of a single RP patient's genome, the researchers found a mutation in a gene called MAK (male germ cell associated kinase). This gene had not previously been associated with eye disease in humans. However, examining tissue from donated eyes showed that MAK protein was located in the parts of the retina that are affected by the disease.

The researchers then generated induced pluripotent stem cells (iPSCs) from the patient's own [skin cells](#) and coaxed these [immature cells](#) to develop into retinal tissue. Analyzing this tissue showed that the [gene mutation](#) caused the loss of the MAK protein in the retina.

"These new technologies have greatly enhanced our ability to find and validate disease-causing [mutations](#), which is critical to our ability to

progress to the next step of actually treating diseases like RP," said Budd Tucker, Ph.D., UI assistant professor of ophthalmology and [visual science](#) and lead study author.

RP is an uncommon, inherited blinding [eye disease](#) that affects about 1 in 4,000 people in the United States. It is thought to be caused by mutations in more than 100 different genes, only half of which have been identified.

Having found the MAK mutation in one patient, UI researchers led by Edwin Stone, M.D., Ph.D., a Howard Hughes Medical Institute investigator and director of the UI Institute for Vision Research, screened the DNA of 1,798 patients with RP and identified 20 additional individuals with the same MAK mutation. This result suggests that the new MAK mutation accounts for about 1.2 percent of RP cases in the general population. Interestingly, all 21 of the RP patients with the MAK mutation were of Jewish descent, suggesting that the mutation may be a significant cause of RP in this population.

Work in the lab of Robert Mullins, Ph.D., UI associate professor of ophthalmology and visual sciences, showed that MAK protein was produced in the cells most affected by RP. These findings prompted Tucker and colleagues to make iPSCs from the original patient.

"Induced [pluripotent stem cells](#) allow us to generate affected tissue from patients with genetic disorders and analyze how specific genetic mutations cause disease," Tucker said. "It's particularly powerful when we are looking at inaccessible tissues such as the retina and brain which are not usually biopsied in living individuals."

Although the MAK gene was previously thought to have 13 protein-coding segments known as exons, when the UI team cloned and sequenced the MAK gene, they discovered a new version of the gene

found only in the retina, which has an extra protein-coding exon.

The team also found that the MAK mutation, which involves an insertion of a large piece of DNA into the MAK gene, disrupts the gene in such a way that retinal cells lose the ability to make the longer version of MAK protein.

"What we found was a new retina-specific exon; no other tissue that we tested had this version of the protein-coding transcript" Tucker said.

"This is important because the gene mutation identified prevents the production of the retina-specific MAK protein.

"Evidence from the iPSC work validated the role of this genetic mutation in retinal disease. Showing that retinal cells generated from the affected patient could not make the mature retinal MAK protein provided strong evidence of the pathophysiologic mechanism of this mutation in RP," Tucker explained.

Based on the new work, the UI team hopes to explore gene therapy and cell replacement strategies as potential therapies for this form of RP.

The study was funded in part by grants from the National Eye Institute, National Institutes of Health New Innovator Award program and the Foundation Fighting Blindness.

"We are excited to see the University of Iowa and its collaborators bringing together several different research modalities, including genetics and stem cells, to save vision," said Stephen Rose, Ph.D., chief research officer, Foundation Fighting Blindness. "Their innovation and teamwork are greatly accelerating the development of treatments which our constituents are depending on."

Provided by University of Iowa Health Care

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