Prevention of macular degeneration possible, research shows

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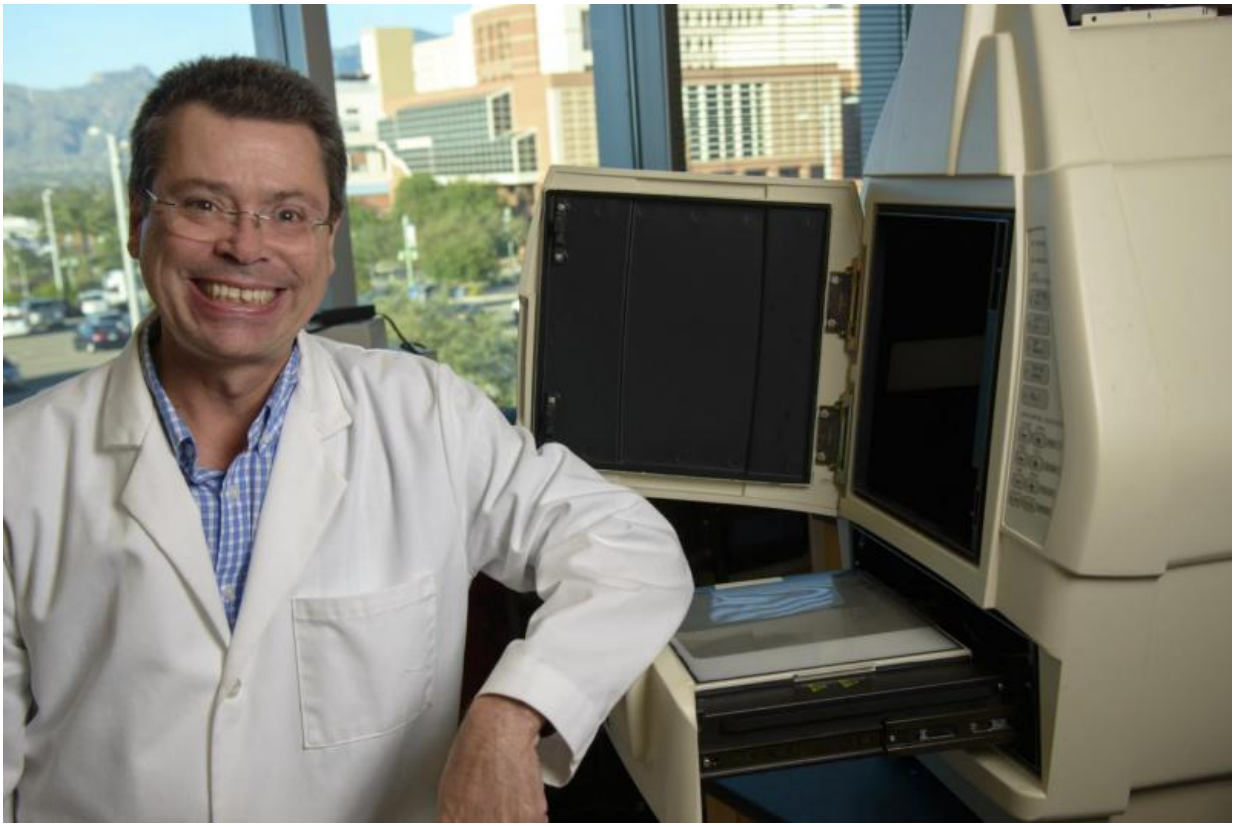

Brian McKay, co-principal investigator and UA associate professor of opthalmology and vision science and cellular and molecular medicine. Credit: Kris Hanning, UAHS BioCommunications, University of Arizona

A University of Arizona-led study on age-related macular degeneration -

the eye disease that gradually destroys the ability to read, drive, write and see close-up in 30 percent of older Americans - likely will lead to a way to delay or prevent the disease, researchers say.

The study led by co-principal investigator Brian S. McKay, associate professor of ophthalmology and vision science and cellular and molecular medicine at the UA College of Medicine - Tucson, found that patients who take levodopa, or l-dopa, a common treatment for Parkinson's disease, appear far less likely to develop macular degeneration. And if they do develop the disease, it is significantly later in life.

L-dopa is a naturally occurring molecule that is made in pigmented human tissue, including the iris of the eye, and has a role in maintaining healthy macula, the part of the retina that provides the most visual acuity. A synthesized form of l-dopa is used to treat Parkinson's and movement disorders.

"It is likely that this will lead to a way to prevent age-related macular degeneration (AMD), and it may also lead to treatment for macular degeneration in the future," Dr. McKay said. "It may also help with other eye diseases characterized by retinal degeneration, such as retinitis pigmentosa," which also can cause blindness.

The research was published online Nov. 4 in the *American Journal of Medicine*.

"Research points to this as a pathway to regulate and prevent this most common cause of blindness in adults," said study co-principal investigator Murray Brilliant, director of the Marshfield Clinic Research Foundation Center for Human Genetics in Marshfield, Wisconsin. "Imagine telling patients we potentially have medication that will allow them to see and continue enjoying life, their family and perform every

day activities as they age. That is very powerful."

Dr. Paul A. Sieving, director of the National Eye Institute, a branch of the National Institutes of Health, said the research "suggests an intriguing link between patients taking l-dopa and a lower incidence and delayed onset of AMD. Showing that l-dopa causes this protective effect will require further investigation, but if confirmed, could lead to new drugs or combination therapies for AMD that target dopa-responsive cells in the retina."

McKay pursued this research after he discovered that the support tissue for the retina expressed a receptor for l-dopa, and that this signaling pathway fostered retinal survival. He and Brilliant, who previously was with the UA, hypothesized that those taking l-dopa may be protected from AMD.

To answer this question they analyzed the health records of 37,000 Marshfield Clinic patients to determine who had macular degeneration, who took l-dopa, or both. Brilliant found that patients who began taking l-dopa before they developed macular degeneration were diagnosed with the eye disease eight years later than those who had never taken l-dopa. They also noted that there were many fewer AMD patients in the group that were prescribed l-dopa.

The next phase of the research involved analysis of a much larger, insurance-industry database of medical records on 87 million patients. The same connection between l-dopa and macular degeneration held. Further, with this enormous dataset, they were able to show that l-dopa both prevented and delayed the "wet" form of AMD, which is far less common than "dry" AMD but is responsible for about 90 percent of AMD-caused blindness.

A clinical trial to further validate these research findings will be the next

step of the research.

"Dr. McKay's efforts likely will change the lives of millions of people worldwide impacted by AMD. While early in the path to new treatment modalities, there also is considerable potential for his discoveries to inform the study of population-wide genetic determinants of susceptibility to AMD and other blinding conditions," said Dr. Kenneth S. Ramos, associate vice president for precision health sciences at the UA Health Sciences.

McKay first became interested in macular degeneration when he was on the faculty at Duke University, when large national and international studies showed that race and pigmentation were the key factors involved in the risk of developing AMD. These studies illustrated that AMD is much less common in the black and Hispanic populations, but is the leading cause of impaired vision in the white population.

In 2002, Dr. Robert Snyder, then head of ophthalmology at the UA, recruited McKay to the department to be part of a macular degeneration research group.

"When I offered him a job, he made an unsolicited promise to me and his benefactors that he would produce a cure for AMD," Snyder recalled. "He is not there yet, but his discovery provides a new candidate drug and opens up a whole new area to look at. McKay's work is a great example of the important role of charitable gifts and unencumbered research funds to support innovative research ideas."

Dr. Joseph Miller, head of the Department of Ophthalmology and Vision Science at the UA College of Medicine - Tucson, said, "Dr. McKay has been tenacious in his investigation of blinding eye disease, and with the help of many others - patients, doctors and public health workers - we now have a new direction for possible interruption of the pathway from

sight to blindness.

"This research started in McKay's laboratory, and has been pursued urgently with the help of many others, including all his supporters who make this happen by believing in the possibility of science to halt the progression of disease."

Other collaborating institutions included the Medical College of Wisconsin, the University of Miami's Bascom Palmer Eye Institute, the University of Southern California, Stanford University, and Essentia Health, a health-care system in Idaho, Minnesota, North Dakota and Wisconsin.

McKay's research was funded by the National Eye Institute; the National Human Genome Research Institute; the National Center for Advancing Translational Sciences; the University of Arizona; the Marshfield Clinic; the Wisconsin Genomics Initiative; Research to Prevent Blindness; Bright Focus; and the Edward N. and Della L. Thome Memorial Foundation.

McKay said his research "never would have been possible" without the added support it received from donor Verna Wineagar and Lions Clubs International.

"Local chapters of Lions Clubs International formed the Lions Eye Bank Express that transported donor tissue from Sun Health Foundation in Phoenix to my laboratory, producing one of the best tissue sources in the country. For our studies, donor eyes need to be studied as soon as possible," he said.

"And I thank all the people who donated their family members' eyes to this research. A lot of people helped make this possible."

More information: Murray H. Brilliant et al. Mining Retrospective Data for Virtual Prospective Drug Repurposing: L-DOPA and Age-related Macular Degeneration, *The American Journal of Medicine* (2015). DOI: 10.1016/j.amjmed.2015.10.015