Researchers Uncover Gene Linked To Blindness That Strikes Elderly

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In a discovery that illuminates the promise and the complexity of genetic research, scientists say they have identified a gene linked to age-related macular degeneration, the leading cause of blindness among the elderly.

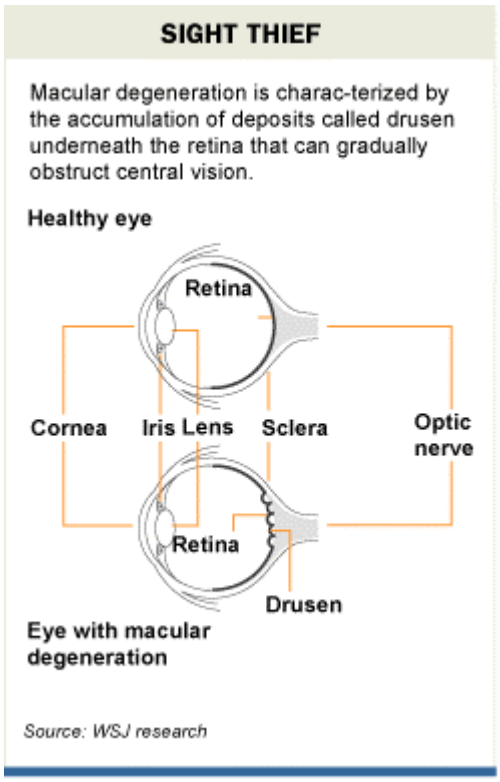
The gene is among the first to be discovered to play a role in the common form of the disease, which afflicts an estimated seven million Americans. Known as fibulin-5, the gene is part of a broader puzzle that is expected to help researchers understand how macular degeneration, or AMD, develops. That, scientists say, could lead in turn to new medicines and preventive strategies for a disease for which few effective options are on the market.

The accomplishment by researchers at the University of Iowa reflects the increasing power of the mapping of the human genome and state-of-the-art gene-hunting technology to help unearth clues about the causes of disease in human DNA. It also underscores the challenges scientists face in tracking down potential genetic causes of common diseases including macular degeneration. Mutations or flaws in the fibulin-5 gene appear to be involved in just 1.7% of cases of the malady, or about 150,000 people in the U.S. That suggests that, genetically speaking, macular degeneration may actually be several diseases, requiring an array of approaches to manage effectively.

Researchers said the finding, being reported today in the New England Journal of Medicine, is pointing to new promising avenues of research. "We have a toehold on Mount Everest," says Edwin Stone of the Center for Macular Degeneration at the University of Iowa and the lead author of the study.

Macular degeneration is characterized by an accumulation of yellowish material called drusen under the retina. In about 10% of cases, the condition leads to abnormal growth of blood vessels under the retina, which can cause severe vision loss. Even in milder cases, the disease can gradually rob people of their central vision. The disease affects about 35% of people over age 75; with the aging of the U.S. population, estimates are that by 2025, more than 11 million people will suffer from the condition.

"It's not an understatement to say there is an impending epidemic of blindness," says Dr. Stone, who also is a Howard Hughes Medical Institute investigator.



That expectation is adding urgency both to learn more about the disease and to develop treatments. Currently, severe cases are treated with lasers and a technique called photodynamic therapy, but they are effective only for a small portion of patients. Several companies, including Alcon Inc., a Swiss company with offices in Fort Worth, Texas, Eyetech Pharmaceuticals Inc., New York, and Genentech Inc., South San Francisco, Calif., have drugs in late stage development aimed at blocking the growth of blood vessels.

"Until just recently, we really have had no clues about the genetic basis of the disease," says Lincoln V. Johnson, associate director of the Center for the Study of Macular Degeneration at University of California at Santa Barbara.

Dr. Stone's lab began searching for AMD genes more than a decade ago, thinking they might find one that accounted for as much as 25% of the disease in the population. Their experiments kept coming up dry. In the late 1990s, they did identify a gene linked to a much rarer eye disease similar to AMD, and it turned out to be one of what are now six so-called fibulin genes. The group wondered if any other members of the fibulin family might factor in more common AMD.

In experiments that spanned four years, the lab obtained DNA from 402 patients with AMD, most of them from their treatment program at University of Iowa Carver College of Medicine, and from 429 patients without the disease who served as controls. They found that seven, or 1.7% of the patients with the disease had a mutation in the fibulin 5 gene, compared with none in the control group. Results from the other four fibulin genes turned up no clear-cut results, though there were enough mutations to lead Dr. Stone to conclude that the fibulin family may account for 7% or 8% of AMD cases.

Fibulin-5, which is present in blood vessels and other organs, contributes to the assembly of a substance called elastin, which in the eye is integral to the Bruch's membrane. The membrane helps support the structure of the eye and serves as a buffer between the retina and a group of blood vessels that supply the back of the eye.

The elastin, says Dr. Stone, "is right where the drusen form." He speculated that there is something about how material crosses the membrane between the retina and the blood vessels that causes the buildup of drusen deposits and leads to the disease.