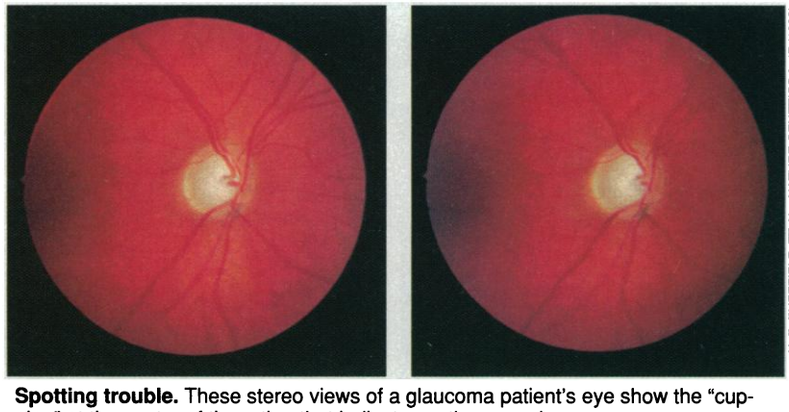
GENETICS RESEARCH

Glaucoma Gene Provides Light at the End of the Tunnel

Glaucoma is an insidious disease. Just ask Kirby Puckett, the former Minnesota Twins outfielder, who was forced to retire from baseball because the disease, which gradually and painlessly destroys peripheral vision, irreversibly damaged his right eye before it was detected. Glaucoma, which blinds almost 12,000 people in the United States each year, has been just as elusive in the laboratory. Although it's apparently caused when pressure builds up in the eye and damages the optic nerve, exactly what causes the increased pressure and how it kills nerve cells is unclear in most cases. Now, new results may lead not only to a better understanding of the biochemical causes of the disease, but to better tools for early diagnosis as well.



V. C. SHEFFIELD *ET AL.*, *NATURE GENETICS* 4, 47 (1993)

Spotting trouble. These stereo views of a glaucoma patient's eye show the "cupping" at the center of the retina that indicates optic-nerve damage.

On page 668, molecular geneticists Edwin Stone and Val Sheffield from the University of Iowa College of Medicine in Iowa City, with colleagues from six other institutions, report that they have identified the gene at fault in juvenile glaucoma, an aggressive hereditary version of the disease that strikes as early as the teenage years. "It's a very exciting find," says Ellen Liberman, a glaucoma expert at the National Eye Institute (NEI). This "is the first time anybody has ever identified something specific ... that indicates what might be going on." The discovery of the gene has researchers scrambling to understand how glaucoma could result from defects in the gene's protein product, which is called TIGR and is made by cells that help control eye pressure.

But perhaps even more important, eye experts say, identification of the gene may aid in glaucoma diagnosis, which is difficult in the early stages of the disease. Although juvenile glaucoma accounts for fewer than 1% of all cases, early indications are that mutations in the TIGR gene cause at least 3%. This means that "the gene could allow us to identify up to 100,000 people in the United States who have this disease and otherwise wouldn't know about it and would risk losing their vision," says Sheffield. These people could then be treated with drugs that, by lowering the pressure inside the eye, can prevent loss of sight if the disease is caught early enough.

To find the gene, Sheffield and his colleagues at Iowa used standard genetic linkage studies to identify DNA markers that are consistently inherited with the disease. By 1993, they had homed in on a region on chromosome 1 that carried several such markers, an indication that it also carried the glaucoma-causing gene. Researchers around the world found more linkages to the region, and a race was on to find the specific gene.

Using genetic data from more than 100 affected people in eight families, the Iowa researchers narrowed their search to a region of about 1 million base pairs. Combing the Human Genome Project's gene catalog, they found three genes within their suspect interval. Closer examination revealed that one, which encodes TIGR, contained mutations in five of the eight families initially tested, but not in any of 100 healthy controls—an indication that the gene is the one at fault.

The gene's effects may not be limited to the juvenile-onset families, however. The Iowa team found that it was also mutated in a family with 15 adult-onset glaucoma victims and in three of 100 randomly chosen adult-onset patients. In all, the researchers screened 330 unrelated glaucoma patients to come up with their estimate of a 3% frequency for TIGR mutations in all glaucoma cases.

That leaves other groups racing to find what may be a multitude of genes responsible for the glaucoma patients who do not seem to carry TIGR mutations. In fact, in the February *American Journal of Human Genetics*, geneticist Mary Wirtz of Oregon Health Sciences University and her colleagues report that they have linked a suspect region on chromosome 3 to adult-onset glaucoma.

But until other genes are found, the TIGR gene provides the only clues to the disease mechanism. For almost 10 years, Jon Polansky, a medical researcher who studies cell biology and hormone action, and molecular biologist Thai Nguyen, both at the University of California, San Francisco (UCSF), have been studying TIGR's connection to a different type of glaucoma. Doctors have known for decades that inflammation-reducing glucosteroids can cause a rise in eye pressure, especially in glaucoma patients and their relatives. Polansky and Nguyen identified the protein while studying the effects of steroids on the trabecular meshwork cells, which Polansky had induced to grow in lab cultures. In the eye, the trabecular meshwork cells help regulate eye pressure by controlling the drainage of fluid from the eye as new fluid is produced.

The cultured cells, when treated with steroids, secreted a protein which Nguyen, who had cloned the corresponding DNA, called TIGR (for trabecular meshwork inducible glucocorticoid response protein). Polansky says more recent experiments have suggested that high levels of the TIGR protein make the meshwork of cells less permeable. He suggests that an excess of TIGR may gum up the space between the meshwork cells and block the normal outflow of fluid from the eye. Whether the mutations in the TIGR gene have a similar effect or lead to glaucoma in some other way remains to be established, however. "We have a lot of work to do to figure out what this protein actually does," NEI's Liberman says.

The Iowa researchers are already on their way. To study the protein's effects in a living system, they are trying to develop genetically engineered mice that produce either the mutated form of the TIGR protein or no TIGR at all. But mouse eyes and human eyes have significant differences, and Iowa's Stone says he and his colleagues also plan "to find as many actual human beings who are running around with this mutation as possible." A larger sample will allow the researchers to get a better fix on how widespread TIGR mutations are and to uncover any correlation between the gene and specific symptoms or response to treatments.

"Until we figure out what TIGR is doing, anything is an open possibility," says Liberman. Julia Richards, a molecular geneticist at the University of Michigan, who has also been searching for the juvenile glaucoma gene, agrees. The discovery, she says, will encourage researchers who have been hunting the gene to "get on with the business of determining the underlying mechanism ... which is why we're really in the field in the first place."

–Gretchen Vogel