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Gene Defects Found in Age-Related Macular Degeneration

Howard Hughes Medical Institute (HHMI) researchers have identified subtle defects in a single gene that underlie a hereditary form of age-related macular degeneration, the leading cause of irreversible vision loss in the developed world.

Although the genetic mutations discovered by the researchers affect only about two percent of patients with the disorder, the findings offer important insights for researchers who seek to understand age-related macular degeneration (AMD).

“The clinical entity that we call AMD is actually as many as fifty diseases,” said the study’s lead author, HHMI investigator Edwin M. Stone, who is at the University of Iowa Carver College of Medicine. “They simply look so similar that clinicians call them the same thing. Because of such complexity, we don’t understand the molecular mechanisms of the disease very well, and this has limited our ability to develop preventive therapy for it.

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- Edwin M. Stone

“Looking for genetic causes of AMD is potentially very meaningful because it will help us identify the mechanisms of the disease,” he said. “Knowing the genetic bases of AMD would also enable us to create an animal model that could be used to test therapies. And, if we understood several of the mechanisms, we could potentially divide the patient population into clinically relevant subgroups, so that we could direct specific treatments to those most likely to benefit from them.”

Stone and HHMI investigator Val C. Sheffield led the research team that published its findings in the July 22, 2004, issue of the *New England Journal of Medicine (NEJM)*. Stone and Sheffield collaborated on the study with colleagues at the University of Iowa and the University of Southampton.

AMD is a worldwide problem, affecting some seven million people in the United States alone. Vision loss occurs when deposits of protein and fat accumulate beneath the center of the retina, compromising and ultimately destroying its function.

For the study published in *NEJM*, the researchers recruited 402 people with AMD and 429 healthy subjects. They obtained blood samples from the study subjects, which they used to extract DNA that was then examined for variations in genes that code for proteins called fibulins. The researchers chose the fibulin genes because previous studies by Stone, Sheffield and their colleagues identified a mutation in one of the genes, *FBLN3*, in a disease resembling AMD.

In their study, the researchers screened the genes *FBLN1*, *FBLN2*, *FBLN4*, *FBLN5*, and *FBLN6* for variations that could affect the function of the resulting fibulin proteins. To determine whether disease-causing mutations existed, they compared the patients' genes with those of control individuals who did not have AMD.

The researchers found variations in *FBLN1*, *FBLN2*, *FBLN4*, and *FBLN6* that could have contributed to AMD, but these changes were not statistically significant in terms of their comparative occurrence in AMD patients and healthy controls.

However, the researchers found that seven of the 402 AMD patients each had a different change in the *FBLN5* gene that was not found in the healthy control group. Six of these seven changes altered an amino acid in the fibulin 5 protein that has been highly conserved during evolution.

“The finding that the fibulin 5 gene is involved in AMD is a big step forward,” said Timothy Schoen, director of the medical therapy program at The Foundation Fighting Blindness. “The more we know about genes causing retinal degenerative disease, the more closely treatments can be tailored to individual patients.”

Stone believes the finding offers an important lesson about searching for genetic causes for AMD. “Fifteen years ago, we and others believed that there would be a single gene that would be responsible for a substantial percentage of AMD,” he said. “This experiment suggests that in reality a significant genetic cause of AMD may affect only two percent of the total. And so, fifteen years ago if we had done an experiment with 100 people and had seen a change in one only person, it wouldn't have fit our concept of the disease, and we would have probably ignored it completely.”

Stone emphasized that future searches for causative mutations of AMD must be painstaking in their precision and involve large numbers of patients. “It may well be that some of the variations we found in the other fibulin genes also cause AMD, but with our current analytical limitations, they are not detectable.”

The researchers' next steps will include producing cell cultures and animal models that harbor the mutations identified in the *NEJM* study. These steps will help researchers determine whether the fibulin proteins do have an altered function that would produce AMD.

The discovery of the AMD-related mutations in the fibulin genes will open the way to exploring whether other components of the cellular machinery involving fibulins might be disrupted by mutations that cause AMD, said Stone.

“The most immediate clinical implication of these findings is that if we can use fibulin gene mutations to distinguish a particular group of AMD patients, we could imagine exploring whether they do better with a certain type of treatment than other AMD patients,” he said. “Such distinctions are important, because pharmaceutical companies might already have a treatment that works for perhaps five percent of AMD patients. But if they treated a hundred patients with such a compound, they would conclude that it didn't work, because it wouldn't work for ninety-five percent of those patients.”