A TRIO OF STUDIES HAS IDENTIFIED a gene variant that may be responsible for about half of the 15 million age-related macular degeneration (AMD) cases in the United States. The finding also suggests that inflammation plays an important role in the etiology of the disease.

The three multi-institution studies were published in an advance online edition of *Science* on March 10 (http://www.sciencexpress.org). The research, which used techniques derived from the Human Genome Project, identified a common variant of the complement factor H (*CFH*) gene that explains about 50% of AMD cases.


Albert O. Edwards, MD, PhD, president of the Institute for Retina Research Laboratory at Presbyterian Hospital of Dallas, said it is remarkable to find a gene that appears to be responsible for so many cases of a complex disease. “It’s the ultimate confirmation of the ‘common disease–common gene’ hypothesis,” said Edwards, previously an assistant professor at the McDermott Center for Human Growth and Development at the University of Texas Southwestern Medical Center in Dallas.

Age-related macular degeneration, the most common cause of blindness in individuals older than 60 years, is a progressive disease that destroys the center of the retina, or macula. Environmental factors, including smoking, obesity, and fat intake, contribute to disease progression. Over time, individuals with the disease may lose their central field of vision, which makes such tasks as reading or driving difficult or impossible.

Currently, there are no treatments available to reverse the progression of the disease, but there are a few measures that can slow disease progression from the dry form to the more advanced wet form. The Age-Related Eye Disease Study, a 10-year cohort study of 3600 individuals with varying stages of AMD, published in 2001, found that individuals could reduce their risk of developing advanced (wet) AMD by about 25% by taking high levels of antioxidants and zinc (AREDS Research Group. *Arch Ophthalmol.* 2001;119:1417-1436). Treatments for advanced AMD, which include laser surgery or photodynamic therapy using a laser in combination with verteporfin, may slow further progression or stop further vision loss, according to the National Eye Institute.

ETIOLOGY CLUES

Though the disease is common, little is known about its etiology. But the new findings that individuals who possess a certain variant of *CFH* are at increased risk of developing AMD have provided scientists with an important clue. The discovery that this *CFH* gene variant is responsible for many cases of AMD suggests that inflammation plays a role in the disease, said Margaret A. Pericak-Vance, PhD, the director of the Duke Center for Human Genetics in Durham, NC.

Edwards hypothesized that the protein encoded by this variant increases AMD risk by failing to bind to receptors on the cells of the retina and the choroid, the layer of blood vessels that feeds the back of the eye, which prevents it from inhibiting the pathway. Unchecked, the pathway would cause inflammation in the retina and the surrounding blood vessels. To verify the hypothesis, scientists will have to test individuals with the *CFH* gene variant to determine if the CFH is indeed inactive.

With decades of research on the complement pathway to build on, Edwards said he hopes that further research will quickly point to potential therapies.

“It gives people hope that for a substantial proportion [of individuals with the disease], we should be able to reduce the excessive complement activation that occurs in AMD and slow down the disease progress,” he said. He noted that because AMD’s onset occurs late in life, slowing disease
progression down by 20% to 30% would be sufficient to preserve a patient’s vision for the rest of his or her life.

Pericak-Vance said the findings suggest new targets for drug development.

Additionally, detecting the gene variant might one day be used in combination with imaging technologies to identify individuals at high risk of developing advanced AMD earlier than is currently possible, Edwards said. He explained that current imaging techniques often do not allow for diagnosis until the disease has progressed for several years.

FRUIT OF THE HUMAN GENOME

In a commentary accompanying the Science articles, Stephen Daiger, PhD, director of the Laboratory for Molecular Diagnosis of Inherited Eye Diseases at the University of Texas, in Houston, said these three studies prove that the Human Genome Project has delivered tools for identifying the genes behind complex and common genetic diseases.

The three independent studies examined genetic data from distinct populations of non-Hispanic whites. One group, led by researchers from Rockefeller University, in New York City, and Yale University, in New Haven, Conn, searched more than 100,000 single-nucleotide polymorphisms (SNPs) in 96 individuals with AMD and 50 controls to find one associated with AMD. A second group, led by researchers from the University of Texas Southwestern and Boston University, tested 400 individuals with AMD and 202 controls for 86 SNPs in a region of chromosome 1 that previously had been associated with AMD. The third group, led by researchers from Vanderbilt University, in Nashville, Tenn, and Duke University, in Durham, NC, conducted further gene linkage testing in that region of chromosome 1 and also tested 61 SNPs in 495 cases and 185 controls.

The three studies pointed to the CFH gene variant. All three groups also homed in on the same gene variant, in which a tyrosine is replaced by a histidine.

“IT shows the power of the genomic approach,” Pericak-Vance said.

Edwards, who worked on early stages of the Human Genome Project, said genetic analysis that once took years can now be accomplished in months.

“The Human Genome Project in my opinion has been one of the most effective and brilliant public health efforts that have been done . . .” he said. “In terms of practical spin-offs and the efficiency of the research enterprise, it has been absolutely unbelievable.”

Diabetes Management Remains Suboptimal
Even Academic Centers Neglect Curbing Risk Factors

Mike Mitka

AS COUNTLESS STUDIES AND TREATMENT GUIDELINES ATTACH, PREVENTING HEART DISEASE, STROKE, AND OTHER COMPLICATIONS OF DIABETES REQUIRES AGGRESSIVE MANAGEMENT OF SUCH RISK FACTORS AS HYPERGLYCEMIA, HYPERTENSION, AND DYSLIPIDEMIA. DESPITE THIS, EVEN VAUNTED ACADEMIC MEDICAL CENTERS CONTINUE TO DO A POOR JOB OF ADDRESSING RISK FACTORS IN PATIENTS WITH THE DISORDER, ACCORDING TO A NEW STUDY PUBLISHED IN FEBRUARY.

Diabetes experts said this neglect of risk factors needs to be addressed. The necessity for aggressive management will only grow as diabetes prevalence is expected to increase dramatically in the upcoming decades. Today, an estimated 16 million to 18 million people (about 6% of the population) in the United States have diabetes. By 2025, an expected 22 million US residents will have the disease (King et al. Diabetes Care. 1998;21:1414-1431). Globally, the World Health Organization said at least 171 million people have diabetes, a figure expected to double by 2030.

In a retrospective cohort study of 1765 patients with type 1 or type 2 diabetes at 30 US academic medical centers, researchers from Harvard Medical School in Boston and the University of North Carolina School of Medicine in Chapel Hill found that the rate at which physicians made appropriate adjustments in medications to properly treat their patients was surprisingly low (Grant et al. Diabetes Care. 2005;28:337-442).

For example, fewer than half of patients with elevated glycated hemoglobin (HbA1c) levels had changes in hypoglycemic therapy instituted during their clinic visit, even when the HbA1c level exceeded 9.0%. Only 10.1% of 208 patients with elevated blood pressure (exceeding 130/80 mm Hg) started antihypertensive therapy; among those with blood pressures greater than 150/100 mg Hg, only 13.9% had therapy initiated. Similarly, physicians failed to initiate lipid-lowering therapy in study participants with elevated low-density lipoprotein levels. Only 24 (5.6%) of 427 patients with levels between 101 and 130 mg/dL, 16 (8.7%) of 185 of those with levels between 131 and 160 mg/dL, and 10 (15.4%) of 65 patient with levels exceeding 160 mg/dL received lipid-lowering drugs.

CLINICAL INERTIA

Although aggressively attacking risk factors with medical interventions is important in treating patients with diabetes, there is no quick fix. Overcoming “clinical inertia” to make changes in treating patients with elevated risk factors requires substantial effort, noted Richard W. Grant, MD, a coauthor of the study and an instructor in medicine at Massachusetts General Hospital, Boston.

“If you’re going to take this complex disease and meet guideline rec-