

# Risk Factors and Prevention of AMD

The extent to which a patient experiences morbidity as a result of AMD depends in part on how the tissue responds to complications.

REVIEWED BY ALBERT O. EDWARDS, MD, PHD

Geneticists think of age-related macular degeneration (AMD) as a complex trait in which multiple environmental and epidemiological risks combine to lead a disease.<sup>1</sup> “We do not yet know, however, what occurs to cause a transition from a normal fundus to one with the maculopathy that characterizes AMD,” said Albert O. Edwards, MD, PhD, during a talk at Retina 2006: Emerging New Concepts, in Las Vegas, held in conjunction with the American Academy of Ophthalmology annual meeting.

There may be initiating factors or triggers that lead to AMD, or chronically abnormal biological pathways may cause cellular responses—leading to subretinal deposits. At some point these deposits will cause retinal dysfunction, and ultimately, complications such as choroidal neovascularization, Dr. Edwards said (Figure 1). The extent to which a patient experiences morbidity as a result of AMD depends in part on how the tissue responds to complications.

“It is likely that at each step in this process there will be genetic and environmental variables which will play a role. Some of those variables may be shared across the spectrum of disease and others may be specific.”

## GENETIC APPROACH TO DISEASE

The genetic approach is a powerful method that can identify biological pathways involved in disease. Commonly, researchers take families and investigate whether chromosomal regions can be linked with segregation of the disease. The end result is the finding that a region of a chromosome segregates with disease in a group of families.

Dr. Edwards explained that researchers might then conduct a genetic association study in which they seek to find if specific DNA sequence changes—polymorphisms—present within a chromosomal region are statistically associated with disease.

“The goal of a genetic association study is to narrow down hundreds of genes and many thousands of polymorphisms to just a few genes and only hundreds of polymorphisms,” Dr. Edwards said.

Genetic association studies are actually very similar to

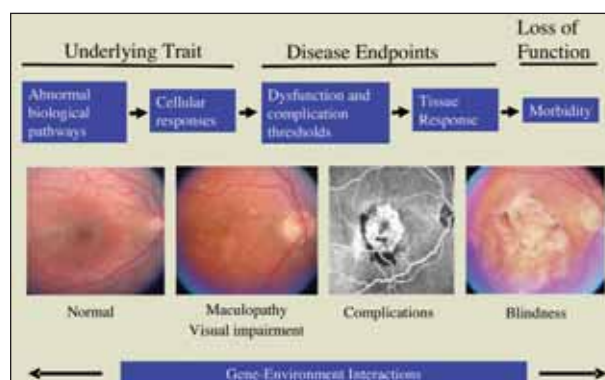


Figure 1. The progression of AMD.

case control studies. First, investigators must collect cases and controls, then test for DNA sequence changes or polymorphisms and their association with disease. For the third step, scientists take advantage of the observation that in any given short segment along a chromosome there are only a limited number of versions of that DNA segment present in the population. Investigators then ask if those haplotypes, or short segments of DNA found in the populations, are specifically associated with the disease. It might be necessary to sequence those DNA segments to determine what the exact causative mutations might be. Findings would then need to be replicated, as with any other case control study, to be sure that the results are true. Finally, functional studies are required to confirm the genetic results and to clarify how those DNA sequence changes might lead to disease.

A large number of genes have been associated with AMD, some of which have been confirmed and some of which have not. The regulation of complement activation locus, found on chromosome 1q31, is one of the two most common and important ones. According to Dr. Edwards, it stretches about 400,000 base pairs and includes the complement factor H (CFH) gene and five related genes that arose through evolutionary duplication, as well as the factor 13 B gene. The genetic risk in this region increases the chance of

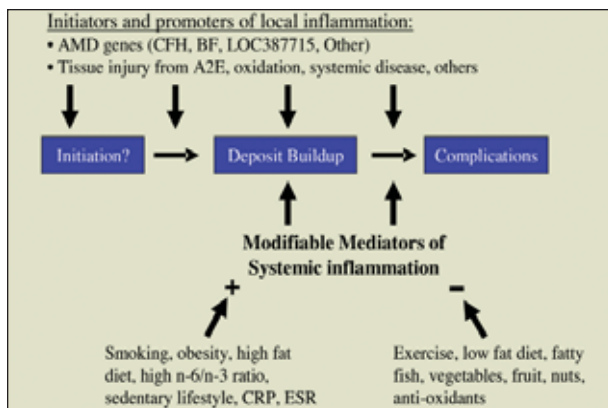


Figure 2. Unifying AMD risk: The inflammatory hypothesis.

getting AMD by about fivefold.

“One of the associated risks is likely to be a tyrosine 402 histidine change in the coding sequence of CFH, and a protective factor may be a deletion of two nearby related genes.”

The second region of importance, he said, is on chromosome 10. This region contains three genes. “As yet it has been difficult to tell which of these might cause AMD, because these genes tend to be inherited on the same haplotypes in the population. The best evidence suggests that the risk for AMD—an increase of about sevenfold—is located on a short segment of DNA. The segment is about 6,000 base pairs long and contains a hypothetical gene called LOC387715 and the promoter region of a serine protease gene called PRSS11.”

### IMPACT OF GENETIC RISK

There is confusion about how to interpret genetic studies. *P*-values are used to ask what was the chance that the observation occurred randomly. “We know that the *P*-values for complement factor H and the chromosome 10 locus are very low, demonstrating that they are not chance findings,” he said.

The use of an odds ratio gives an idea of how important that genetic alteration is for a person who has it. “The odds ratios are for CFH and 10q26 are very high for a complex trait and in the five- to sevenfold range.”

Another way to calculate the impact of genetic risk is by using attributable fraction to determine how important the genetic variation is at the population level. “For example, the CFH and 10q26 changes are common and have relatively high odds ratios; therefore they have attributable fractions of 50% and 36% respectively. By comparison, smoking has an attributable fraction for AMD of 20%. It is important to remember that attributable fractions cannot be added together and it is reasonable for them to exceed 100% when studied separately.”

Combined risk is more difficult to estimate, Dr. Edwards said. To date, researchers believe that the genetic risks that have been identified act independently of each other.

Therefore, their odds ratios can be multiplied and give very high relative risks in patients, as much as 40-fold or higher.

It is well established that gene and environmental interactions are important. While genetic risk may explain the majority of risk for AMD, possibly as much as 75%, environment and modifiable exposure, such as smoking and lifestyle, likely interact with these genetic variables. “For example, in the Rotterdam study, complement factor H and smoking combined together to increase the risk for late AMD by 34-fold,” he said. The inflammatory markers C reactive protein and erythrocyte sedimentation rate plus CFH carried a 20- to 28-fold risk. In another study, obesity plus CFH had an 11-fold increased risk for new incident AMD.<sup>2,3</sup>

Researchers are not clear on how to combine these genetic and environmental exposures into a unifying hypothesis. Currently, however, a favorite model is the inflammatory hypothesis, Dr. Edwards said (Figure 2). “In this hypothesis, promoters and initiators of local inflammation such as AMD genes and tissue injury from A2E, oxidation, and other causes lead to the initiation of subretinal deposits and then complications develop. On the other hand, modifiable mediators<sup>4,5</sup> such as smoking, obesity, and a high-fat diet, alter the risk of developing AMD and complications.”

Exercise, a low-fat diet and other heart-healthy behaviors are protective against AMD in observational studies, but have not been tested in a prospective clinical trial.

Genes play an important role in AMD. This has been clearly demonstrated, and researchers will find additional genetic variants in the upcoming years, Dr. Edwards said.

Gene-environment interactions are probably important, and ophthalmologists should counsel patients to make lifestyle choices that reduce their risk of developing AMD. “It is important to remember, however, that prospective treatment studies proving that modification of behavior or serum markers of inflammation are lacking.”

There is a great deal of interest regarding genetic testing. “Although we could easily perform these genetic tests on patients, at present, our knowledge of the genetic risk will not alter the advice that we give our patients, their family members, or the public,” he said. ■

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