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THE Current

April 30, 2005
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Blinding Disease and Rare Kidney Disease Have Genetic Link, Reports International Group of Scientists

Alterations in a gene involved in the body's immune system dramatically increase the likelihood of developing a blinding disease late in life, according to new findings by an international team of scientists. Similar alterations in the same gene were found to be associated with a rare and often fatal kidney disease.

The findings, which represent the culmination of studies conducted over several years, will be published the week of May 2, in the online edition of the Proceedings of the National Academy of Sciences. Two co-authors are from the University of California, Santa Barbara.

The blinding disease, age-related macular degeneration (AMD), is characterized by a progressive loss of central vision due to degeneration of the macula, a region of the retina in the back of the eye that measures a quarter of an inch across. It has been known for many years that the earliest signs of degeneration appear at the boundary between the macula and a layer of connective tissue called the choroid.

AMD is the leading cause of irreversible blindness in individuals over the age of 60. At least 50 million people worldwide are at risk for the severe vision loss. No cure currently exists, and the therapeutics currently available treat only the vascular complications in the eye that occur in 10-15 percent of AMD patients.

The researchers believe that the new genetic findings will lead to the development of diagnostic and therapeutic treatments which will benefit a much larger proportion of the early AMD patient population.

Don Anderson, director of the Center for the Study of Macular Degeneration in the Neuroscience Research Institute at UCSB, and Lincoln Johnson, associate director of the center, co-authored the publication. Anderson and Johnson worked closely with lead author Gregory Hageman and his colleagues in the Department of Ophthalmology and Visual Sciences at the

University of Iowa Carver College of Medicine, and geneticist Rando Allikmets at Columbia University in New York. Other collaborating scientists included Richard Smith and Giuliana Silvestri of Queens University, Belfast, Northern Ireland, and Michael Dean of the National Cancer Institute at the National Institutes of Health (NIH).

Together the scientists discovered that a pattern of inherited variants in Factor H---a gene that regulates the body's immune defense against infection by bacteria, viruses, and other microbes---dramatically increases one's susceptibility to AMD late in life.

The "complement system" is a key concept in this study.

The complement system is poised to recognize, attack, and kill invading microorganisms by creating a hole in their cell walls. In some cases, however, the immune system mistakes its own cells for foreign cells. When that happens, tissue damage and local inflammation can occur. To prevent such damage, a number of proteins, including Factor H, have evolved to keep the system under tight control.

In studies dating to 1999, Hageman and Robert Mullins at the University of Iowa, and Anderson and Johnson at UCSB, implicated the complement cascade in the formation of drusen---the hallmark ocular deposits that usually accompany AMD. Based upon those studies, the scientists hypothesized that chronic local inflammation and activation of the immune system are responsible for drusen formation, and lead eventually to the ocular symptoms recognized clinically as AMD.

"When we began to look at the molecular composition of drusen a few years ago, it became evident that many of the proteins were either part of the complement system or, like Factor H, were involved in regulating it," said Anderson. "That led us

to the nearly inescapable conclusion that AMD, like many other age-related diseases such as Alzheimer's disease and atherosclerosis, had an inflammatory component.

Now that the genetic evidence for Factor H involvement is in, it looks like the inflammation model of AMD is correct. Molecules involved in complement activation and its regulation will now move to the forefront as prime targets for the development of early diagnostic tests and therapeutic treatments for AMD.

Individuals who are most susceptible to AMD, and to the rare fatal kidney disease called membranoproliferative glomerulonephritis type II (MPGN II), most likely have a functional defect in the Factor H protein. This causes over-activation of the complement system or interferes with its ability to recognize bacteria or other pathogens. When combined with triggering events such as infection, the result is local tissue damage, particularly at vulnerable locations in the kidney and in the macula, which have similarities in both structure and function.

The first hint of a possible link between AMD and MPGN II came when it was discovered earlier that individuals with MPGN II also develop ocular drusen, but at a much earlier age. "Our study approach was unique in having a connection to a rare kidney disease that, while very different from AMD in many ways, has eye symptoms that are nearly indistinguishable from AMD," said Hageman. "The genetic key was that people with MPGN II and people with AMD had both already been linked to a region on chromosome 1. We decided to look at that region in both groups."

In addition to AMD and MPGN II, local inflammation and activation of the immune system are recognized contributors to a number of other age-related diseases, such as Alzheimer's disease and atherosclerosis, both of which are also characterized by the progressive buildup of plaques and deposits that contain complement components.

"In the near term, a key issue will be to determine the extent to which those individuals with the same inherited pattern of Factor H variants are susceptible to other chronic, immune-mediated diseases," said Anderson.

The study was supported in part by grants from the National Eye Institute/NIH, Research to Prevent Blindness, Inc., Pfizer, Inc., the American Macular Degeneration Foundation, the Milton and Ruth Steinbach Fund, the International Retina Research Foundation, the Eye Research Institute, and unrestricted gifts to the Center for the Study of Macular Degeneration at UCSB.

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