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Additional genes associated with age-related macular degeneration identified

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A large genetic study of age-related macular degeneration (AMD) has identified three new genes associated with this blinding eye disease—two involved in the cholesterol pathway. Results of this large-scale collaborative study, supported by the National Eye Institute (NEI), part of the National Institutes of Health, were published online April 12 in the *Proceedings of the National Academy of Sciences*.

"Genome-wide association studies require large numbers of patients to discover significant genetic associations. The success of this effort was made possible by a community-wide scientific collaboration of sharing DNA samples and analyzing the genomes of more than 18,000 people," said Paul A. Sieving, M.D., Ph.D., NEI director. "This study increases our understanding of DNA variations that predict individual risks of AMD and provides clues for developing effective therapies."

AMD is a leading cause of visual impairment and blindness in older Americans. Researchers have previously discovered genes that account for a significant portion of AMD risk through genome-wide association studies (GWAS), which scan the entire DNA of individuals to uncover genetic variations related to certain diseases.

The recent large GWAS was led by Anand Swaroop, Ph.D., currently chief of the NEI Neurobiology-Neurodegeneration and Repair Laboratory, and Goncalo Abecasis, D.Phil., professor of biostatistics at the University of Michigan, Ann Arbor.

The strongest AMD genetic association found in the study was in a region on chromosome 22, near a gene called metalloproteinase inhibitor 3 (TIMP3). Mutations in the TIMP3 gene were previously found to cause Sorsby's fundus dystrophy, a rare inherited early-onset form of macular degeneration. Although further research is needed, it is likely that the genetic region pinpointed influences the expression of TIMP3.

The study has also shed light on a new biological pathway for AMD disease development, by uncovering two genes associated with AMD risk in the high-density lipoprotein (HDL) cholesterol pathway: human hepatic lipase (LIPC) and cholesterol ester transfer protein (CETP). Scientists identified two additional genes, lipoprotein lipase (LPL) and ATP binding cassette transporter 1 (ABCA1), that may be involved in the cholesterol pathway as well, but more research is needed to confirm these findings.

HDLs are among a family of lipoproteins that transport essential fats, such as cholesterol, through the bloodstream. It is believed that early stages of AMD are affected by accumulation of oxidation products of cholesterol and other lipids in the retinal pigment epithelium, a layer of cells in the back of the eye. However, the relationship between HDL cholesterol levels in the blood and AMD is still unclear.

"We suspect that these genetic variations found in the cholesterol pathway impact the retina differently from the circulatory system, so cholesterol levels in the blood may not provide meaningful information about AMD risk," Swaroop explained. "Nonetheless, we have uncovered a major biochemical pathway that may be a target for future AMD treatments."

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