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Seven genetic risk factors found to be associated with age-related macular degeneration

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An international group of researchers has discovered seven new regions of the human genome—called loci—that are associated with increased risk of age-related macular degeneration (AMD), a leading cause of blindness. The AMD Gene Consortium, a network of international investigators representing 18 research groups, also confirmed 12 loci identified in previous studies. The findings are reported online today in the journal *Nature Genetics*. Supported by the National Eye Institute (NEI), a part of the National Institutes of Health, the study represents the most comprehensive genome-wide analysis of genetic variations associated with AMD.

"This compelling analysis by the AMD Gene Consortium demonstrates the enormous value of effective collaboration," said NEI Director Paul A. Sieving, M.D., Ph.D. "Combining data from multiple studies, this international effort provides insight into the molecular basis of AMD, which will help researchers search for causes of the disease and will inform future development of new diagnostic and treatment strategies."

AMD affects the macula, a region of the retina responsible for central vision. The retina is the layer of light-sensitive tissue in the back of the eye that houses rod and cone photoreceptor cells. Compared with the rest of the retina, the macula is especially dense with cone photoreceptors and is what humans rely on for tasks that require sharp vision, such as reading, driving, and recognizing faces. As AMD

progresses, such tasks become more difficult and eventually impossible. Some kinds of AMD are treatable if detected early, but no cure exists. An estimated 2 million Americans have AMD.

Scientists have shown that age, diet, and smoking influence a person's risk of developing AMD. Genetics also plays a strong role. AMD often runs in families and is more common among certain ethnicities, such as Asians and people of European descent.

Since the 2005 discovery that certain variations in the gene for complement factor H—a component of the immune system—are associated with major risk for AMD, research groups around the world have conducted genome-wide association studies to identify other loci that affect AMD risk. These studies were made possible by tools developed through the Human Genome Project, which mapped human genes, and related projects, such the International HapMap Project, which identified common patterns of genetic variation within the human genome.

The AMD Gene Consortium combined data from 18 research groups to increase the power of prior analyses. The current analysis identified seven new loci near genes. As with the previously discovered 12 loci, these seven loci are scattered throughout the genome on many different chromosomes.

"A large number of samples was needed to detect additional genetic variants that have small but significant influences on a person's disease risk," said Hemin Chin, Ph.D., NEI associate director for ophthalmic genetics, who assembled the consortium and helped coordinate the study. "By cataloging genetic variations associated with AMD, scientists are better equipped to target corresponding biological pathways and study how they might interact and change with age or other factors, such as smoking."

The consortium's analysis included data from more than 17,100 people with the most advanced and severe forms of AMD, which were compared to data from more than 60,000 people without AMD. The 19 loci that were found to be associated with AMD implicate a variety of biological functions, including regulation of the immune system, maintenance of cellular structure, growth and permeability of blood vessels, lipid metabolism, and atherosclerosis.

"Like a map that identifies neighborhoods where the electricity has been knocked out by a storm, the AMD Gene Consortium's study effectively tagged regions within the genome where researchers are most likely to find short circuits in DNA that cause AMD," said Anand Swaroop, Ph.D., chief of the NEI Laboratory of Neurobiology and Neurodegeneration and Repair, and one of the group leaders of this consortium effort. "Once you are in the right neighborhood, going block to block or house to house to look for downed power lines goes much faster. Likewise, by limiting their search to the 19 genomic regions identified by the AMD Gene Consortium, scientists can more efficiently search for specific genes and causative changes that play a role in AMD."

As with other common diseases, such as type 2 diabetes, an individual person's risk for getting AMD is likely determined not by one but many genes. Further comprehensive DNA analysis of the areas around the 19 loci identified by the AMD Gene Consortium could turn up undiscovered rare genetic variants with a disproportionately large effect on AMD risk. Discovery of such genes could greatly advance scientists' understanding of AMD pathogenesis and their quest for more effective treatments.

More information: dx.doi.org/10.1038/ng.2578

For more information about AMD, visit

www.nei.nih.gov/health/maculardegen/index.asp

Provided by National Eye Institute