

# Two more genetic risk factors for Alzheimer's disease found

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An international team of scientists has identified two more genetic risk factors for Alzheimer's disease. The findings are reported in the online edition of the journal *Nature Genetics*.

The group, led by investigators from the School of Medicine at Cardiff in the United Kingdom and including scientists from Washington University School of Medicine in St. Louis, completed the largest genome-wide association study ever involving patients with [Alzheimer's disease](#). The study pooled DNA samples from more than 19,000 older European and U.S. residents. Seven thousand had Alzheimer's disease, and the others had no clinical symptoms of the disorder.

Prior to this study, only four genes had been definitively associated with Alzheimer's disease. Three [genetic mutations](#) have been identified as causes of rare, inherited forms of early-onset Alzheimer's. The fourth gene, APOE4, is the only one previously linked to the more common late-onset form of the disease.

By looking at more than 600,000 common DNA markers, researchers on the current study were able to identify two new genes that appeared to be involved in elevated risk for Alzheimer's and confirmed the importance of APOE4.

"There's good evidence that these new genes may be novel risk factors, the first discovered since APOE in 1993," says Washington University researcher and co-author Alison M. Goate, D.Phil. "So it's a very

important observation because this study is the first to provide such significant evidence of novel genetic risk factors for the most common form of Alzheimer's disease."

Goate, who in 1991 led a team in England that identified the first early-onset Alzheimer's mutation in the APP gene on [chromosome 21](#), is now the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry and professor of [neurology](#) at Washington University. She says the new genes identified in this study are APOJ, also called clustrin on [chromosome 8](#), and PICALM on chromosome 11.

"The power of the new Genome Wide Association Study methods is that with large datasets we can now identify genes that earlier techniques were unable to confirm," says co-author John C. Morris, M.D., of Washington University. "These new genes associated with Alzheimer's disease provide new clues about how the illness develops."

Morris, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology, is the director of Washington University's Alzheimer's Disease Research Center (ADRC). He says previous ADRC research suggests that in mice, the clustrin gene may be involved in the formation of amyloid deposits in the brain. Amyloid makes up the senile plaques that dot the brains of people with Alzheimer's.

"These genes are both significant, but their effect appears to be much smaller than that of the APOE gene," Goate says. "Using statistical methods, we've been able to estimate the amount of risk attributable to APOE at about 19 or 20 percent. The newly identified genes each come in under 10 percent, so it appears they have a much smaller effect."

But not an insignificant one, Goate says, noting that although it isn't yet clear how these new genes influence Alzheimer's disease risk, levels of clustrin tend to rise when brain tissue is injured or becomes inflamed,

and some researchers have noted increased clustrin levels in the brain and cerebrospinal fluid of Alzheimer's patients.

The other gene, PICALM, appears to be involved in the breakdown of synapses, structures that allow neurons in the brain to communicate. Some scientists also hypothesize that the gene may be involved in the development of amyloid deposits, but Goate says much more work is required to identify exactly how PICALM elevates Alzheimer's risk.

She expects many more genes also are involved in Alzheimer's risk. In fact, this study identified 13 more gene variants worthy of further investigation.

More information: Harold D, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nature Genetics*, advance online publication. Sept. 6, 2009

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