

Scientists Find New Genetic Clue to Cause of Alzheimer's Disease

Variations in a gene known as SORL1 may be a factor in the development of late onset Alzheimer's disease, an international team of researchers has discovered. The genetic clue, which could lead to a better understanding of one cause of Alzheimer's, is reported in *Nature Genetics* online, Jan. 14, 2007, and was supported in part by the National Institutes of Health (NIH).

The researchers suggest that faulty versions of the SORL1 gene contribute to formation of amyloid plaques, a hallmark sign of Alzheimer's in the brains of people with the disease. They identified 29 variants that mark relatively short segments of DNA where disease-causing changes could lie. The study did not, however, identify specific genetic changes that result in Alzheimer's.

Richard Mayeux, M.D., of Columbia University, Lindsay Farrer, Ph.D., of Boston University, and Peter St. George-Hyslop, M.D., of the University of Toronto, led the study, which involved 14 collaborating institutions in North America, Europe and Asia, and 6,000 individuals who donated blood for genetic typing. The work was funded by NIH's National Institute on Aging (NIA) and National Human Genome Research Institute (NHGRI), as well as by 18 other international public and private organizations.

"We do not fully understand what causes Alzheimer's disease, but we know that genetic factors can play a role," says NIA director Richard J. Hodes, M.D. "Scientists have previously identified three genes, variants of which can cause early onset Alzheimer's, and one that increases risk for the late onset form. This discovery provides a completely new genetic clue about the late onset forms of this very complex disease. We are eager to investigate the role of this gene further."

Scientists think that in Alzheimer's disease, amyloid precursor protein, or APP, is processed into amyloid beta protein fragments that make up plaques in the brain. The researchers began their search for genetic influences amid a group of proteins that transport APP within cells, looking for small changes, or "misspellings," in seven genes involved in moving APP within cells.

To start, the scientists combed two large data sets of genetic information from families in which more than one person has Alzheimer's disease. They were soon able to see that many of the families with Alzheimer's had variations in the SORL1 gene but not consistently in any of the other six genes.

They then expanded their search to genetic data sets from families of Northern European, Caribbean Hispanic, Caucasian, African American, and Israeli Arab heritage for changes in the SORL1 gene. Again, they found the same association between SORL1 variations and Alzheimer's disease. Searching additional data sets provided by Steven Younkin, M.D., Ph.D., of the Mayo Clinic further confirmed the association of SORL1 variations and Alzheimer's.

"We are seeing the gene implicated in multiple data sets, across ethnic and racial groups,"

says Farrer. He adds that the group was "encouraged and excited" by cell biology experiments that demonstrate SORL1's role in production of beta amyloid fragments.

Examining blood cells from people with and without Alzheimer's, the researchers found less than half the level of SORL1 protein in people with Alzheimer's compared to people without the disease. In laboratory experiments, they found that altering the levels of SORL1 changed the way APP was moved around in cells, with low levels of SORL1 resulting in increased production of amyloid beta fragments while high levels decreased production. However, the researchers note, other genetic and non-genetic factors are likely to affect SORL1 production in people, and more research is needed to determine how different versions of the SORL1 gene influence production of the harmful protein fragments.

NIA and NHGRI support a number of studies looking at genetic factors that may be involved in Alzheimer's disease. For information on the NIA Alzheimer's Disease Genetics Study, which is currently recruiting volunteers from families with two or more siblings affected by late onset Alzheimer's disease, visit the study web site, www.ncrad.org <http://www.ncrad.org/>, call 1-800-526-2839, or email alzstudy@iupui.edu.

NIA leads the federal effort supporting and conducting research on aging and the medical, social and behavioral issues of older people, including Alzheimer's disease and age-related cognitive decline. For information on dementia and aging, please visit the NIA's Alzheimer's Disease Education and Referral Center at www.nia.nih.gov/alzheimers <http://www.nia.nih.gov/alzheimers>, or call 1-800-438-4380. For more general information on research and aging, go to www.nia.nih.gov <http://www.nia.nih.gov>.

NHGRI's Division of Extramural Research supports grants for a wide range of genetic and genomic research, as well as for training and career development, at sites across the nation. For more information about genomic research or NHGRI, go to www.genome.gov <http://www.genome.gov/>.

NIH--the nation's medical research agency--includes 27 institutes and centers and is a component of the U.S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical and translational medical research, and it investigates the causes, treatments and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov <http://www.nih.gov/>.

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References: E Rogaeva *et al.* The neuronal sortilin receptor SORL1 is genetically associated with Alzheimer's Disease http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&opt=AbstractPlus&list_uids=17220890 . *Nature Genetics* (2006). DOI: 10.1038/ng1943