Alzheimer's gene identified: study

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An international effort led by scientists at the University of Toronto, Columbia University and Boston University has isolated another gene responsible for Alzheimer's disease.

The discovery, outlined in the Jan. 14 advance on-line edition of *Nature Genetics* (February print edition), shows how a team of researchers analyzed the faulty processing of the amyloid precursor protein (APP) – long associated with Alzheimer's disease – and linked it to a new gene (SORL1). The five-year study included multiple centres such as Columbia University, Boston University and the Mayo Clinic and tested over 6,000 DNA samples from Caucasians, Hispanics, Israeli-Arabs and African Americans and uncovered two consistent patterns that linked the SORL1 gene to people afflicted with Alzheimer's.

"Instead of scanning all the genes in the entire genome, we had an idea of what an Alzheimer's disease-causing gene would look like based on past discoveries," says senior author University Professor Peter St. George-Hyslop, director of the Centre for Research in Neurodegenerative Diseases (CRND) at the University of Toronto. "We knew that the abnormalities in APP processing and the accumulation of its toxic amyloid beta (A□) peptide derivative cause Alzheimer's, so we hypothesized that other genes associated with APP regulation might also cause the disease."

SORL1 governs the distribution of APP inside nerve cells of the brain. When working properly, the SORL1 protein regulates APP by diverting it into specific certain regions of the cell. When the level of the SORL1

gene is reduced, APP accumulates in a different region of the cell, where it is degraded into Abeta fragments – abnormal protein fragments – which then cause Alzheimer's disease.

"We discovered two different variants in the SORL1 gene that are associated with increased risk of AD in different ethnic groups, says Dr. Ekaterina Rogaeva, first author of the study and also part of CRND. "This emphasizes the complexity of the genetics of common late-onset form of Alzheimer's disease, and has important implications for replication studies that would need to assess SORL1 variations in datasets with similar genetic background."

Because these genetic association studies are very complex, the next step must be to get the result replicated by other groups. "Despite the breadth of the study, it's important to have independent replication, which is the only way to be certain that the results are generalizable," says Professor Richard Mayeux, co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University. "SORL1 represents another critical piece of the Alzheimer's disease-amyloid puzzle, but the work of identifying the actual disease- causing mutations in SORL1, and understanding exactly how they reduce SORL1 function remain ahead of us."

Professor Lindsay Farrer, chief of the Genetics Program at Boston University, also cautions that more studies are needed. He says that while they have identified several variants in SORL1 that show the same pattern of association across multiple ethnic groups with very different genetic makeup and lifestyle characteristics, it is unclear whether these variants influence the disease process directly or merely mark the location in the SORL1 gene of the biologically important variants which have not yet been tested. "SORL1 is a big gene containing at least 500 known variants called single nucleotide polymorphisms (SNPs)," Farrer says. "We examined a representative sample of about 30 SNPs across

SORL1 and, unfortunately, have not yet found a 'smoking SNP' for Alzheimer's disease."

This isn't the first Alzheimer's gene to be identified by U of T's Centre for Research in Neurogenerative Diseases. In 1995 they identified two defective genes that cause aggressive early-onset forms of Alzheimer's (Presenilin 1 and Presenilin 2) and in 1990 they were the first to show Alzheimer's is a complex disorder with many causes, some of which are genetic.

"The recurring theme that genetic causes of Alzheimer's all seem to impact the accumulation of amyloid β-peptide in the brain, and that potential therapies which block Aß production or toxicity seem to block the disease in animal models, suggests that we're on the right track," says Professor Steven Younkin, chair of Department of Pharmacology at the Mayo Clinic College of Medicine.

Source: University of Toronto