

JANUARY 14, 2007

Scientists Discover a New Risk Factor for Alzheimer's

Researchers led by Howard Hughes Medical Institute (HHMI) international research scholar Peter St George-Hyslop have identified a new genetic risk factor associated with the most common form of Alzheimer's disease. The research implicates a gene called *SORL1* in late-onset Alzheimer's, which usually strikes after age 65.

In an advance online publication in *Nature Genetics* on January 14, 2007, St George-Hyslop and colleagues connected the gene to the disease in six different groups of people, although they did not pinpoint the exact genetic mutations in *SORL1* responsible for Alzheimer's. In their studies, the researchers used databases that include genetic information about people with and without Alzheimer's disease. More than 6,800 individuals—45.8 percent of them affected with the disease—were included in the analysis, which is considered a large data set in the field, said St George-Hyslop.

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"We looked for variations of *SORL1* in nine different groups of people and found those variations to be associated with an increased risk of Alzheimer's in six of them," St George-Hyslop said. "That implies that *SORL1* is not the only cause of Alzheimer's, but it's one of several. Some people with the disease will have a *SORL1*-related cause, and some won't." St George-Hyslop is a professor in the department of medicine and director of the Center for Research in Neurodegenerative Disease at the University of Toronto and an HHMI international research scholar. Through its international research scholars program, HHMI supports leading scientists in 28 countries outside the United States. The researchers studied several groups of Caucasians, one group of African Americans, one group of Hispanics from the Dominican Republic, and a group of Israeli Arabs. They tracked the *SORL1* genes via

single nucleotide polymorphisms, or SNPs, which are single-letter changes in a gene's sequence. They found that the Caucasians with Alzheimer's displayed a certain SNP signature at one end of the gene, while the African Americans, Hispanics, and Israeli Arabs with the disease displayed another SNP signature. "This implies that there are at least two, and possibly more, gene variants at work here," said St George-Hyslop. "That's not unusual—in many diseases you see multiple variations that all impact a specific gene."

The team used the SNP databases to track the *SORL1* gene in the populations studied, but did not actually pinpoint the precise changes in the gene that contribute to disease. "Now we need to go back and look in the regions around the clusters of SNPs that we tracked and see if we can find additional genetic changes that are either unique or enriched in the individuals with Alzheimer's," said St George-Hyslop. "Then we'll have the actual genetic variations that lead to the disease."

After linking *SORL1* to late-onset Alzheimer's, the team investigated the gene's function. Using cell culture studies, they discovered that decreasing the amount of *SORL1* increased cells' production of amyloid-beta, a toxic fragment of another protein that destroys neurons. Production of amyloid-beta is the key event in the progression of Alzheimer's disease.

Amyloid-beta is made when cells improperly break down a protein called amyloid precursor protein (APP). Previous research had revealed that APP is subjected to a sequence of cellular events that either properly recycles APP or shunts it into cellular structures called endosomes, where it is chopped into amyloid-beta. Researchers had identified several genes involved in this cellular sorting process. St George Hyslop and his team reasoned that inherited defects in some of these proteins might cause more APP to be shunted into endosomes, causing more amyloid-beta to be made, thereby increasing risk for Alzheimer's. When the team investigated these genes, only *SORL1* was associated with an increased risk of Alzheimer's.

"What we have now are three independent sets of observations, all implicating the *SORL1* gene in Alzheimer's disease," said St George-Hyslop. "We started with an observation from pathologists, showing reduced *SORL1* protein levels in the brains of patients with Alzheimer's. Then we have the observation by us and other groups that if you reduce *SORL1* expression—in either cell cultures or mice—you get an increase in the production of amyloid-beta. Now we can add our new observation that variants of the *SORL1* gene are associated with an increased risk of Alzheimer's."

St George Hyslop said that other researchers need to replicate the results in other groups. “Even though we've seen it in six different groups of people, seeing it in eight, nine, or ten is even better,” he explained. Three of the nine data sets that St George-Hyslop's team studied did not reveal a significant association between *SORLI* and Alzheimer's. Non-*SORLI* causes might have been overrepresented and *SORLI*-associated causes underrepresented in these data sets, St George-Hyslop explained. Alternatively, these data sets may have contained several different Alzheimer's variants of *SORLI*, but each variant might have been associated with a different SNP pattern. That complexity would have obscured the SNP marker patterns that the researchers were tracking.

The importance of this work is that it identifies a new player among the mechanisms causing Alzheimer's disease, St George-Hyslop said. “This will lead to the real endgame, which is to see how to exploit the findings as a new diagnostic or therapeutic target.”