Genetic Variant Tied to Amyloid-β in Alzheimer's

BY JEFF EVANS
Senior Writer

Genetic variants of a protein involved in determining the fate of amyloid precursor protein are associated with an increased risk of developing Alzheimer's disease, reported Dr. Ekaterina Rogaeva of the University of Toronto and her associates.

The increased risk for the disease appears to be caused by certain haplotypes of the SORL1 gene that decrease the expression of the gene. As a result, more amyloid precursor protein follows a pathway in which excess amyloid-β peptide is produced in the brain—one of the central events in the pathogenesis of Alzheimer's disease (AD), according to the investigators.

Dr. Samuel E. Gandy, director of the Farber Institute for Neurosciences at Thomas Jefferson University, Philadelphia, said the study's results "fit well into the amyloid model for Alzheimer's, and that's certainly the one that's getting the most attention and most assessment clinically."

'Genetic and possibly environmentally specified changes in SORL1 [protein] expression or function are causally linked to the pathogenesis [of AD].'

Dr. Rogaeva and her colleagues found that several overlapping haplotypes in two different regions of the SORL1 gene increased the likelihood of developing late-onset familial Alzheimer's disease (FAD), based on results obtained from two cohorts of families with late-onset FAD and later replicated in a cohort of cases and controls in other studies.

"Taken together, our results suggest that genetic and possibly environmentally specified changes in SORL1 [protein] expression or function are causally linked to the pathogenesis [of Alzheimer's disease] and have a modest effect on risk for this disease," the researchers reported (Nat. Genet. 2007 Jan. 14 [Epub doi:10.1038/ng1943]).

The initial "discovery cohort" comprised 124 northern European FAD families and 228 Caribbean Hispanic FAD families.

The "replication cohort" consisted of northern European individuals from a case-control study (178 cases with sporadic AD and 242 controls with self-identified white European ancestry), 276 white sibships from the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, 238 African-American sibships from the MIRAGE study, and Israeli-Arab individuals (111 with AD and 114 normal controls from the Wadi Ara population study).

The researchers confirmed the association between AD and the SORL1 gene by genotyping the single-nucleotide polymorphisms that were contained in the haplotypes and then analyzing them at an independent facility in three series of cases and controls of European ancestry from different Mayo Clinic centers (totaling 1,405 late-onset AD cases and 2,124 controls).

In genetic studies, particularly those involving Alzheimer's disease, there has "been an issue of one group making a report and then a number of other groups being unable to replicate [the results] across different ethnic groups," Dr. Gandy said in an interview. "The good thing about this paper is that they've already tested several totally independent ethnic groups, so you can feel a bit more confident that this is true."

SORL1 protein directly binds amyloid precursor protein and differentially regulates whether it sorts into a recycling pathway or into a pathway that generates amyloid-β.

Experiments that suppressed SORL1 protein expression—mimicking what is speculated to be the effects of AD-associated variants in the SORL1 gene—led to an overproduction of amyloid-β.

The actual disease-causing variants of the SORL1 gene are unlikely to be the single-nucleotide polymorphisms and haplotypes that were identified in the SORL1 gene's exons, the researchers noted. Instead, the pathogenic variants are likely located in sequences in the introns of the SORL1 gene and may "modulate the cell type-specific transcription or translation of the SORL1 gene in carriers of the Alzheimer's disease–associated haplotypes," the investigators said. "This hypothesis would be supported by the recent observation of reduced expression of SORL1 protein in neurons but not glia of some individuals with sporadic Alzheimer's disease."

One of the disease-associated haplotypes of the SORL1 gene was expressed in AD haplotype carriers at less than half the levels of carriers of nondisease haplotypes. But univariate regression analyses showed that the disease variants of the SORL1 gene accounted for about only 14% of the variance in SORL1 protein expression that was seen in those individuals.

"This latter result implies that other genetic and nongenetic factors can also modulate SORL1 [protein] expression and, perhaps, therefore, risk for Alzheimer's disease," the researchers said.

Although variants of the SORL1 gene may not raise the risk of AD as much as the apolipoprotein E ε4 allele, Dr. Gandy noted that the results point out a new target for drug therapy that can raise SORL1 protein levels.

"We never know when we're going to encounter side effects, so it's good to have multiple possible targets," he said. ■

Simvastatin Found to Reduce Alzheimer's, Parkinson's Risk

BY AMY ROTHMAN SCHONFELD
Contributing Writer

ATLANTA — Simvastatin use for at least 7 months reduced the incidence of Alzheimer's disease by 30% and Parkinson's disease by 24% in older people, according to an analysis of a Department of Veterans Affairs pharmaceutical database.

Neither lovastatin nor atorvastatin provided similar benefits.

The protective effects of simvastatin were more prominent in people who do not have hypertension. In this subgroup, the incidence of Alzheimer's disease was reduced by 76% and the incidence of Parkinson's disease was reduced by 65%, the study's lead investigator Dr. Benjamin Wolozin reported at the annual meeting of the Society for Neuroscience.

Dr. Wolozin, a professor of pharmacology at Boston University, analyzed data from a large VA pharmaceutical database that included 4.5 million patients and more than 110 million annual medication prescriptions. Individuals were excluded if they were less than 65 years of age or had a pre-existing diagnosis of senile dementia of the Alzheimer's type.

The incidence of Alzheimer's disease among patients taking statins was compared with the incidence among patients who were not taking statins. After adjusting for age, cardiovascular disease, hypertension, and diabetes, only simvastatin use significantly lowered the incidence of Alzheimer's disease (hazard ratio 0.694).

Two different mechanisms might explain the unique effects of simvastatin compared with those of the other two statins analyzed, Dr. Wolozin said. For atorvastatin, the inability to cross the blood-brain barrier may explain its ineffectiveness. Lovastatin and simvastatin both reduce inflammation, he explained. Only simvastatin, however, inhibits cholesterol strongly enough to reduce inflammation sufficiently to protect against Alzheimer's or Parkinson's disease.

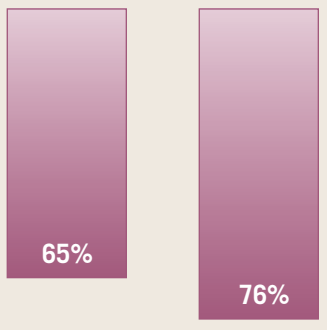
Only simvastatin inhibits cholesterol enough to reduce inflammation to protect against AD and Parkinson's.

DR. WOLOZIN

Studies have shown that a biosynthetic precursor of cholesterol is required to signal inflammation. Why simvastatin is unable to reduce inflammation associated with hypertension is unclear.

Dr. Wolozin is currently analyzing the effects of several medications used chronically by older patients to investigate their impact on the incidence and progression of Alzheimer's disease. "In addition to finding medications that are therapeutically beneficial, these analyses may also tell us what kinds of factors precipitate AD in elderly people." ■

Disease Incidence Reduced With Simvastatin in Nonhypertensive Patients



Note: Based on a database study of more than 4.5 million patients.

Source: Dr. Wolozin

ELSEVIER GLOBAL MEDICAL NEWS

NSAID Preserves Brain Integrity

Aspirin *from page 1*

ues in gray matter and higher fractional anisotropy (FA) values in white matter, compared with controls, are thought to reflect preservation of brain integrity.

Dr. Ryan found that aspirin users had significantly lower hippocampal mean ADC values and higher mean FA values in the adjacent white matter region than did controls.

About 25% of both groups were positive for apolipoprotein E (ApoE), and similar protective effects from aspirin were found in individuals regardless of their ApoE status.

ADC values were not significantly different between groups in the posterior cingulate. Aspirin did, however, appear to prevent age-related functional changes in the posterior cingulate and splenium that were seen in those who did not take aspirin.

'Our data support the idea that aspirin, even at low doses,' may positively affect brain function.

DR. RYAN

"We can't say anything about the mechanism of why diffusion is changing, but our data support the idea that aspirin, even at low doses, may confer some positive effect on brain function," Dr. Ryan said. "Diffusion MRI may be a sensitive measure for assessing the influence of anti-inflammatory drugs and interventions that might decrease the risk of Alzheimer's disease." ■