Genetic Variant Tied to Amyloid-β Generation 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 Rogova 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.”

Dr. Rogova 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 said (Nat. Genet. 2007 Jan 14 [Epub doi: 10.1038/ng1943]).

The initial “discovery cohort” comprised 124 northern European FAD families and 128 Caribbean Hispanic FAD families. The replication cohort consisted of northern European individuals from a case-control study (178 cases with sporadic AD and 128 controls with self-identified white European ancestry), 276 white subjects from the Multi-Institutional Research in Alzheimer’s Genetic Epidemiology (MIREG) study, 238 African American subjects from the MIREG study, and Israeli Arab individuals (111 with AD and 114 normal controls from the Wadi Ara population).

The investigators 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 acute 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 sequence 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.

One of the disease-associated haplotypes of the SORL1 gene was expressed in AD amyloid plaque carriers at less than half the level of controls in carriers of disease haplotypes. But univariate regression analyses showed that the disease variants of the SORL1 gene accounted for about 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 modulate SORL1 [protein] expression and, perhaps, therefore, risk for Alzheimer’s disease,” the researchers said.

Although variants of the SORL1 gene may not raise SORL1 protein levels as much as the apo E ɛ4 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.