NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Polymorphism Predicts Age of Late-Onset AD

The age at which individuals who are at risk for developing late-onset Alzheimer's disease actually begin to show symptoms of dementia may now be accurately predicted to within 7 years, according to a phylogenetic analysis of three cohorts of individuals with and without the disease.

In the study, Dr. Allen Roses of the Deane Drug Discovery Institute at Duke University, Durham, N.C., and his colleagues found that people who carried a long poly-T polymorphism in the translocase of outer mitochondrial membrane 40 (TOMM40) gene and the e3 allele of the apolipoprotein E (APOE) gene on the same chromosome developed late-onset Alzheimer's disease (LOAD) an average of 7 years earlier than those who carried a shorter poly-T polymorphism in TOMM40 and the APOE e3 allele (Pharmacogenomics J. 2009 Dec. 22 [doi:10.1038/tpj.2009.69]).

BY RICHARD J. CASELLI, M.D.

Most people who develop LOAD are APOE e3 carriers, and these results may explain their risk for the condition. The length of the poly-T variant in TOMM40 also could help to determine the risk of LOAD in carriers of APOE e4 and e2 alleles. The APOE e4 allele is the strongest genetic risk factor for developing LOAD and is known to be associated with a younger age of LOAD onset, whereas the e2 allele is thought to be relatively protective against LOAD.

Previous genetic studies of LOAD may have missed the TOMM40-APOE association because of strong linkage disequilibrium between the two genes, which are separated by about only 2,000 nucleotide bases on chromosome 19. To work around that problem, Dr. Roses and his associates constructed a phylogenetic analysis of the chromosomal region in one cohort of white patients to see if they could identify collections of related haplotypes with common ancestral history that were enriched with LOAD-causing polymorphisms. They showed that they could match the phylogenetic structure of the APOE-TOMM40 chromosomal region in the first cohort with two additional case-control cohorts of white individuals. A key poly-T polymorphism in TOMM40 distinguished the age of onset of LOAD in patients who were homozygous for APOE e3 or carried both e3 and e4 alleles.

In patients from one cohort for whom disease-onset data were available, repeats of 27 or more thymidine bases were associated with disease onset at a significantly younger age than were shorter poly-T alleles (77.6 years vs. 70.5 years). The distribution of the lengths of the poly-T variant seemed to be inherited faithfully along with specific alleles of APOE, suggesting that they "do not represent dynamic mutations as observed in other neurological diseases," the authors wrote.

All of those who were homozygous for the APOE e4 allele had poly-T polymorphisms with lengths of 21-30 thymidine bases, except for two subjects who had lengths of 15 bases, who had a later stage of LOAD onset than would normally be expected. Individuals with APOE genotypes of e2/e2 or e2/e4 also seemed to carry variable-length, poly-T repeats similar to those of APOE e3 carriers.

"It is highly probable that African, Asian, Caucasian and other ethnic groups have very different phylogenetic patterns in the APOE-TOMM40 region. This may affect the clinical usefulness, for non-Caucasians, of the data presented here and this could be especially problematic in the pharmacogenomic interpretation of global clinical trials. This factor must be considered when large phase III trials do not confirm the efficacy found in original phase II experiments based solely on Caucasians," the authors cautioned.

They plan to validate the association between the poly-T polymorphism and age of LOAD onset and determine the value of the APOE and TOMM40 alleles in predicting age of onset in a 5-year, prospective, population-based study of several ethnic groups. They hope to conduct this study in combination with a prevention or delay of disease-onset drug trial for those whose genetics and age would predict that they are at high risk of developing LOAD within 5-7 years.

Dr. Roses is president of Zinfandel Pharmaceuticals Inc., the Durham, N.C.–based company conducting the trial. The trial results are open for validation, but patent applications have been filed for the use of the polymorphism as a genetic marker for AD. The research was funded through grants from institutions of the National Institutes of Health, the National Science Foundation, the Arizona Alzheimer's Consortium, and the State of Arizona. It also was supported by an anonymous gift and the Deane Drug Discovery Institute.

Other ethnic groups might have different phylogenetic patterns, which must be noted when phase III trials don't confirm the efficacy seen in phase II experiments based solely on Caucasians.

Dr. Caselli's comment: The discovery in the early 1990s that allelic variants of APOE strongly influenced susceptibility to Alzheimer's disease caused a paradigm shift in our approach to AD research.

First, it was a discovery that seemed to bear little relationship to amyloid or tau pathology, opening the door for other pathophysiological models as well as considerable controversy (and still seems to be a source of divisiveness among some groups of researchers).

Second, although the allelic variant was initially found in familial cases of LOAD, it was then found in "sporadic cases," providing convincing evidence that even patients lacking a family history could nonetheless have genetically determined (or influenced) disease.

Third, the APOE e4 allele is present in 20%-25% of people in North America, so screening could identify those at elevated risk levels, including e4 noncarriers (further subdivided by the protective e2 allele), e4 heterozygotes, and e4 homozygotes who could then be studied prospectively.

Dr. Roses was the team leader for the APOE research and so his assertion that TOMM40 may underlie part or all of APOE's effect is startling and likely to provoke what he calls a "spirited debate." TOMM40 was identified by a search of the APOE-TOMM40 linkage disequilibrium region because the TOMM40 gene product has been shown to interact with amyloid and APOE protein, thus presenting a potentially key target in AD pathogenesis (Proc. Natl. Acad. Sci. U.S.A. 2005;102:18694-9; J. Neurosci. 2006;26:9057-68). More work is needed to tease out important questions, including what are the TOMM40 poly-T tract lengths that are in nonwhite populations, associated with the e2 allele, and associated with other neurodegenerative diseases. It is still unclear whether TOMM40 explains the entire APOE effect, or only a part of it. If it is the latter, then more questions arise as to the synergistic interactions of several genes in linkage disequilibrium, possibly including other genes in the region.

TOMM40 is not yet ready for clinical prime time, but given Dr. Roses' previous work, and the impact that APOE has had on our field, it is likely that this is just the beginning of an important story regarding TOMM40. ■

Clinical perspective by DR. CASELLI, *professor of neurology at the Mayo Clinic College of Medicine and the outgoing chair of neurology at the Mayo Clinic Arizona. Dr. Caselli collaborated with Dr. Roses on a follow-up study exploring the relative contributions of APOE and TOMM40 to AD age of onset, but he has no financial interest in the discovery.*

Research report by Jeff Evans, Clinical News Editor.

Natriuretic Peptide Linked to Cognitive Deficits in Elderly

BY MITCHEL L. ZOLER

ORLANDO — High blood levels of a brain natriuretic peptide were associated with poor cognitive function in a study of 950 community-dwelling, healthy, elderly adults.

"This is the first time this [association] has been shown," Dr. Lori B. Daniels said at the annual scientific sessions of the American Heart Association.

Dr. Daniels, a cardiologist at the University of California, San Diego, suggested that several mechanisms that might link production of natriuretic peptide to poor cognitive function including reduced cardiac output that drops oxygen or nutrient supplies to the brain, atrial fibrillation that creates microemboli, microcirculation deficits that harm both the heart and brain, and genetic predisposition.

Cognitive function data and blood specimens were analyzed from 950 of 5,000 participants enrolled in the Rancho Bernardo study of the early 1970s.

The average age of the participants was 77 years; 61% were women. The researchers used three tests to evaluate cognitive function: The Mini-Mental State Exam (MMSE), the Trail-Making Test B, and a category fluency test that asked participants to name as many animals as they could in 1 minute.

MMSE results identified poor function in 7%, the trail-making test B identified poor function in 30%, and category fluency identified poor function in 15%.

Natriuretic peptide levels in the blood specimens were measured using a test that detects N-terminal pro-B-type natriuretic peptide (NT-proBNP). Among the 950 participants, 79% had a low level of NT-proBNP,and 21% had a high level.

In the low level group, poor cognitive scores occurred in 5%, 23%, and 12% of subjects for the three cognitive function tests, respectively. In the high level group, 17%, 54%, and 26% of the subjects scored poorly on the three tests, respectively.

When the results were adjusted for age, education, and other factors, participants with high NT-proBNP levels had significantly worse cognitive function scores on the MMSE and the Trail-Making Test B. Scores for category fluency were lower in people with high NT-proBNP in the fully-adjusted model, but the difference fell short of statistical significance.

In the fully-adjusted model, people with high levels of NT-proBNP were 82%, 75%, and 37% more likely to have poor cognitive function on the three tests, respectively, compared with people with low levels.

Dr. Daniels received research support from Roche Diagnostics, which markets an NT-proBNP assay. ■