Polymorphism Predicts Age of Late-Onset AD

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BEHAVIORAL NEUROLOGY

T he 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 e4 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 (dec 10.1038/tpj.2009.69)).

Most people who develop LOAD are APOE e4 carriers, and these results may explain their risk for the condition. The length of the poly-T variant in TOMM40 also helped 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 only about 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 discriminated an age of onset of LOAD in patients who were homozygous for APOE e4 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 neurodegenerative 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 vary in terms of their poly-T repeats. Other ethnic groups have very different polygenetic patterns in the APOE-TOMM40 region. This may affect the clinical usefulness, for non-Caucasians, of the data presented here and thus should be especially taken into account 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 that were done in nonwhite populations, associated with the e2 allele, and associated with other ethnic groups. 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 other 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 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 MITCHELL 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 17%, and 25% of the subjects scored poorly on the three tests, respectively. In the fully-adjusted model, people 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%, 79%, and 37% more likely to have poor cognitive function in the three tests, respectively, compared with people with low levels.

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