Gene Variant May Enable Early AD Treatment

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

People who have a newly discovered gene variant that increases the risk of Alzheimer's disease appear to experience subtle changes in both cognition and brain structure years before even the earliest signs of Alzheimer's appear.

The gene, TOMM40, was associated with small but measurable declines in verbal learning and memory, and with decreases in gray matter volume, particularly in the posterior cingulate and precuneus—both areas that are highly involved with memory retrieval.

"Brain changes in these regions are particularly interesting because they are also associated with a high amyloid burden in people with Alzheimer's," Sterling Johnson, Ph.D., said in an interview. "Many studies have shown that these areas are active when you are recalling the recent past. So seeing changes there fits very nicely with a major symptom of Alzheimer's: recent memory loss."

VITALS

Major Finding: Particular variants of the TOMM40 gene are associated with declines in regional gray matter volume and in verbal learning and memory that may presage Alzheimer's disease.

Data Source: Two prospective studies of healthy volunteers with TOMM40 genotyping, one involving MR imaging of 117 participants and another involving verbal learning and memory testing in 337 participants.

Disclosures: Both studies were funded by the National Institute on Aging. Neither investigator had any potential financial conflict.

Dr. Johnson and his colleague, Dr. Mark Sager, both of the University of Wisconsin, Madison, both said the work may open an important door on the ability to risk-stratify patients for early treatment, potentially identifying them before they experience significant brain damage from the disease.

"Right now we're spending billions of dollars on trying to find a disease-modifying therapy, but we don't really know who we would give that to," Dr. Johnson said.

In the same way that those with high cholesterol benefit most from statins, patients with a demonstrated risk of Alzheimer's would be the best candidates for any drug therapy, he noted. "Our work may eventually be able to identify in a much more targeted way groups of people who could benefit the most from early intervention, hopefully early enough to prevent them from having serious cognitive loss from Alzheimer's."

TOMM40 has variable lengths that are defined by how many thymidine bases are contained in a specific section of the gene. The very long form (30 or more thymidine bases) is associated with an earlier onset of Alzheimer's disease, while the very short length (20 or fewer) is associated with a later onset. Some people have a long form (between 20 and 30 bases) that confers intermediate risk for Alzheimer's disease.

In 2009, Dr. Allen D. Roses of Duke University, Durham, N.C., first showed that among patients who developed Alzheimer's after 60 years of age and were homozygous or heterozygous for the apolipoprotein E e3 (APOE-3) allele, those with two copies of the long TOMM40 developed the disease an average of 7 years earlier than did those with shorter TOMM40 lengths (Pharmacogenomics J. 2009 Dec. 22 [doi:10.1038/tpj.2009.69]).

Dr. Johnson's study consisted of 117 healthy middle-aged volunteers (mean age, 57 years) who were known to be homozygous for the APOE-3 allele. APOE-3 homozygotes are thought to have a neutral risk for Alzheimer's disease. He then tested the subjects to determine what variant of TOMM40 they had.

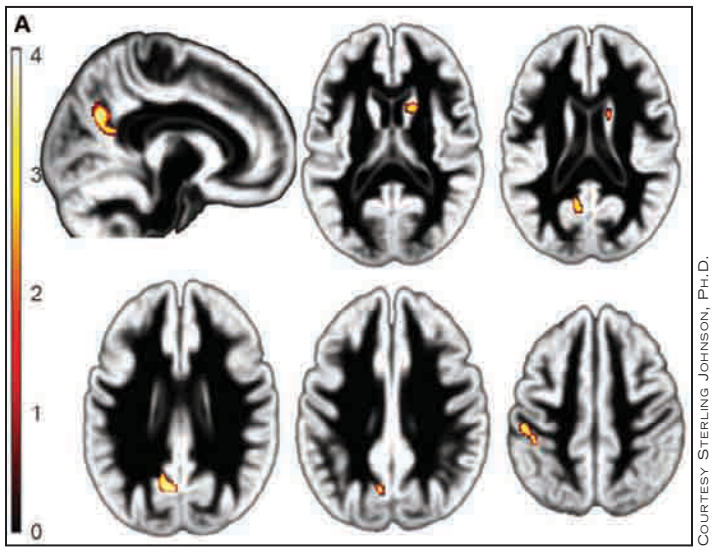
In Dr. Johnson's study group, 38 patients were homozygous for the very short-length TOMM40, 44 had one short and one long or very long allele, and 35 were homozygous for the very long form of TOMM40.

All of the volunteers underwent brain scanning with voxel-based morphometry to assess gray matter volume in different brain regions.

The subjects with two copies of the very long TOMM40 allele had significantly less gray matter in both the ventral posterior cingulate and the precuneus than did those with two short alleles. These are both regions that show early deterioration in late-onset Alzheimer's disease.

"This is very important, because we are finding brain changes in people who are quite young," Dr. Johnson said.

"The brain differences between the groups were very similar to, but less severe than, what is observed in full-blown Alzheimer's. It may be that the TOMM40 gene will be a useful measure of Alzheimer's risk in middle age, but additional research with longitudinal follow-up is necessary."



COURTESY STERLING JOHNSON, PH.D.

Patients with short TOMM40 had greater gray matter volume than did those patients with two very long versions.

Dr. Sager examined the gene's potential effect on memory in a cohort of 337 adults (mean age, 54), who were genotyped for APOE and TOMM40. Of these, 128 were homozygous for the short form of TOMM40, indicating a lower risk. The long or very long forms were seen in 219 subjects. In the low-risk group, 57% had a family history of Alzheimer's, compared with 77% of the high-risk group—a significant difference.

All subjects took the Auditory-Verbal Learning Test, which involves five trials of learning two 15-word sets. While the mean scores for both subject groups were within the normal range, the mean was significantly lower in the group with longer forms of TOMM40.

"We found significant changes in verbal learning and memory—changes that are traditionally the first cognitive changes seen in Alzheimer's," Dr. Sager said. "Even after adjustment for age, gender, and education, people with the long form of TOMM40 were performing lower than those without it."

He stressed that none of the subjects in either the brain volume study or the memory study had any observable memory difficulties in their everyday life. "But these findings of gray matter loss and cognitive changes in these relatively young people are very important"and suggest that "we may have the ability to find people at risk of Alzheimer's very early on in the disease process, far in advance of any significant cognitive problems." ■

Childhood Epilepsy Linked to Psychiatric and Learning Problems

BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE AMERICAN EPILEPSY SOCIETY

BOSTON — Children with benign focal epilepsy with centrotemporal spikes had a higher incidence of psychiatric illnesses, attention-deficit/hyperactivity disorder, and developmental delay compared with the estimated incidence in the general population.

These children "are not sufficiently screened for psychological and other cognitive problems. The nocturnal seizures are often missed, unless the child generalizes; and most institutions lack a good neuropsychiatry division to assess for learning difficulties. Subtle learning difficulties often go undetected," Dr. Shalaka Indulkar said in a poster presentation.

Dr. Indulkar and colleagues reviewed consecutive routine EEGs from 1995 through 2004 for pediatric patients with benign focal epileptiform discharges. They identified 117 whose seizures were consistent with benign focal epilepsy with centro-temporal spikes (BECTS). These features included either typical brief hemifacial seizures associated with speech arrest, drooling, and preservation of consciousness; gurgling or grunting noises with loss of consciousness and terminating in vomiting; or nocturnal secondarily generalized seizures. Data included general demographics and neurologic, behavioral, and psychiatric disorders and used descriptive data and the Fisher's exact test for analysis.

Of the 117 patients, 51 were girls and 66 were boys. Mean age at initial diagnosis of EEG abnormality was 6.8 years (6.2 in girls and 7.0 in boys), said Dr. Indulkar, a neurology resident at the Cleveland Clinic.

The prevalence of co-existing psychiatric problems, including anxiety, schizophrenia, obsessive compulsive disorder, and depression in the study population was 9.4%—substantially higher than the estimated 1%-4% in the general pediatric population.

ADHD was seen in 11% of the seizure population, compared with an estimated prevalence rate of 3%-7% in school-aged children. Developmental delay, including pervasive developmental disorder, language disorder, and autism, was seen in 10.2% of the seizure population, and tics were noted in 5.1%. There was also a high incidence of migraine and headaches in the study population.

Investigators have postulated that there is a link between the benign and more serious epilepsy syndromes, based on the presence of epileptiform disturbances in children who have epilepsies of varying severity and learning, and other CNS-related comorbidities. However, "children with typical [BECTS] do not necessarily have abnormal EEGs in sleep, but they still may have learning difficulties, so the mechanism [for the CNS-related comorbidities] remains elusive," Dr. Indulkar said in an interview.

The investigators did not consider the influence of antiseizure medications on children in this study. "Not all children with BECTS are treated, as most seizures are rare, occur nocturnally, and are self-limited, so it's unlikely that medications alone could explain the cognitive problems," she said.

Dr. Indulkar reported no conflicts of interest with respect to her presentation. ■