Genetic Variant for Late-Onset AD Identified

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Contributing Writer

Strategies for the prevention and treatment of late-onset Alzheimer's disease may be improved by the identification of a gene variant that seems to increase the risk of Alzheimer's disease, according to a report by Lars Bertram, M.D., of MassGeneral Institute for Neurodegenerative Diseases, Charlestown, Mass., and his associates.

Variants in the ubiquilin 1 (*UBQLN1*) gene, located on chromosome 9, may substantially increase the risk of late-onset Alzheimer's disease, which accounts for over 90% of the disease, investigators have reported.

Dr. Bertram and his associates examined two groups of patients. The first group of patients consisted of 1,439 subjects from 437 families with Alzheimer's disease who participated in the National Institute of Mental Health multiplex family study between 1991 and 1997.

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Of those 1,439 individuals, 994 patients had Alzheimer's, 411 were unaffected, and 34 had unknown phenotypes. Mean age at disease onset was 72 years, the investigators reported (N. Engl. J. Med. 2005;352:884-94).

Evaluation of 19 single-nucleotide polymorphisms in three genes within the chromosome 9q linkage region showed that Alzheimer's disease was significantly associated with two single-nucleotide polymorphisms in *UBQLN1* and one in *APBA1*.

Haplotype block structure estimates showed that the single haplotype (H3), almost exclusively defined by the risk allele of UBQ-8i, was associated with a significantly increased rate of transmission to affected subjects.

The testing of *APBA1* polymorphisms did not show such transmission.

Ubiquilin 1 has a number of known functions: It encodes the protein ubiquilin 1, regulates protein degradation, interacts with presenilin 1 and presenilin 2, and promotes the accumulation of presenilin in vitro.

Findings from the second investigation, the Consortium on Alzheimer's Genetics study, showed that the rate of transmission of the H3 haplotype was increased among subjects with Alzheimer's disease. Investigators found no association with rs1411483 in *APBA1*.

Specimen collection began in 1999 and has been completed for 224 Alzheimer's patients and 265 unaffected siblings.

Affected participants were at least 50 years old at disease onset. Individuals' mean age at onset 71 years.

Analyses by Dr. Bertram and colleagues on data merged from the two family groups showed the most pronounced single-local signals for UBQ-8i followed by rs2781002 and rs2780995.

Dr. Bertram's group also studied RNA extracts from neocortical brain tissue samples to see if the risk allele UBQ-8i affects the splicing of exon 8 in the *UBQLN1* message.

They found a relationship between the UBQ-8i allele and a *UBQLN1* transcript lacking exon 8 in the 25 samples from patients with Alzheimer's disease.

In an accompanying editorial, Thomas D. Bird, M.D., called *UBQLN1* "intriguing as a candidate gene because of its potential role in the proteasome degradation of proteins and its interaction with *PS1* and *PS2*."

"As always, this new association requires replication and confirmation in additional populations," wrote Dr. Bird, who is a professor of neurology, medicine, and psychiatry at the University of Washington, Seattle (N. Engl. J. Med. 2005;352:862-4). Dr. Bird also is a research neurologist at the Veterans Affairs Medical Center in Seattle.

Dr. Bertram's research group observed that "the rampant inconsistencies encountered in genetic analyses of putative candidate genes for Alzheimer's disease in the literature to date" may stem from the fact that most studies in the field are done on groups whose numbers are too small to show moderate genetic effects like that of *UBQLN1*, instead of the more pronounced effects of *APOE*. ■