Early-Onset Alzheimer Disease Caused by a New Mutation (V717L) in the Amyloid Precursor Protein Gene

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**Context:** Alzheimer disease is the most common form of dementia. Mutations in the genes amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) have been found in early-onset familial forms of Alzheimer disease.

**Objective:** To determine the cause of dementia in a family with early-onset illness.

**Design, Setting, and Participants:** A family with a history of dementia was referred to the Indiana Alzheimer Disease Center, Indianapolis. All the research in this study was done in a university or university hospital. The proband and her 4 siblings took part in the study. The proband, who is still alive, showed symptoms of Alzheimer disease at 38 years of age. Genomic DNA was obtained from blood samples of 5 family members. The APP and PS1 genes of the proband were screened for mutations by amplification followed by direct sequencing.

**Results:** Sequence of exon 17 of the APP gene revealed a single nucleotide (guanine to cytosine) substitution in 1 allele, resulting in an amino acid change at codon 717 (valine to leucine). Each of the proband’s siblings were tested for this mutation by direct sequencing. Two of the 4 were found to have the mutation; one of whom was recently clinically diagnosed at the age of 36 years.

**Conclusions:** A novel mutation in the APP gene (V717L) has been found in a family with a history of dementia, beginning in the mid to late 30s. The age of onset in this family is earlier than most of the other families with Alzheimer disease who also have APP mutations.

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°FAMILY ASCERTAINMENT

Genomic DNA was obtained from blood samples of 5 family members. Informed consent for this study was obtained from each participating subject after the nature of the project had been fully explained. **Figure 1** shows a 5-generation pedigree of the family.
The proband was analyzed for mutations in 2 of the known genes causing AD. Direct sequencing of the PS1 exons 5, 6, 7, 8, 11, and 12 and APP exons 16 and 17 was done.6 The resulting sequence was compared with normal control sequences. Primers 5′GACCAAACGATTGGGCAAG3′ and 5′CATGGAAGCACACTGATTCG3′ were used in amplification and direct sequencing of APP exon 17. A smaller product was produced when primers 5′CCAAATGTCCCCTGCATT3′ and 5′CTCTCATAGTCTTAATTCCCAC3′ were used for amplification. The resulting 147–base pair product was digested with MnII and run on a 4% composite gel (3.0% Nuseive agarose [FMC BioProducts, Rockland, Me]/1.0% agarose). Apolipoprotein E (APOE) was also analyzed by amplification followed by HhaI digestion.7 The resulting products were run on a 4% Nuseive agarose gel.

GENETIC STUDIES

The DNA sequence of exons 5, 6, 7, 8, 11, and 12 of PS1 and exon 16 of APP were normal in the proband. Sequence of exon 17 of the APP gene revealed a single nucleotide (guanine to cytosine) substitution in 1 allele (Figure 2). This causes an amino acid change in codon 717 (valine to leucine). This mutation was not observed in 50 normal control subjects (100 normal chromosomes). This particular mutation creates a MnII-restriction enzyme site. Four of the proband’s siblings (IV:4, IV:5, IV:8, and IV:9) were tested for this mutation by direct sequencing and MnII digestion. One sibling (IV:7, chose not to

GENETIC ANALYSES

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RESULTS

FAMILY HISTORY

The proband’s father (III:2) had mild, progressive memory loss and difficulty driving during the 2 years preceding his death of a myocardial infarction at the age of 40 years. The proband’s grandfather (II:2) had a progressive severe dementia of 10 years’ duration that was diagnosed as “shell shock”; he died at the age of 49 years. The proband’s great-grandmother (I:2) died at approximately age 50 years after a progressive dementia of several years’ duration.

CLINICAL FEATURES

Clinical studies of affected members of this family show clinical onset of disease with short-term memory problems in their mid to late 30s, with gradually worsening deficits of cognitive functions and activities of daily living as the disease progresses. Disease duration is approximately 10 years based on family history data.

The proband (patient IV:2) developed deficits in short-term memory and concentration at the age of 38 years. Her family and friends noticed that she was having difficulty caring for her 2 children, driving her car, and managing her household. During the subsequent 2 years, her cognitive problems progressed to the point that it became necessary for her to move to her sister’s home. On neurological examination, 5 years after the onset of symptoms, she was repetitive in speech, but had no focal abnormalities or involuntary movements. Neuropsychological testing included a Mini-Mental State Examination (MMSE) score of 21 of the possible 30, with severe impairment seen in memory and new learning, and lesser degrees of deficits in visuococonstructive skills, visuomotor coordination, and sequential tracking. Manual motor skills testing revealed intact speed and strength but decreased dexterity. Very mild depressive symptoms were reported on a screening questionnaire. Over the next year, the patient’s memory dysfunction progressed and she became intermittently agitated, necessitating her placement in an assisted living facility. On reevaluation, 6 years after the onset of symptoms, her general neurological examination remained unremarkable but neuropsychological testing revealed an MMSE score of 16 of the possible 30, with a decline in new learning, memory, fluency, manual motor speed, and executive functions. Mood was within normal limits on a screening questionnaire.

Patient IV:5 began to notice mild problems with short-term memory when she was approximately 35 years old. He occasionally misplaced items and forgot the directions to a friend’s house. On evaluation, 2 years after the onset of symptoms, a neurological examination was normal. Neuropsychological testing revealed an MMSE score of 28 of the possible 30. Mild deficits were seen in verbal and visual memory, new learning, and sequential tracking. On reevaluation, 1 year later, the MMSE score was 27 of the possible 30; there was a moderate decline in memory compared with the previous testing, as well as a mild decline in executive functioning and dexterity, and an increase in perseveration. He was, however, still functioning well at work and at home.

The 4 asymptomatic siblings (ages 39, 38, 35, and 29 years at the time of initial evaluation) in generation IV were also examined. All had normal findings on physical, neurological, and neuropsychological examinations, with no significant changes seen on reevaluation 1 year later.

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We report a novel mutation in the APP gene (V717L) in a family with onset of dementia in the mid to late 30s. Sequencing of the APP gene in the proband revealed a guanine-to-cytosine transversion changing the predicted amino acid at codon 717 from valine to leucine. The mutant allele has been found in 2 other family members, one who was just recently diagnosed with AD. The mutant allele was found in 2 other family members, one who was just recently diagnosed with AD.

This is the fourth mutation associated with AD. Nevertheless, the V717L mutation seems to be a particularly promising candidate for the production of transgenic mice. Other factors may lie in the genetic background of the family and its interaction with the environment. The particular malignancy of this condition with regard to the very early onset age, interestingly is not associated with a rate of disease progression any more rapid than has been seen in the other families with APP mutation associated with AD. Nevertheless, the V717L mutation seems to be a particularly promising candidate for the production of transgenic mice.

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