Novel Presenilin 1 Mutations Associated With Early Onset of Dementia in a Family With Both Early-Onset and Late-Onset Alzheimer Disease

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Two children of an adult with early-onset, autopsy-confirmed Alzheimer disease (AD) developed dementia in their late 20s and were subsequently found to have novel mutations in codon 434 of the presenilin 1 (PS1) gene on chromosome 14, a G-to-T substitution at nucleotide 1548 and a C-to-G substitution at nucleotide 1549. The younger of the 2 children had AD confirmed at postmortem examination. The disease course in these 3 individuals was characterized by cognitive and behavioral problems accompanied by myoclonus, seizures, and aphasia within 5 years after onset. Two grandparents had clinically diagnosed AD with stroke beginning at ages 78 and 66 years, but neither had a PS1 mutation. No other living family member was demented, nor did any other family member have the PS1 mutation. We conclude that the affected parent of the proband was a likely recent founder for these novel mutations in PS1. The family demonstrates the clinical and genetic heterogeneity of AD.

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Mutations in 3 genes, the amyloid precursor protein (APP) gene on chromosome 21, the presenilin 1 (PS1) gene on chromosome 14, and the presenilin 2 (PS2) gene on chromosome 1, result in an autosomal dominant form of Alzheimer disease (AD), beginning as early as the third decade of life.1 Together the PS1 and APP mutations account for 71% of early-onset AD with nearly complete penetrance, but the results of a population-based study suggest that mutations in PS1 may be the most common form of familial early-onset AD.2

We identified a family with both early- and late-onset AD. All living family members were examined by the same physician (G.D.) using a structured neurological examination and had been followed up for several years at the time of this report. The parent of the proband was dead at the time of the initial evaluation of the children, but the history and autopsy findings were obtained from the family and from an extensive review of medical records.

RESULTS

The proband (person IV:4 [Figure]), an electrician, developed progressive mood swings, depression, and apathy at age 29 years. He was unresponsive to antidepressant therapy. By age 30, this individual was misplacing things and repeating statements and could not function at work (eg, showing up at the wrong addresses and unable to follow job-site blueprints). Irritability and serious behavioral disturbances followed. Results of neuropsychological tests at age 31 revealed severe dementia with normal brain imaging. By age 33, dysarthria and aphasia had developed, and a positron emission tomographic scan was reported to show biparietal lobe hypometabolism. Donepe-
PARTICIPANTS AND METHODS

Family members were examined in person and underwent neuropsychological testing. All affected individuals met the standard criteria for probable or possible AD. Deoxyribonucleic acid was extracted from peripheral blood lymphocytes of 10 family members. The apolipoprotein E (APOE) genotype was determined from genomic DNA, as described by Hixson and Verrier. Messenger RNA was isolated from lymphoblast cells using the RNeasy Mini Kit (Qiagen, Venlo, the Netherlands), and a first strand complementary DNA was synthesized using a Reverse Transcriptase–Polymerase Chain Reaction Kit (Stratagene, LaJolla, Calif). Mutations were sought in the open reading frames of the PS1 gene as previously described.

The presence of a GC-to-TG double substitution in codon 434 was confirmed in genomic DNA using intronic oligonucleotide primers flanking exon 12 (1706 [5′-GTCTTTCCCATTTCTGCAC-3′] and 1707 [5′-GGATTCTAACCAGAAATAT-3′]). Polymerase chain reaction amplification conditions were 300 ng of genomic DNA, 1.5-mmol/L magnesium chloride, 50 pmol of each primer, 2 U of Taq polymerase, and 250-µmol/L deoxynucleotide triphosphates in a final reaction volume of 30 µL. The polymerase chain reaction mix was cycled through 35 cycles at 94°C for 20 seconds, 62°C for 20 seconds, and 72°C for 20 seconds. To determine whether the mutations were in cis, ie, on the same chromosome (GC-to-TG), or in trans, ie, on different chromosomes (G-to-T and C-to-G), we cloned and sequenced 4 additional independent clones containing the exon 12 genomic polymerase chain reaction products from 1 affected family member using the TA cloning kit (Invitrogen, Carlsbad, Calif). These studies revealed only the presence of wild-type (GC) and double-mutant (TG) clones.

Zol hydrochloride, 10 mg/d, was used for the treatment of the dementia, and paroxetine hydrochloride, 20 mg/d, was used for management of the behavioral problems. By age 34, myoclonus had developed and the aphasia had become more severe. Later, visual and auditory hallucinations occurred accompanied by physical aggression. At age 36, the first generalized tonic-clonic seizure occurred. One year later, the patient was found to be immobile, mute, and incontinent, and required institutionalization. The APOE genotype was ε3/ε3. Sequencing of the open reading frame of PS1 revealed a GC-to-TG substitution at nucleotides 1548 and 1549 encoding codon 434. This mutation was not observed in any of the more than 100 control subjects.

The proband’s parent (person III:5) developed mood swings at age 33 years with irrational behavior and impaired judgment. At age 38, this individual developed myoclonus, episodes of violent behavior, and generalized seizures. A computed tomographic scan was normal, but a pneumoencephalogram indicated both atrophy and hydrocephalus. At age 41, an electroencephalogram revealed a periodic pattern with spikes and slow waves. A clinical diagnosis of Creutzfeld-Jakob disease was made. Because of seizures, immobility, and deterioration in activities of daily living, the patient was institutionalized at age 42. Four years later, a persistent vegetative state developed, but the patient survived another 13 years before dying at age 59. Autopsy findings revealed amyloid angiopathy and widespread amyloid plaques in the cerebral cortex confirmed by amyloid β peptide immunostaining, consistent with published criteria for AD. Results of a screen for prion protein scrapie were negative, excluding prion disease. No frozen tissue specimen or blood sample was available for further analysis.

The proband’s younger sibling (person IV:5) found it difficult to finish a book by age 27 years and began to forget appointments. By age 28, this individual could not use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person could follow only simple commands. Rigidity in the right arm and leg and incontinence also developed. The APOE genotype was ε3/ε3. Results from the genotyping for PS1 revealed the same GC-to-TG substitution at nucleotides 1548 and 1549 encoding codon 434. This individual died 1 year later. Postmortem examination results showed numerous diffuse and neuritic plaques with a dense amyloid core throughout the neocortex. Neurofibrillary tangles and Hirano bodies were also abundant in the neocortex, and neuritic plaques and neurofibrillary tangles were found in the amygdala and nucleus basalis. Moderate cell loss and gliosis were evident in the hippocampus, amyg-
dala, and nucleus basalis. A pathological diagnosis of AD was established.

At the time of this analysis, the proband’s youngest sibling (person IV:6; age 29 years) had no symptoms. In a recent examination, this individual was found to be healthy, and the results of neuropsychological tests showed no evidence of cognitive or emotional dysfunction. The APOE genotype was ε3/ε4.

The proband’s grandparent (person II:2) had persistent memory problems from age 78 years that became worse approximately 1 year after a stroke at age 79. This individual also had a history of hypertension, hypercholesterolemia, and a hip fracture at age 81. By age 82, difficulty with recent memory was apparent and assisted living was required. On examination, this individual was disoriented in regard to time and date and was unable to learn new material, but could eat, dress, and go to the bathroom independently. A diagnosis of possible AD with stroke was made based on the report of a magnetic resonance imaging scan that was said to have revealed “strokes.” At the time of this analysis, this individual was alive at age 84, though both cognitive and functional deterioration had continued. The APOE genotype was ε3/ε4. Person II:1, the spouse of person II:2 and the parent of person III:5, had no history of dementia and died at age 85.

The proband’s other living grandparent (person II:9) began to have impaired memory at age 66 years. By age 84, this individual was in a nursing home and was disoriented in regard to place and time; had poor recall, attention, and calculation; and needed assistance to dress and go to the bathroom. Examination showed left hemiparesis and peripheral sensory neuropathy. A clinical diagnosis of possible AD with stroke was made, and the APOE genotype was ε2/ε3. The spouse of this person (person II:8) died at age 35 years with no history of dementia.

Siblings of the affected parent (person III:5) examined with a standardized neurological, psychiatric, and neuropsychological battery of tests included persons III:2 (APOE ε3/ε4; age 65 years) and III:4 (APOE ε3/ε3; age 63 years). Person III:6 (APOE ε3/ε3; age 56 years) was the proband’s unaffected parent, and persons III:8 (APOE ε2/ε3; age 59 years) and III:9 (APOE ε3/ε3; age 53 years) were the siblings of this individual. There was no evidence of significant cognitive deficit or neurological abnormalities in any of these individuals. Person II:10 had a history of dementia with stroke, but died at age 89 years. Person III:7 committed suicide at age 34 years and had a history of alcohol abuse, but there was no history of dementia. No other family members shown in the pedigree (Figure) were reported to have dementia prior to death.

**COMMENT**

This is one of many mutations in the PS1 gene found in families with early-onset AD. The family described herein demonstrates the genetic and clinical heterogeneity that characterizes AD. The living grandparents of the proband had late-onset AD complicated by stroke, while the proband, a sibling, and a parent developed AD earlier in life, most likely resulting from new, unusually unidentified mutations in the PS1 gene on chromosome 14.

We believe that the affected parent (person III:5) had a spontaneous mutation in the PS1 gene that was transmitted to 2 of the offspring. Neither grandparent had a similar early onset of disease, nor did either grandparent carry the mutation. The parents of the affected parent (person III:5) as well as their siblings lived into the eighth or ninth decade of life, making it unlikely that any of them had the mutation. Siblings of the proband’s parents were also unaffected in the sixth and seventh decades of life and were noncarriers. The unaffected parent did not have the mutation. Though we did not sequence the gene in the parent of the proband, it is likely that this individual was the founder. The alternative explanations are unlikely, but they may include nonpaternity in the affected parent or new identical double mutations in the proband and sibling.

The presence of fluent aphasia, behavioral disturbance, myoclonus, and extrapyramidal signs occurring at various intervals during the course of disease in all 3 individuals who were carriers of the same double PS1 mutation is not unusual. The survival time of the affected parent was extremely long, but 1 offspring of that individual (person IV:5) had a more typical disease course. Families with similar characteristics, early age at onset, and motor and behavioral manifestations have been previously reported.

Despite being distinct from the immediate regulatory and coding regions of the gene encoding the APP, mutations in the PS1 gene can lead to cerebral amyloidogenesis and familial AD by promoting a relative overproduction of longer isoforms of the amyloid β peptide. Compared with sporadic disease, AD associated with PS1 mutations has been associated with higher amounts of amyloid β peptide deposition in the brain, with a disproportionate increase in species terminating at amino acid residue 42. The protease thought to be responsible for cleavage of the carboxyl terminus of the amyloid β peptide that resides in the intramembranous domain of the APP has been designated as γ-secretase. The PS1 gene appears to be closely associated with γ-secretase function. Wolfe et al suggested that PS1 and γ-secretase might be the same protein. An alternative role has been proposed by Yu et al, who suggested an indirect role for PS1 in activating γ-secretase or in adapting substrates to γ-secretase.

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