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.

**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 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.
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.3

Deoxyribonucleic acid was extracted from peripheral lymphocytes of 10 family members. The apolipoprotein E (APOE) genotype was determined from genomic DNA, as described by Hixson and Vervier.4 Messenger RNA was isolated from lymphoblast cells using the RNaseasy 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.5

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-GTCCTTTCCATCTTCAC-3'] and 1707 ['5-GGATTCTAAACCGAATAAT-3']). Polymerase chain reaction amplification conditions were 300 ng of genomic DNA, 1.5-mmol/L magnesium chloride, 50 pmol of each primer, 2U 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.

zil 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 unable to use a calculator, and 3 years later developed aphasia, gen-

eralized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, 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 unable to use a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 32, this person was able to use only a calculator, and 3 years later developed aphasia, generalized seizures, and myoclonus. At age 38, myoc-
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, possibly 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.10-12

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.

Accepted for publication March 31, 2000.

This work was supported by grants AG15473 and AG08702 from the National Institutes of Health, Bethesda, Md, and by the Charles S. Robertson Memorial Gift for Alzheimer’s Disease from the Banbury Fund, Cold Spring Harbor, NY. Support was also provided by the Medical Research Council of Canada, the Howard Hughes Medical Research Foundation (Dr St George-Hyslop), and the Peterborough-Burgess Fellowship (Dr Rogaeva), Toronto, Ontario.

Corresponding author: Richard Mayeux, MD, MSc, 630 W 168th St, Department of Neurology, Gertrude H. Sergievsky Center, Columbia University, New York, NY 10032 (e-mail: rpm@columbia.edu.).

©2000 American Medical Association. All rights reserved.
REFERENCES