Autopsy-Confirmed Familial Early-Onset Alzheimer Disease Caused by the L153V Presenilin 1 Mutation

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Background: Three affected individuals are described from a small English kindred with early-onset autosomal dominant familial Alzheimer disease (FAD) caused by a leucine-to-valine change at codon 153 (L153V) of the presenilin 1 (PSEN1) gene.

Methods: Clinical information on the pedigree was collected directly from family members and from hospital records. Samples of DNA were screened by means of direct sequencing of all coding exons of PSEN1. One patient underwent neuropathological examination.

Results: Mean age at onset of symptoms was 35.3 years (95% confidence interval [CI], 34.6-36.0 years); at death, 44.0 years (95% CI, 39.1-48.9 years). Mean duration of illness was 8.3 years (95% CI, 4.7-11.9 years). Myoclonus was a late feature in 1 patient; seizures were not reported in any subjects. Spastic paraparesis and extrapyramidal signs were absent. The neuropsychometric profile of 1 patient showed relatively preserved naming skills in the setting of global cognitive deficits. Results of neuropathological examination demonstrated the signature lesions of Alzheimer disease and the presence of occasional cortical Lewy bodies.

Conclusions: The PSEN1 L153V mutation lies in the main mutation cluster of PSEN1 in the second transmembrane domain. It causes early-onset FAD with clinical features similar to those of other reported FAD pedigrees.

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TO DATE, the following 3 causative genes have been identified in autosomal dominant familial Alzheimer disease (FAD): amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2. Approximately 55% of early-onset FAD cases are associated with PSEN1 mutations. More than 80 PSEN1 mutations have now been reported, and although an intronic mutation has been identified, most are missense point mutations, about half of which occur in exons 5 and 8. Recently, a leucine-to-valine change at codon 153 (L153V), another mutation in exon 5, was identified in a French pedigree without neuropathological confirmation. We report the clinical and neuropathological features of members of family 177 in whom we have demonstrated the L153V mutation.

RESULTS

The clinical findings are summarized in Table 1. Mean AAO of symptoms was 35.3 years (95% confidence interval [CI], 34.6-36.0 years); mean age at death, 44.0 years (95% CI, 39.1-48.9 years); and mean duration of illness, 8.3 years (95% CI, 4.7-11.9 years).

PATIENT II:5

A right-handed factory worker presented at 40 years of age with a 5-year history of progressive memory problems. Results of neurologic examination and baseline dementia screening blood tests were normal. A ventriculogram showed good filling of the ventricular system without evidence of a space-occupying lesion. A diagnosis of presenile dementia was established. He died of bronchopneumonia 2 years later without undergoing neuropathological examination.

PATIENT III:2

A draughtsman was referred at 38 years of age with a 3-year history of personality change, progressive memory impairment, and difficulties at work. A full-scale IQ of 71 was obtained on the Revised Wechsler Adult Intelligence Scale (WAIS-R) and a premorbid IQ estimate.
SUBJECTS AND METHODS

Family 177 (Figure 1) is British. Information was collected from hospital records and family members. Age at onset (AAO) was defined as the age at which an individual first demonstrated signs of memory loss or personality change. Patients III:2 and III:3 underwent clinical assessment. Informed consent for genetic screening was obtained.

Patient III:3 underwent neuropathological examination. Blocks were taken from the frontal, temporal, parietal, and occipital lobes; the basal ganglia; the thalamus with the subthalamic nucleus; the midbrain; the pons; the medulla oblongata; and the cerebellar hemisphere and vermis. Sections were stained with hematoxylin-eosin and impregnated with silver according to the modified Bielschowsky method and with Luxol fast blue and cresyl violet (only on selected sections). Antibodies were used to immunostain beta amyloid, glial fibrillary acidic protein, tau protein (DAKO, Ely, England), and α-synuclein (D.P.H.). The DNA was extracted from frozen brain tissue, and all coding exons of PSEN1 were screened by means of direct sequencing. In addition, 100 healthy, unrelated white control subjects also underwent sequencing.

of 106 was obtained on the National Adult Reading Test (NART).6 Deficits were also recorded in memory, spelling, writing, and reading. He had a brisk pout and positive grasp reflex. Results of dementia screening blood tests were normal. Computed tomographic brain scan, electroencephalography, electromyography, and cerebrospinal fluid examinations showed no abnormalities. He deteriorated progressively and died without undergoing neuropathological examination.

PATIENT III:3

A left-handed bookkeeper presented at 37 years of age with a 1-year history of memory impairment and anxiety symptoms. She complained of difficulty with mental arithmetic and impaired episodic memory. Her medical history was unremarkable. Results of verbal and performance IQ measures were average, in keeping with her optimal level of functioning as estimated using the NART (Table 2). Results of the Recognition Memory Test (RMT)7 showed a mild global weakness in memory functions. Nominal skills were preserved. She performed flawlessly on the Unusual Views Test10 and the fragmented letters subtest of the Visual Object and Space Perception Battery (VOSP).11 Results of an unenhanced computed tomographic brain scan were interpreted as being normal. During the next 18 months, she was downgraded at work and reported further deterioration of her episodic memory. A second computed tomographic brain scan showed cortical atrophy, but she failed to attend follow-up until she underwent reassessment at 41 years of age, when her Mini-Mental State Examination12 score was 12/30. Examination demonstrated evidence of dyspraxia, with impaired copying of gestures and limb substitution.

Repeated neuropsychometry (Table 2) showed a borderline defective verbal IQ and a defective performance IQ. Performance on the RMT for words was at chance; for faces, below the first percentile. Nominal skills were relatively well preserved on the Oldfield Picture Naming Test.7 Visuoperceptual functions had deteriorated; she scored below the fifth percentile on the silhouettes subtest of the VOSP. There was no evidence of frontal executive dysfunction (Weigl Sorting Test13). She performed poorly on a letter cancellation task. Results of dementia screening blood tests and cerebrospinal fluid examination were normal. A magnetic resonance brain scan (Figure 2) showed marked atrophy of the parietal lobes and posterior parts of the frontal lobes. The temporal lobes were relatively spared, although the amygdala were slightly atrophied. There was no white matter disease. The ventricles were enlarged. The following year, myoclonus developed, which was treated with carbamazepine. She died of bronchopneumonia at the age of 49 years. The brain weighed 930 g; the brainstem and cerebellum, 128 g. The leptomeninges were thickened. Severe, generalized atrophy affecting all lobes of the brain was seen. Results of histological examination showed features of severe AD, ie, neurofibrillary tangles, neuritic plaques, and neurophil threads were abundant in the hippocampus and cerebral cortex (Figure 3). In the hippocampus, severe neuronal loss was accompanied by astrocitosis. Superficial status spongiosis and astrocitosis were noted locally in the cerebral cortex, indicating severe neuronal loss. Neurofibrillary tangles occurred also in the deep gray matter, including the nucleus basalis of Meynert, the lentiform nucleus, the substantia nigra, the locus ceruleus, the periaqueductal gray matter, and the raphe nuclei. Immunohistochemical analysis for α-synuclein revealed an occasional Lewy body in the substantia nigra, the locus ceruleus, the periaqueductal gray matter, and hippocampus, and in the deep gray matter, including the nucleus basalis of Meynert (Figure 4). There was extensive deposition of beta amyloid in the cerebral parenchyma and in the blood vessels (Figure 5).

The L153V mutation was demonstrated in patient III:3 and was absent in 100 unrelated healthy controls from the same ethnic background.
The PSEN1 gene consists of 13 exons, of which exons 3 through 12 code for a 467-amino acid-length protein.14,15 This serpentine protein is believed to consist of 6 to 8 transmembrane domains, where mutations tend...
to be concentrated. The L153V mutation is part of and extends a previously described mutation cluster on the second transmembrane domain (Table 3). The mutations in this cluster occur every third or fourth amino acid. Consequently, it has been suggested that they line up on the same side of an \( \alpha \) helix, disrupting the structure and function of \( PSEN1 \).1 The other major mutation cluster is in exon 8, near the \( PSEN1 \) cleavage site.2 Together, these major mutation clusters account for more than 50% of \( PSEN1 \) mutations.3

Most \( PSEN1 \) mutations have been missense mutations, leading to the hypothesis that mutant proteins result in disease by means of toxic gain of function.3 In common with \( APP \) mutations, they mediate their pathogenic effect by means of increased beta amyloid 42(43) formation.33-35

Unlike other \( PSEN1 \) mutation pedigrees, myoclonus was a feature in only 1 patient.36-39 Seizures are a well-recognized feature of younger-onset FAD,36-38,40,41 but were absent in family 177 as in FAD due to \( PSEN1 \) leucine-to-serine change at codon 250 (L250S).42 Spastic paraparesis was absent in our patients, and there was no neuropathological evidence of the “fluffy cotton wool” plaques reported in association with mutations causing paraparesis.43 The French family with the L153V mutation has not been described in detail, but myoclonus, seizures, and spastic paraparesis were not reported.4

The main phenotypic difference between the families with the L153V mutation and most \( PSEN1 \) kindreds appears to be a very early AAO. In a review of 38 published pedigrees with 22 different \( PSEN1 \) mutations, only 7 pedigrees had a mean AAO in the fourth decade of life.7 There appears to be no clear correlation between AAO and the site of the mutation. Even for the second transmembrane domain mutation cluster, where the 12 known mutations are in close juxtaposition, there is a 23-year range in AAO. Data for this cluster are available for 25 of the 29 published pedigrees (Table 3); 11 families had a mean AAO in the fourth decade of life, and 13 families in the fifth decade. For 1 family, the mean AAO was in the sixth decade of life. The nature of

![Figure 5. Immunostaining of beta amyloid in the cerebral parenchyma and the leptomeningeal and cerebral blood vessels (original magnification ×30).](image)

**Table 3. Mutation Cluster in Transmembrane Domain of \( PSEN1^{*} \)**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Family Identity</th>
<th>Mean Age at Onset, y</th>
<th>Ethnicity</th>
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<td></td>
<td>35</td>
<td>Mexican American</td>
<td>Crook et al39</td>
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*PSEN1 indicates presenilin 1 gene; N135D, asparagine-to–aspartic acid change at codon 135; M139I, methionine-to–isoleucine change at codon 139; M139K, methionine-to-lysine change at codon 139; M139V, methionine-to-valine change at codon 139; I143F, isoleucine-to-phenylalanine change at codon 143; I143T, isoleucine-to-isoleucine change at codon 143; I147I, threonine-to-isoleucine change at codon 147; L153V, leucine-to-valine change at codon 153; and ellipses, not available.
individual mutations may account for a degree of this variation as illustrated by the 2 mutations at codon 143: a nonconservative change (isoleucine to threonine) has a mean AAO of 35 years, whereas a semiconservative change (isoleucine to phenylalanine) has a mean AAO of 55 years. However, this would not account for the variation in AAO seen in some families. For families with an APP mutation, the dose of apolipoprotein E ε4 alleles has been shown to reduce the AAO, but in families with PSEN1 mutations, this effect is absent. Further unidentified genetic factors have been proposed for these families.

It is generally agreed that the neuropathological changes of FAD are indistinguishable from those of sporadic AD, but our patient undergoing neuropathological evaluation also has sufficient Lewy bodies to consider a secondary diagnosis of dementia with Lewy bodies (transitional or limbic type). Although the coexistence of Lewy body and Alzheimer lesions is recognized in sporadic AD, it is more common in FAD. In a neuropathological series of 74 patients with FAD, Lewy bodies were demonstrated in 22%, when α-synuclein immunostaining was used to define them. The Lewy body abnormalities in our patient are negligible compared with the AD changes, and there were no clinical Lewy body symptoms to support the diagnosis in this family. The original Newcastle criteria could not be maintained in the light of α-synuclein immunostaining and have been revised. For these reasons, we believe that a secondary diagnosis of dementia with Lewy bodies cannot be justified.

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