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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O 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.

From the Dementia Research Group, Institute of Neurology (Drs Janssen, Fox, Harvey, and Rossor), the Departments of Neuropathology (Dr Lantos) and Neuroscience (Dr Hanger), Institute of Psychiatry, the Medical Research Council Prion Unit, Department of Neurogenetics, Imperial College School of Medicine (Messrs Beck and Dickinson, Ms Campbell, and Dr Collinge), and the Departments of Clinical Neuropsychology (Dr Cipolotti) and Neuroradiology (Dr Stevens), National Hospital for Neurology and Neurosurgery, London, England.

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; thepons; 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.

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 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.

When her Mini-Mental State Examination 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. Visuoperceptual functions had deteriorated; she scored below the fifth percentile on the silhouette subtest of the VOSP. There was no evidence of frontal executive dysfunction (Weigl Sorting Test). 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 amygdalae 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 neurofilament threads were abundant in the hippocampus and cerebral cortex (Figure 3). In the hippocampus, severe neuronal loss was accompanied by astrogliosis. Superficial status spongiosis and astrogliosis 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 transenthorinal, cingulate, insular, and parietal cortices, and in 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.
Table 1. Clinical Features of Family 177*

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age at Onset, y</th>
<th>Age at Death, y</th>
<th>Duration of Illness, y</th>
<th>First Symptom</th>
<th>Cause of Death</th>
<th>Psychiatric Features</th>
<th>Neurologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:1</td>
<td>NA</td>
<td>65</td>
<td>NA</td>
<td>Unaffected</td>
<td>Myocardial infarction</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>I:2</td>
<td>NA</td>
<td>73</td>
<td>NA</td>
<td>Unaffected</td>
<td>Carcinomatosis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>II:5</td>
<td>35</td>
<td>42</td>
<td>7</td>
<td>Memory</td>
<td>Bronchopneumonia</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>III:2</td>
<td>35</td>
<td>41</td>
<td>6</td>
<td>Memory</td>
<td>Bronchopneumonia</td>
<td>Personality change</td>
<td>. . .</td>
</tr>
<tr>
<td>III:3</td>
<td>36</td>
<td>49</td>
<td>12</td>
<td>Memory</td>
<td>Bronchopneumonia</td>
<td>Myoclonus</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*NA indicates not applicable; ellipses, absent.

Table 2. Neuropsychometry Results in Patient III:3*

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Test Occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R full IQ†</td>
<td>98 72</td>
</tr>
<tr>
<td>WAIS-R verbal IQ†</td>
<td>99 76</td>
</tr>
<tr>
<td>WAIS-R performance IQ†</td>
<td>97 65</td>
</tr>
<tr>
<td>NART‡</td>
<td>102</td>
</tr>
<tr>
<td>RMT words§</td>
<td>43/50 27/50</td>
</tr>
<tr>
<td>RMT faces§</td>
<td>41/50 33/50</td>
</tr>
<tr>
<td>Description naming‖</td>
<td>14/15</td>
</tr>
<tr>
<td>Oldfield Picture Naming Test§</td>
<td>. . . 22/30</td>
</tr>
<tr>
<td>Unusual Views Test#</td>
<td>20/20</td>
</tr>
<tr>
<td>Fragmented letters subtest of VOSP**</td>
<td>20/20</td>
</tr>
<tr>
<td>Silhouettes subtest of VOSP**</td>
<td>. . . 15/30</td>
</tr>
</tbody>
</table>

*Ellipses indicate not performed. WAIS-R indicates Revised Wechsler Adult Intelligence Scale; NART, National Adult Reading Test; RMT, Recognition Memory Test; and VOSP, Visual Object and Space Perception Battery.
†Described in Wechsler.5
‡Described in Nelson and Willison.6
§Described in Warrington.7
‖Described in Coughlan and Warrington.8
¶Described in Oldfield and Wingfield.9
#Described in Warrington and James.10
**Described in Warrington and James.11

Figure 2. Axial T2-weighted magnetic resonance image of patient III:3 showing biparietal atrophy.

Figure 3. Senile plaques, neurofibrillary tangles, and neuropil threads in the temporal cortex. Immunostaining of tau protein (original magnification ×70).

Figure 4. Lewy bodies in the amygdala. Immunostaining of α-synuclein (original magnification ×120).

COMMENT

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 α helix, disrupting the structure and function of PSEN1. The mutations in this cluster are in exon 8, near the PSEN1 cleavage site. Together, these major mutation clusters account for more than 50% of PSEN1 mutations. Most PSEN1 mutations have been missense mutations, leading to the hypothesis that mutant proteins result in disease by means of toxic gain of function.

Unlike other PSEN1 mutation pedigrees, myoclonus was a feature in only 1 patient. Seizures are a well-recognized feature of younger-onset FAD, but were absent in family 177 due to PSEN1 leucine-to-serine change at codon 250 (L250S). 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. The French family with the L153V mutation has not been described in detail, but myoclonus, seizures, and spastic paraparesis were not reported.

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. 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 x30).)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Family Identity</th>
<th>Mean Age at Onset, y</th>
<th>Ethnicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N135D</td>
<td>. . .</td>
<td>35</td>
<td>Mexican American</td>
<td>Crook et al 16</td>
</tr>
<tr>
<td>M139I</td>
<td>AD1674</td>
<td>. . .</td>
<td>American</td>
<td>Boteva et al 17</td>
</tr>
<tr>
<td>M139K</td>
<td>ALZ034</td>
<td>37</td>
<td>French</td>
<td>Dumanchin et al 18</td>
</tr>
<tr>
<td>M139T</td>
<td>CAE010</td>
<td>49</td>
<td>French</td>
<td>Campion et al 19</td>
</tr>
<tr>
<td>M139V</td>
<td>F148</td>
<td>44</td>
<td>English</td>
<td>Alzheimer’s Disease Collaborative Group 14</td>
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<tr>
<td></td>
<td>F206</td>
<td>38</td>
<td>English</td>
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</tr>
<tr>
<td>AD1421</td>
<td>. . .</td>
<td>40</td>
<td>American</td>
<td>Boteva et al 17</td>
</tr>
<tr>
<td></td>
<td>#3</td>
<td>32</td>
<td>German</td>
<td>Finck et al 20</td>
</tr>
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<td></td>
<td>. . .</td>
<td>43</td>
<td>German</td>
<td>Hull et al 21</td>
</tr>
<tr>
<td>I143F</td>
<td>F156</td>
<td>55</td>
<td>English</td>
<td>Rossor et al 22</td>
</tr>
<tr>
<td>I143T</td>
<td>AD/A</td>
<td>35</td>
<td>Belgian</td>
<td>Cruts et al 23</td>
</tr>
<tr>
<td>M146I</td>
<td>. . .</td>
<td>44</td>
<td>Danish</td>
<td>Jorgensen et al 24</td>
</tr>
<tr>
<td></td>
<td>. . .</td>
<td>43</td>
<td>Danish</td>
<td>Gustafson et al 25; Essen-Möller 26</td>
</tr>
<tr>
<td>M146L</td>
<td>FAD4, Tor1.1</td>
<td>40, 43</td>
<td>Italian</td>
<td>Sherrington et al 27</td>
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<tr>
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<td>Okla1</td>
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<td></td>
<td>AR1</td>
<td>39</td>
<td>Argentinian</td>
<td>Morelli et al 28</td>
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<td>1, 2, 3</td>
<td>45, 36, 35</td>
<td>Italian</td>
<td>Sorbi et al 29</td>
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<tr>
<td>M146V</td>
<td>Fin1</td>
<td>36</td>
<td>French</td>
<td>Campion et al 30</td>
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<tr>
<td></td>
<td>Man92/20</td>
<td>40</td>
<td>Finnish</td>
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<tr>
<td></td>
<td>NYS201</td>
<td>37</td>
<td>English</td>
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<td>. . .</td>
<td>American</td>
<td>Cervenakova et al 31</td>
</tr>
<tr>
<td>T147I</td>
<td>ALZ047</td>
<td>42</td>
<td>French</td>
<td>Raux et al 32</td>
</tr>
<tr>
<td>L153V</td>
<td>. . .</td>
<td>36</td>
<td>French</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*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-lysine change at codon 143; I143L, methionine-to-leucine change at codon 146; T147I, 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 within 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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