

Novel Presenilin 1 Mutation (S170F) Causing Alzheimer Disease With Lewy Bodies in the Third Decade of Life

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Background: Cases of early-onset Alzheimer disease (AD) with an autosomal dominant inheritance pattern (familial AD [FAD]) are rare but have greatly advanced our understanding of the molecular pathogenesis of AD. We describe herein a kindred with very early-onset FAD (age, <40 years) with unusual pathological features and a novel mutation in the presenilin 1 (*PSEN1*) gene (S170F) and review the existing literature on very early-onset FAD.

Objective: To analyze the neuropathological and genetic features of a family with onset of AD in the third decade of life.

Design, Setting, and Participants: The proband underwent full clinical assessment and postmortem examination at the Washington University Alzheimer's Disease Research Center, St Louis, Mo. Limited pathological samples and autopsy records of 2 affected family members were available. The proband underwent screening for mutations in genes linked with FAD.

Results: Dementia developed in 3 family members in this kindred at a mean age of 27 years; the proband had myoclonus, seizures, and rigidity, similar to findings in previously described kindreds with *PSEN1* mutations. All 3 family members were confirmed to have AD by neuropathological examination. The proband also had widespread Lewy body pathology in the brainstem, limbic areas, and neocortex; specific staining for Lewy bodies was not performed in the other 2 family members. The proband had a single mutation (S170F) in exon 6 of the *PSEN1* gene, which segregates with disease.

Conclusions: A novel *PSEN1* mutation causes very-early-onset FAD with associated Lewy bodies. To our knowledge, this kindred has the earliest reported onset of pathologically confirmed FAD and dementia with Lewy bodies.

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THE GENETIC AND MOLECULAR mechanisms responsible for Alzheimer disease (AD) are not well understood. Most cases of AD are sporadic and of late onset; a positive family history modestly increases AD risk. The apolipoprotein E4 allele, found in about half of all patients with AD, remains the only confirmed genetic risk factor identified with sporadic late-onset AD.¹ Early-onset AD, defined by onset of dementia at younger than 55 years (60-65 years in some studies), accounts for less than 1% of all AD cases. Some patients with early-onset AD have a family history consistent with autosomal dominant inheritance (familial AD [FAD]). Mutations in the genes encoding the amyloid precursor protein (APP), presenilin 1 (*PSEN1*), and pre-

senilin 2 (*PSEN2*) can be identified in about half of the families with early-onset FAD, with no mutation yet identified in the remainder of families.²⁻⁷ Mutations are found most frequently in *PSEN1*,

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with 144 identified to date.^{8,9} Mutations in the APP gene account for only about 5% of early-onset AD cases, and *PSEN2* gene mutations have been described in only a few kindreds.¹⁰ The age at onset of dementia typically is earlier for families with identified mutations.¹¹ Symptoms manifest earliest in cases linked to *PSEN1* (usually in the fifth decade of life), with a slightly later age at onset in APP-linked cases and even later onset in cases linked to *PSEN2*.^{12,13}

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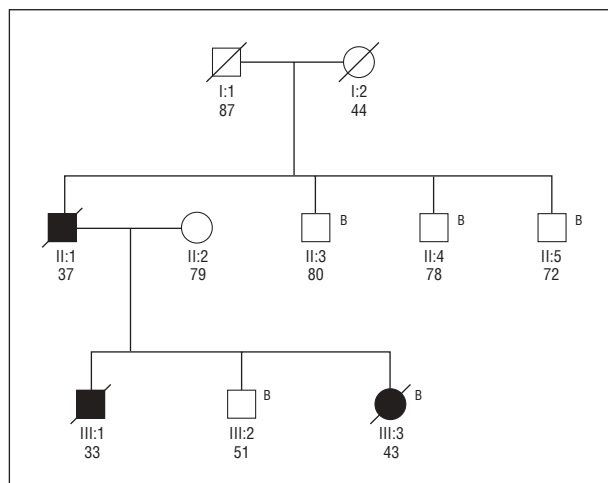


Figure 1. Pedigree of the cases described herein (represented by the filled shapes). Numbers shown below the family designators indicate age at death or age at time of the report. The superscript *B* indicates blood samples were available for genotyping. Circles indicate female; slashes, deceased; and squares, male.

We describe a family with a novel *PSEN1* mutation that is associated with a very early age at onset in FAD and concomitant Lewy body (LB) pathology.

METHODS

CLINICAL EVALUATION

The pedigree is shown in **Figure 1**. Dementia developed in 3 individuals in 2 generations of this family in the third decade of life. The proband (subject III:3) was referred to the Alzheimer's Disease Research Center at Washington University School of Medicine, St Louis, Mo, at 35 years of age. According to standard protocol, the initial evaluation involved a detailed interview with a collateral source (the proband's husband), an examination of the proband, and a review of medical records. Subsequent follow-up was performed annually and included collateral-source interview and examination of the proband at her nursing home. Clinical information for the deceased affected relatives (subjects II:1 and III:1) was obtained by interview of collateral sources and review of available medical records.

NEUROPATHOLOGICAL EXAMINATION

Informed consent for the neuropathological examination was obtained ante mortem in the case of subject III:3. We performed hematoxylin-eosin, Gallyas silver, and Bielschowsky staining and immunohistochemistry for β -amyloid (10D5 at 1:40 000; Athena Diagnostics, Worcester, Mass), paired helical filaments/hyperphosphorylated tau (AT8 at 1:50; PolyMedCo Inc, Cortland Manor, NY), α -synuclein (Zymed clone LB-509 at 1:100; Zymed Laboratories, San Francisco, Calif), and ubiquitin (at 1:8000; East Acres Biologicals, Southbridge, Mass) on cortical, subcortical, brainstem, and cerebellar tissues. Incomplete neuropathological findings for the other affected members were obtained by review of available medical records (subjects II:1 and III:1) and microscopic sections (subject III:1).

GENETIC SCREENING

We extracted DNA from blood or brain tissue using standard procedures. Intronic polymerase chain reaction primers were designed from DNA sequences for the *PSEN1*, *PSEN2*, and *APP* genes and were used to amplify each exon separately from genomic DNA. Product sizes ranged from 400 to 500 base pairs. Purified polymerase chain reaction products were sequenced on both strands using the ABI terminator mix (Perkin Elmer, Foster City, Calif). Products underwent electrophoresis on an ABI automated DNA sequencer, and the electropherograms were analyzed using ABI DNA sequencing analysis software (Navigator version 3.4; Applied Biosystems, Foster City). Details of the polymerase chain reaction primers are available from the authors on request.

RESULTS

CASE REPORTS AND NEUROPATHOLOGY

Subject III:3

The proband (subject III:3) graduated from college with honors, was married without children, and worked at a bank. There was no history of head trauma or toxic exposure. Gradual onset of memory loss began at 26 years of age and progressed such that she was dismissed from her job a year later because of calculation errors and misplaced files. She frequently repeated questions and was unable to balance her checkbook. She often forgot where she parked her car and even whether she had driven it. She purchased unnecessary items. During the next year, she became suspicious, eg, accusing her husband of being her jailer and stealing items (including money) she had misplaced. Word-finding difficulty and trouble completing sentences developed. Frequent falls occurred and she was noted to "toe walk." At 28 years of age, she experienced generalized tonic-clonic seizures and started phenytoin sodium therapy. A nasogastric feeding tube was placed at 30 years of age and she became mute, immobile, and incontinent and was placed in a nursing home at 32 years of age, where she required total care.

At the physical examination at 35 years of age, she was awake with occasional spontaneous movements but was mute and did not respond to commands or stimuli. Muscle tone was increased, with all 4 extremities flexed and rigid; there were no tremors. She had frequent diffuse myoclonus, both spontaneous and provoked by auditory and tactile stimuli. Deep tendon reflexes were increased symmetrically with bilateral extensor plantar reflexes and a snout reflex. She was given a Clinical Dementia Rating^{14,15} score of 3 at this first evaluation.

Her clinical course was marked by recurrent urinary tract infections. Her second evaluation at 36 years of age revealed no verbal output and no voluntary movement with flexion contractures of all 4 extremities. Her clinical state slowly deteriorated. She died at 43 years of age of a pulmonary embolus, 17 years after onset of disease.

Gross examination showed an atrophic brain weighing 600 g with severe generalized atrophy except for relative sparing of the cerebellum. Gray and white matter structures were involved, with knife-edge sulci and se-

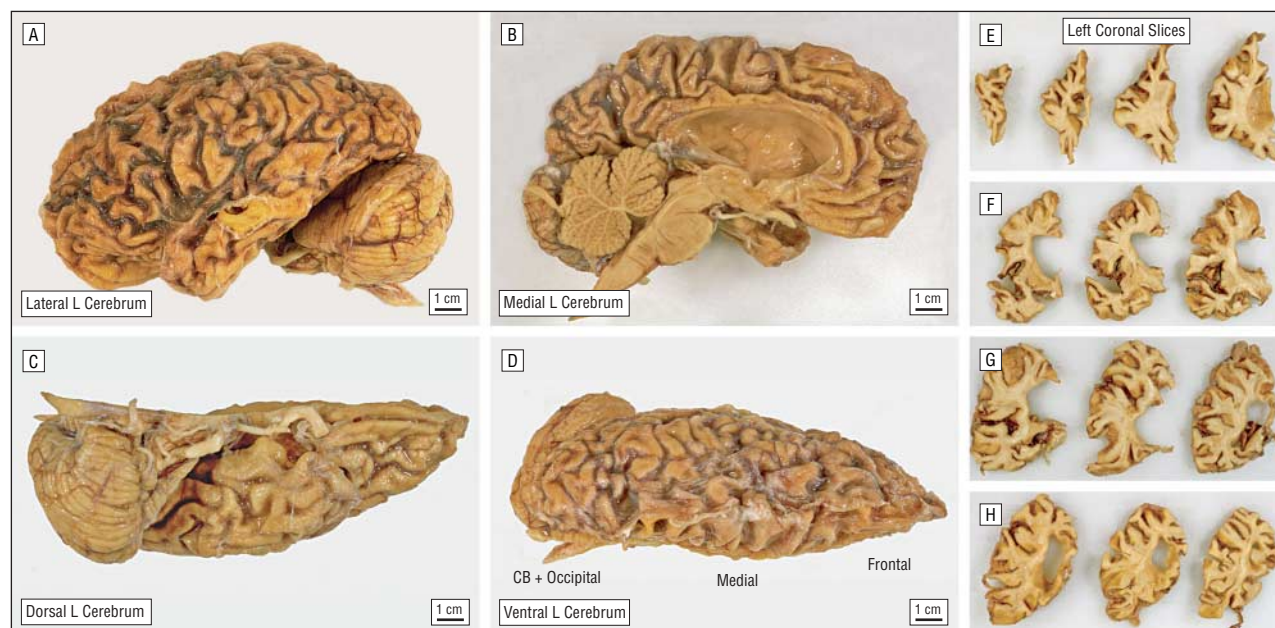


Figure 2. Gross pathological findings for subject III:3. A through D, Fixed brain was sectioned as indicated. E through H, Coronal slices (1 cm thick), anterior to posterior. L indicates left; CB, cerebellum.

vere thinning of the corpus callosum (**Figure 2**). The substantia nigra and locus coeruleus were pale. Microscopic examination of hematoxylin-eosin- and modified Bielschowsky silver-stained sections revealed severe neuronal loss with extensive neuritic plaques and neurofibrillary tangles involving the entire neocortex (Braak neurofibrillary and amyloid stages VI-C¹⁶; **Figure 3A**). β -Amyloid and paired helical filament tau immunohistochemistry results showed massive deposition of amyloid plaques, significant amyloid angiopathy, and numerous neurofibrillary tangles and tau-immunopositive neuropil threads (Figure 3B-D). The modified Bielschowsky silver staining of white matter revealed severe axonal loss (Figure 3E). There was widespread plaque deposition with neurofibrillary tangles and neuropil threads in the hippocampus, with extensive involvement of area CA1 (cornu ammonis 1) (**Figure 4A-B**). Moderate to severe neuritic plaques were observed in the molecular layer of the dentate fascia and area CA3; area CA4 showed widespread loss of pyramidal cells but no senile plaques. Ubiquitin-positive oval intraneuronal inclusions were observed in the dentate fascia; these inclusions did not stain with Gallyas silver or with tau or α -synuclein antibodies (Figure 4D; other data not shown). The subiculum (Figure 4C), presubiculum, parasubiculum, and entorhinal cortex contained numerous neuritic plaques and neurofibrillary tangles, spanning the “silent” zone, where little pathology is seen in less severe cases of sporadic AD. The basal ganglia demonstrated severe neuronal loss, reactive gliosis, and neurofibrillary inclusions. Pigmented neurons were only rarely present in the substantia nigra and locus coeruleus.

Immunohistochemical screening with hematoxylin-eosin and the α -synuclein monoclonal antibody revealed classic LBs within the substantia nigra and widespread massive deposits of cortical LBs and Lewy neurites (including mega ones) in the midbrain, pons (locus coe-

ruleus), nucleus basalis of Meynert, amygdala, entorhinal and perirhinal cortices, hippocampus (**Figure 5A-C**), and prefrontal, superior, and middle temporal and anterior cingulate cortices (Figure 5D-E). All regions contained far more than 5 cortical LBs per section, often attaining 10 to 13 cortical LBs/mm². The McKeith 1996 international consensus workshop criteria for neocortical dementia with LBs¹⁷ were amply fulfilled pathologically to establish a consensus diagnosis of neocortical dementia with LBs.

Subject III:1

Development of progressive memory loss developed in the proband's brother (subject III:1) starting at 27 years of age. He was diagnosed as having AD at 28 years of age. He lost his job owing to forgetfulness and complained of forgetting the daily whereabouts of his children. During a hospitalization, he repeatedly introduced himself to the same nurse. He forgot by the afternoon that a medical procedure had been performed earlier in the day. At 29 years of age, the neurological examination was unremarkable, but the neuropsychological examination revealed difficulty with verbal short-term memory and verbal abstract reasoning, although the Wechsler Adult Intelligence Scale¹⁸ full-scale, verbal, and performance IQ scores were all within the reference range. Long-term memory was intact, but integration of new information was significantly impaired as tested by the Wechsler Memory Scale.¹⁹ He gradually became bedridden, mute, and unresponsive and died at 35 years of age, 8 years after disease onset; an autopsy was performed at another institution.

The autopsy cited atrophic frontal and temporal lobes without any lobar or lateral predominance. Only Bodian silver-stained slides from this case were available for our review; widespread cortical and hippocampal neurofibril-

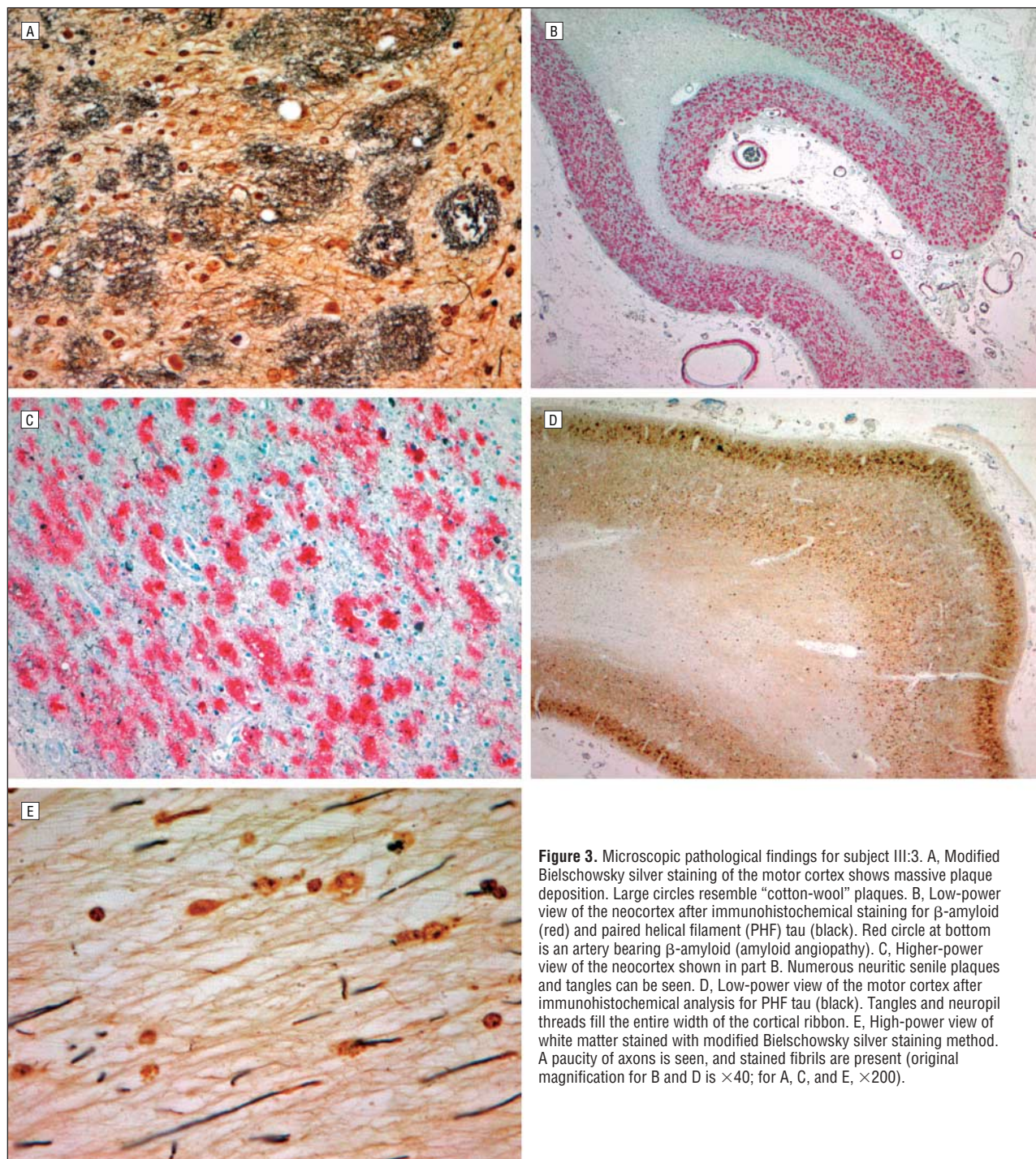


Figure 3. Microscopic pathological findings for subject III:3. A, Modified Bielschowsky silver staining of the motor cortex shows massive plaque deposition. Large circles resemble "cotton-wool" plaques. B, Low-power view of the neocortex after immunohistochemical staining for β -amyloid (red) and paired helical filament (PHF) tau (black). Red circle at bottom is an artery bearing β -amyloid (amyloid angiopathy). C, Higher-power view of the neocortex shown in part B. Numerous neuritic senile plaques and tangles can be seen. D, Low-power view of the motor cortex after immunohistochemical analysis for PHF tau (black). Tangles and neuropil threads fill the entire width of the cortical ribbon. E, High-power view of white matter stained with modified Bielschowsky silver staining method. A paucity of axons is seen, and stained fibrils are present (original magnification for B and D is $\times 40$; for A, C, and E, $\times 200$).

lary tangles and neuritic senile plaques, sufficient to establish a confident diagnosis of AD, were present.

Subject II:1

The father (subject II:1) of the other 2 affected individuals began to experience memory loss and decreased word enunciation at 27 years of age. He was discharged from his position as a military officer and within a year was unable to hold even minimally demanding jobs. He wrote duplicate checks and demonstrated poor judgment in financial mat-

ters. By report, physical examination showed right central seventh cranial nerve palsy, increased deep tendon reflexes on the left side, dysarthria, and ataxia. At 36 years of age, he experienced a generalized tonic-clonic seizure. He died at 37 years of age, 9 years after disease onset. An autopsy was performed; only the report is now available. The report indicated that there was severe diffuse cerebral atrophy. Marked gliosis and neocortical neuronal loss were observed on microscopic sections. Staining for neurofibrillary tangles and senile plaques was not performed. The post-mortem diagnosis was AD.

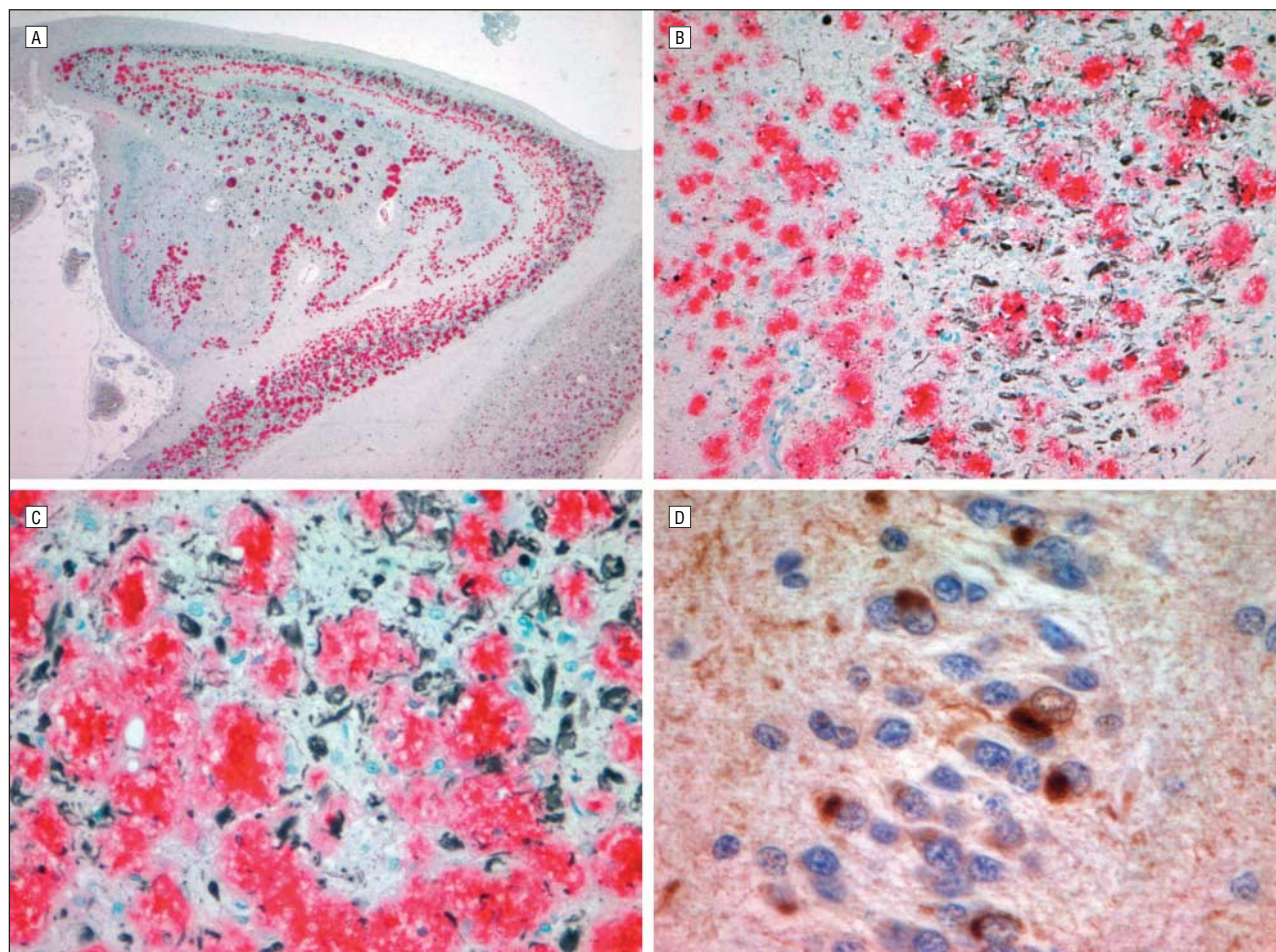


Figure 4. Hippocampal pathological findings for subject III:3. A, Low-power view of the hippocampus and surrounding structures after immunohistochemical staining for β -amyloid (red) and paired helical filament (PHF) tau (black). The β -amyloid outlines the CA (cornu ammonis) fields, dentate fascia molecular layer, subiculum, and adjacent allocortex forming the collateral sulcus at the far right of this panel. B, Higher-power view of area CA1 stained for β -amyloid (red) and PHF tau (black). C, Higher-power view of the subiculum stained for β -amyloid (red) and PHF tau (black). D, Ubiquitin immunohistochemical analysis of the dentate fascia showing ubiquitin-positive, oval cytoplasmic inclusions (brown). These inclusions were not stained by Gallyas silver stain or by tau or α -synuclein antibodies (data not shown) (original magnification for A is $\times 40$; for B-D, $\times 200$).

GENETICS

A single base-pair substitution (C \rightarrow T), resulting in an amino acid change from serine to phenylalanine, was found at codon 170 of the *PSEN1* gene in the proband (subject III:3). This mutation was not present in the unaffected siblings of the proband's father (subjects II:3, II:4, and II:5) or in the unaffected sibling of the proband (subject III:2). The mutation was confirmed in DNA extracted from the blood and brain samples of the proband; no material from the other 2 affected family members was available for genetic analysis. No mutations were found in the coding region of the *PSEN2* gene or in exons 16 and 17 of the *APP* gene. The proband was homozygous for the apolipoprotein E3 allele.

COMMENT

We describe 3 family members in 2 generations with clinical features consistent with early-onset AD. Neuropathological examination in these cases confirmed the diagnosis of AD. The 3 affected individuals developed gradual

onset of memory loss beginning at 26 to 27 years of age, with an average duration of disease of 11 years before death. The clinical courses were complicated by myoclonus, seizures, and extrapyramidal signs. Genetic analysis of the proband (subject III:3) demonstrated a single base-pair change in the region of the *PSEN1* gene encoding transmembrane domain III; to our knowledge, this mutation has not been previously described. Two mutations at codon 169 (S169L and S169P) also result in a change from an uncharged polar to a nonpolar amino acid and cause very-early-onset AD with myoclonus.²⁰⁻²³

We reviewed the literature to identify reported cases with 3 or more affected family members with very early-onset AD, empirically defined here as a mean age at onset of 40 years or younger. We found 106 individuals in 18 families (**Table 1**). Mutations were found in all 17 families with genetic data available; 15 families had *PSEN1* mutations and 2 families³⁸ had *APP* mutations. The clinical phenotype of these very early-onset cases is summarized in Table 1. Myoclonus was present in all but 1 family with sufficient clinical information to determine its presence or absence and was typically diffuse, although in 1 case it

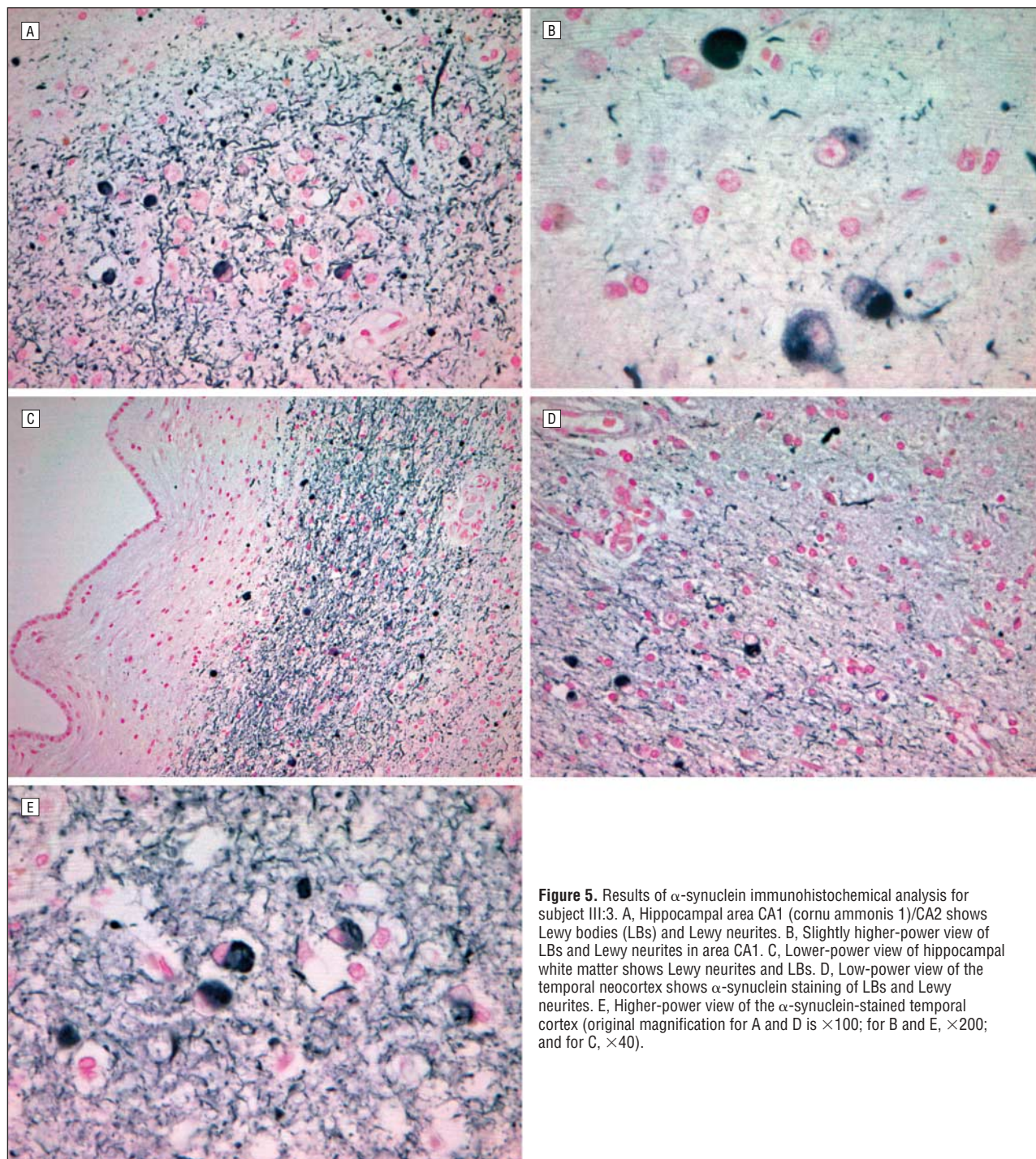


Figure 5. Results of α -synuclein immunohistochemical analysis for subject III:3. A, Hippocampal area CA1 (cornu ammonis 1)/CA2 shows Lewy bodies (LBs) and Lewy neurites. B, Slightly higher-power view of LBs and Lewy neurites in area CA1. C, Lower-power view of hippocampal white matter shows Lewy neurites and LBs. D, Low-power view of the temporal neocortex shows α -synuclein staining of LBs and Lewy neurites. E, Higher-power view of the α -synuclein-stained temporal cortex (original magnification for A and D is $\times 100$; for B and E, $\times 200$; and for C, $\times 40$).

was described as irregular, asymmetric, and asynchronous.³² Generalized seizures were reported in 9 families. Pyramidal signs (eg, increased tone, heightened deep tendon reflexes, and Babinski signs) were reported in 10 families. Spastic paresis occurred late in several families and was reported at onset in 3 additional families with a “cotton-wool” plaque pathology.²⁴ Extrapyrarnidal signs were reported in only 3 families.²⁶ Although other families and individuals with AD associated with *PSEN1* mutations with an age at onset younger than 40 years have been described, insufficient clinical information or too few af-

ected family members precluded inclusion in this analysis.^{7,11,22,30,39-46} The APPT714I mutation has also been reported to cause dementia with onset at less than 40 years of age, but previous reports did not include sufficient clinical information for inclusion.⁴⁷

The clinical features of the family presented here closely resemble those reported for very early-onset AD linked to *PSEN1*, as summarized in Table 1, with myoclonus, epilepsy, and pyramidal signs. These signs have been described in late-onset sporadic AD and in older individuals with early-onset AD, but are less common in those

Table 1. Clinical Features in Very Early-Onset AD*

Source	Mutation	AAO, y	Initial Symptom(s)	Myoclonus	Seizure	Extrapyramidal Signs	Pyramidal Signs
Houlden et al, ²⁴ 2000 (family EB)	<i>PSEN1</i> Delta Ile83/Met84	36	Spastic paraparesis	NR	NR	NR	Y
Wisniewski et al, ²⁵ 1998	<i>PSEN1</i> Pro117Leu	30	Memory loss, mood changes, disorientation	Y	N	NR	NR
Martin et al, ²⁶ 1991 (family A)	<i>PSEN1</i> Ile143Thr	35	Memory loss, irritability, speech disturbance	Y	Y	Y	Y
Morelli et al, ²⁷ 1998	<i>PSEN1</i> Met146Leu	39	Memory loss, behavioral changes	Y	Y	NR	NR
Ezquerro et al, ²⁸ 2000	<i>PSEN1</i> Leu166Arg	38	Memory loss, aphasia, akinesia	N	NR	NR	NR
Ezquerro et al, ²⁰ 1999	<i>PSEN1</i> Ser169Pro	33	Memory loss, irritability, slovenliness	Y	N	NR	NR
Goldman et al, ²⁹ 2002	<i>PSEN1</i> Gly206Val	35	Memory loss, disorientation	NR	NR	NR	NR
Miklosy et al, ³⁰ 2003	<i>PSEN1</i> Gln222His	Late 30s	Memory loss	Y	NR	NR	NR
Houlden et al, ³¹ 2001	<i>PSEN1</i> Met223Val	33	Memory loss, trouble at work	Y	Y	N	NR
Campion et al, ³² 1996	<i>PSEN1</i> Leu235Pro	32	Memory loss, language impairment	Y	Y	NR	Y
Ikeda et al, ³³ 1996	<i>PSEN1</i> Ala260Val	40	Memory loss, personality changes	Y	Y	N	Y
Martin et al, ²⁶ 1991	<i>PSEN1</i> Gly384Ala	35	Memory loss	Y	Y	Y	Y
Devi et al, ³⁴ 2000	<i>PSEN1</i> Ala434Cys	30	Mood changes, memory loss	Y	Y	NR	Y
Houlden et al, ²⁴ 2000 (family D)	<i>PSEN1</i> Pro436Gly	29	Spastic paraparesis	NR	NR	NR	Y
Ishikawa et al, ³⁵ 2005	<i>PSEN1</i> 440 deletion	35	Parkinsonian symptoms, then dementia	NR	Y	Y	Y
Edwards-Lee et al, ³⁶ 2005	APPT714I	30s	Memory loss, visual perceptual changes	Y	Y	N	Y
Mangone et al, ³⁷ 1995; Murrell et al, ³⁸ 2000	<i>APP</i> Val717Leu	39	Memory loss, language impairment, personality change	Y	N	N	N
Houlden et al, ²⁴ 2000 (family CO)	No DNA analysis	31	Spastic paraparesis and/or memory loss	NR	NR	NR	Y

Abbreviations: AAO, average age at onset for affected family members; AD, Alzheimer disease; *APP*, amyloid precursor protein gene; N, feature was specifically stated as not present; NR, not reported (ie, feature was not mentioned in the published report); *PSEN1*, presenilin 1 gene; Y, feature was present.

*We reviewed published cases of familial AD (≥ 3 affected family members) with an AAO at younger than 40 years. Cases with insufficient clinical information (eg, reports that include DNA sequence data but little clinical information or a kindred with <3 affected family members) were not included (see "Comment" section for references).

cases. In cases of very early-onset AD, these features tend to appear earlier in the clinical course than is typical for late-onset AD.

Pathological information was available for 10 of the families presented in Table 1; all of these families had mutations in the *PSEN1* gene (**Table 2**). The amount of material available for neuropathological examination and the staining techniques reported were variable, but features consistent with AD were found in all cases, including neuronal loss, gliosis, and senile plaques and neurofibrillary tangles throughout the neocortex and hippocampus. At least a modest degree of amyloid angiopathy was reported in all but 1 family.²⁰ In 1 case, round cytoplasmic inclusions that stained with silver and were immunoreactive with anti-ubiquitin antibodies were observed in neurons in the dentate gyrus. These inclusions were found nowhere else and were described as "Pick like"; tau immunostaining was not performed.³³ The ubiquitin-positive inclusions in the den-

tate fascia seen in subject III:3 described here (Figure 4D) did not stain with the Gallyas silver stain or with tau antibodies, and thus were not Pick bodies. Tau- and silver-positive Pick bodies have been reported in at least 1 family with very early-onset AD associated with a *PSEN1* mutation.⁴⁹ Ubiquitin-positive tau-negative inclusions in the dentate fascia have been reported in frontotemporal dementia and amyotrophic lateral sclerosis, but have not typically been associated with AD. Further study will be required to determine whether such lesions will be a common feature of AD pathology when ubiquitin immunohistochemistry is performed.

In 1 very early-onset case with typical AD pathology reported by Revesz et al,⁴⁸ in which immunohistochemistry for ubiquitin and α -synuclein was used, numerous LBs were observed in the substantia nigra and sparse LBs were detected in the cingulate, temporal, and insular cortices (case 3). Cortical and nigral LBs, in addition to neu-

Table 2. Additional Neuropathological Features in Very-Early-Onset AD*

Source	Mutation	AAO, y	AAD, y	Angiopathy	Cortical and Nigral LBs	Other Findings
Wisniewski et al, ²⁵ 1998	<i>PSEN1</i> Pro117Leu	30	34	Congophilic		
Martin et al, ²⁶ 1991	<i>PSEN1</i> Ile143Thr	35	41	Congophilic		Hirano bodies and granulovacuolar degeneration in hippocampus
Mangone et al, ²⁷ 1995; Morelli et al, ²⁷ 1998	<i>PSEN1</i> Met146Leu	39	48	Mild amyloid deposition in vessels		
Ezquerro et al, ²⁰ 1999	<i>PSEN1</i> Ser169Pro	33	38	NR		Neuronal lipofuscin
Revesz et al, ⁴⁸ 1997 (case 3); Houlden et al, ³¹ 2001	<i>PSEN1</i> Met223Val	28-34	34-37	Amyloid	Nigral LBs frequent; scarce cortical LBs (ubiquitin)	
Campion et al, ³² 1996	<i>PSEN1</i> Leu235Pro	32	36	Amyloid		
Ikeda et al, ³³ 1996	<i>PSEN1</i> Ala260Val	40	54	Amyloid		Pick body
Martin et al, ²⁶ 1991	<i>PSEN1</i> Gly384Ala	35	42	Amyloid		
Portet et al, ⁴⁵ 2003	<i>PSEN1</i> Met223Leu	28		NR; biopsy sample only		
Devi et al, ³⁴ 2000	<i>PSEN1</i> Ala434Cys	30	46	Amyloid		Hirano bodies
Ishikawa et al, ³⁵ 2005	<i>PSEN1</i> 440 deletion	35	49	Amyloid	Nigral and cortical LBs	Cotton-wool plaques

Abbreviations: AAD, average age at death; AAO, average age at onset for affected family members; AD, Alzheimer disease; *APP*, amyloid precursor protein gene; LBs, Lewy bodies; NR, not reported (ie, feature was not mentioned in published report); *PSEN1*, presenilin 1 gene.

*We reviewed published neuropathological data for cases of familial AD (≥ 3 affected family members) with an AAO at less than 40 years (same as shown in Table 1). Not all cases presented in Table 1 included sufficient neuropathological information for inclusion here. Cases with insufficient clinical information (eg, reports that included DNA sequence data but little clinical information) were not included. Information on LB pathology is included only for the 1 case in which ubiquitin staining was performed. The other reports used hematoxylin-eosin staining only, so LBs could have escaped detection.

rofibrillar plaques and tangles, were also detected in a Japanese family with very early-onset-dementia with parkinsonism.³⁵ Lewy bodies were also detected in the substantia nigra and cortex in 1 of 3 single cases with the cotton-wool plaque variant of AD, as reported by Yokota et al⁵⁰; their patient (case 3) presented with parkinsonian symptoms. The hematoxylin-eosin–based assessment of LBs used in the pathological examination of the other cases may have failed to detect LBs that might have been observed with ubiquitin or α -synuclein immunohistochemistry.⁵¹

Lewy body pathology is frequently observed in brains with FAD and sporadic late-onset AD. In the largest series to date in which ubiquitin staining was used, LBs were observed in the amygdala in more than 60% of FAD cases and in the periamygdaloid cortex in almost 50%. Lewy bodies were less frequent in the middle frontal cortex (13%) and were reported in the substantia nigra in only 13% of FAD cases.⁵² In contrast to the predominantly subcortical distribution of LBs in that series,⁵² the very early-onset case reported here had widespread neocortical LB pathology. Most cases analyzed in the earlier studies had onset of disease at greater than 40 years of age. Additional studies will be required to determine whether widespread LB pathology is also a common feature of very early-onset FAD, or whether the frequency or location of coexisting LB pathology is affected by apolipoprotein E genotype, the disease-causing mutation, or disease duration.

Although we had material available to confirm the presence of the mutation in only 1 affected family member, the consistent clinical and neuropathological features in this family strongly suggest that all affected members share the same underlying genetic mutation. The pedigree is consistent with autosomal dominant inheritance with high penetrance, similar to the inheritance pattern observed for AD-related mutations in the *APP*, *PSEN1*, and *PSEN2* genes. Although the studies we cited in this section and other studies in the literature do not provide a representative sample of very early-onset AD, it is striking that mutations in *PSEN1* or *APP* were found in all the families with very early-onset AD for which genetic information was available (Table 1), including the pedigree presented here. Undiscovered loci also may be associated with FAD, but the present case and the literature suggest that most cases with onset at younger than 40 years (very early-onset AD) and a family history consistent with autosomal dominant inheritance will be associated with a mutation in *PSEN1* or, less commonly, *APP*.

The pathological features described in the literature and in the proband here are similar to those seen in late-onset AD of prolonged duration and suggest that early-onset AD and sporadic AD share a very similar neuropathological profile, despite differences in genetics and clinical presentation. This family provides an additional example of the coexistence of AD and LB pathology in early-onset AD. We will have a clearer understanding of the prevalence of LB

pathology in very early-onset AD as ubiquitin and α -synuclein immunohistochemistry are used more frequently. Understanding the contribution of these pathological features to the pathogenesis of the clinical symptoms and unraveling the interactions between β -amyloid and α -synuclein will require further study.

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