Phenotypic similarities between late-onset autosomal dominant and sporadic Alzheimer disease: A single-family case-control study

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Abstract

Importance—The "amyloid hypothesis" posits that disrupted amyloid-beta (Aβ) homeostasis initiates the pathological process resulting in Alzheimer disease (AD). Autosomal dominant Alzheimer disease (ADAD) has an early symptomatic onset and is caused by single gene mutations that result in overproduction of $A\beta_{42}$. To the extent that "sporadic" late-onset Alzheimer disease (LOAD) also results from dysregulated $A\beta_{42}$, the clinical phenotypes of ADAD and LOAD should be similar when controlling for the effects of age.

Objective—To use a family with late-onset ADAD caused by a *presenilin 1* (*PSEN1*) mutation to mitigate the potential confound of age when comparing ADAD and LOAD.

Design—Case-control study of a family with late-onset ADAD and individuals with histopathologically-proven LOAD.

Setting—The Knight Alzheimer Disease Research Center, Washington University, St Louis, and other National Institutes of Aging-funded Alzheimer Disease Centers in the United States.

Participants—Ten *PSEN1 A79V* mutation carriers from multiple generations of a family with late-onset ADAD (median age-at-onset, 75.0 [63–77] years) and 12 noncarrier family members, followed at the Knight Alzheimer Disease Research Center (1985–2015); and 1115 individuals with neuropathologically confirmed LOAD (median age-at-onset, 74.0 [60–101] years) from the National Alzheimer Coordinating Center database (09/2005-12/14).

Main Outcome and Measure—Planned comparison of clinical characteristics between cohorts, including age at symptomatic onset, associated symptoms and signs, rates of progression, and disease duration.

Results—Seven (70%) mutation carriers developed AD dementia, while three are yet asymptomatic in their 7th and 8th decades of life. No differences were observed between mutation carriers and individuals with LOAD concerning age at symptomatic onset, presenting symptoms and duration, and rate of progression of dementia. Early emergence of comorbid hallucinations and delusions were observed in 57% of individuals with ADAD versus 19% of individuals with LOAD (p=.03). Three of twelve (25%) noncarriers from the *PSEN1 A79V* family are potential phenocopies as they also developed AD dementia (median age at onset=76.0 years).

Conclusions and Relevance—In this family, the amyloidogenic *PSEN1 A79V* mutation recapitulates the clinical attributes of LOAD. Previously reported clinical phenotypic differences between individuals with ADAD and LOAD may reflect age- or mutation-dependent effects.

Introduction

A central tenet of the "amyloid hypothesis" is that accumulation and aggregation of insoluble amyloid beta peptide ($A\beta_{42}$) represents a critical, causative step in the pathogenesis of Alzheimer disease (AD).[1] Perhaps the strongest supporting evidence for the amyloid hypothesis is the finding that rare, dominantly-inherited pathogenic mutations in the *amyloid precursor protein (APP), presenilin 1* (*PSEN1*), and *presenilin 2 (PSEN2)* genes lead to clinically-symptomatic autosomal dominant Alzheimer disease (ADAD) by enhancing the conversion of APP to amyloidogenic $A\beta_{42}$.[1–5] Longitudinal analyses of cohorts of individuals with ADAD have informed the understanding of the clinical and paraclinical disease phenotypes resulting from disrupted cerebral $A\beta_{42}$ metabolism.[6,7] However, compared with sporadic late-onset AD (LOAD), the symptomatic onset of ADAD usually begins at a much earlier age (46.2 versus 72.0 years).[7,8] Also, ADAD may be characterized by clinical features that are unusual in LOAD, including pyramidal signs, hypo/hyperkinetic movement disorders, ataxia, and early myoclonus and seizures.[9–18] Additional differences in the pattern of cerebral $A\beta_{42}$ deposition are reported in some ADAD cases, including [6,16,19,20] higher $A\beta_{42}$ burden and greater densities of neurofibrillary tangles;[21–23] increased $A\beta_{42}$ deposition within the cerebellum[24–26] and basal ganglia;[19,20]; and higher prevalence of cerebral amyloid angiopathy and large diffuse so-called "cotton wool" plaques.[12,22,24,27] Such clinical and pathological differences may challenge whether findings from studies of early-onset ADAD, including current trials of anti-amyloid therapies,[28] can be extrapolated to the understanding of the far more common LOAD.[29,30] Clinical differences may also be interpreted to suggest that ADAD and LOAD are etiologically distinct.

A pathogenic *PSEN1 A79V* mutation was identified in members of a family followed at the Knight Alzheimer Disease Research Center (ADRC) who developed late-onset AD dementia, with symptoms beginning in the 7th and 8th decades of life, and who were initially presumed to have sporadic LOAD.[31] The *PSEN1 A79V* mutation is known to cause early-onset ADAD in other families.[11,32,33] *PSEN1* knockout cells transfected with the *A79V* mutant *PSEN1* showed significantly increased $A\beta_{42}$ secretion, confirming the amyloidogenic potential of this mutation.[31] Reports of individuals with late-onset ADAD are rare[16,33,34] but offer the opportunity to mitigate the confound of age in comparisons with LOAD. Because dysregulation of $A\beta_{42}$ metabolism appears central to both ADAD and LOAD,[29,30,35] we hypothesized that the clinical characteristics of our cohort of *PSEN1 A79V* mutation carriers (MCs) with late-onset ADAD would overlap with those of LOAD.

Methods

Participant identification and recruitment

Twenty-two members of a family now known to carry the *PSEN1 A79V* mutation were research participants in longitudinal studies at the Knight ADRC across a 30 year period (1985–2015). Ten of these 22 individuals were *PSEN1 A79V* MCs. MCs were clinically assessed with semi-structured interviews with a knowledgeable collateral source and with the symptomatic individual, and detailed neurological examinations were performed on the individual. The remaining two MCs were not examined; history was obtained through

interviews with a reliable collateral source. Dementia severity was determined at each assessment with the Clinical Dementia Rating (CDR),[36] a global dementia rating scale that determines the presence or absence of dementia, rates dementia severity when present, and provides a composite measure of dysfunction across six cognitive and functional domains. Summation of scores across these domains yields the CDR Sum of Boxes score (CDR-SB), which can be used longitudinally to quantify AD progression.[37] All staff involved in assessments were blinded to mutation status. All studies were approved by the Washington University School of Medicine Human Studies Committee. Informed consent was obtained from all research participants, including permission for autopsy.

Comparative data from deceased individuals with LOAD was obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS)[38] and Neuropathology Data Set (NPDS), including participants assessed from September 2005 to December 2014 from 34 current and past National Institute on Aging (NIA) Alzheimer Disease Centers. NACC data were selected to provide a national representation of LOAD. Individuals were included from NACC if they met the following criteria: (1) neuropathologic assessment that yielded an "intermediate" or "high" probability of causing AD dementia;[39] (2) UDS data for at least one clinical visit preceding death; and, (3) a diagnosis of AD dementia at their last clinical assessment, with age-at-symptomatic onset (CDR 0.5) 60 years. AD neuropathologic change was based on a modification of the NIA-AA criteria for neuropathologic AD "ABC score",[39] reported previously.[40,41]

The phenotypes of *PSEN1 A79V* MCs were compared with those of LOAD across predetermined clinical measures. Demographic details were reported at the time of first assessment for all individuals, including age, gender and education. Dementia features were extrapolated from the UDS for NACC individuals, and from the UDS recorded within the Knight ADRC research records for *PSEN1 A79V* family members assessed since implementation of the UDS (i.e., 2005).[38] Assessed features included dementia mode of symptom onset (i.e., gradual, subacute, abrupt, other); presenting symptom(s) of dementia (i.e., impairment of memory, orientation, language, visuospatial function, executive function, attention, other); rate of dementia progression, as operationalized by annualized change in CDR-SB); and duration from symptomatic onset to death. Similarly, the prevalence of associated symptoms, signs, and comorbidities in individuals with very mild (CDR 0.5) and mild (CDR 1.0) dementia were determined from review of UDS data for all participants assessed since 2005. The prevalence of depressive symptoms was estimated based on clinician reporting of active depression (UDS Form D1: Clinician Diagnosis) and/or the presence of depressive symptoms for two weeks or more in the past year (UDS Form B9, Clinician Judgement of Symptoms). "Psychiatric symptoms or signs" were deemed present when hallucinations (visual or auditory) or delusions were reported by assessing clinicians (UDS Form B9: Clinician Judgement of Symptoms), or when severe agitation was noted within the month preceding the clinical assessment (UDS, Neuropsychiatric Inventory Questionnaire[42]). Language deficits, visuospatial impairment, and parkinsonism were inferred from the UDS Form B9 (Clinician Judgement of Symptoms) or D1 (Clinician Diagnosis). A history of recent/active seizures was extracted from the UDS Form A5 (Subject Health History). In Knight ADRC participants assessed prior to 2005, clinical information was derived through direct review of research records, including detailed

interviews with knowledgeable collateral sources who were directly asked about the presence of symptoms, signs and comorbidities associated with dementia, and neurological examinations performed on participants. Apolipoprotein E (*APOE)* ε4 allele status was reported for NACC participants, and determined within the Knight ADRC Genetics Core for *PSEN1 A79V* MCs.

Neuropathology

By the end of 2015, five *PSEN1 A79V* MCs with late-onset ADAD had died; by December 31, 2015 all had brain autopsy. Autopsies were limited to the removal of the brain. Four of these cases were examined at the Knight ADRC; the fifth case was examined at an outside site. The four Knight ADRC brains were examined macroscopically, tissue blocks dissected, and histological stains and immunohistochemistry applied following established protocols.[43] Formalin-fixed, paraffin wax-embedded tissue blocks representing 16 areas were taken, including the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobe (angular gyrus), occipital lobe (to include the calcarine sulcus and peristriate cortex), anterior cingulate gyrus at the level of the genu of the corpus callosum, posterior cingulate gyrus and precuneus at the level of the splenium, amygdala and entorhinal cortex, hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus, striatum (caudate nucleus and putamen) at the level of the anterior commissure, lentiform nuclei (globus pallidus and putamen), thalamus and subthalamic nucleus, midbrain, pons, medulla oblongata, cerebellum with dentate nucleus, and spinal cord. Sections were stained with hematoxylin and eosin and a modified Bielschowsky silver impregnation. Immunohistochemistry was performed using the following antibodies: Aβ (10D5; Eli Lilly, Indianapolis, IN, USA), phospho-tau (PHF1; a gift of Dr. P. Davies), phospho-α-synuclein (phospho-α-synuclein (Ser129); Cell Applications, Inc., San Diego, CA, USA), and phospho-TDP-43 (Cosmo Bio USA, Inc., Carlsbad, CA, USA). The National Institute on Aging-Alzheimer's Association criteria for the neuropathologic diagnosis of AD were applied.[39]

Statistical Analysis

Clinical variables from *PSEN1 A79V* MCs and individuals with LOAD were summarized using descriptive statistics. Continuous numerical variables were compared using the non-parametric Mann-Whitney U-test. Categorical data was compared using Fisher's exact test. The relationship between *APOE ε4* carrier status and age at symptomatic onset (AAO) was considered through a Kaplan-Meier survival analysis. Overall differences in survival were assessed using the Mantel-Cox (log-rank) statistic. Statistical analyses were conducted using statistical software (IBM SPSS Statistics 23, IBM Corporation; and R Statistical Computing Software, www.r-project.org). Statistical significance was reported when $p<0.05$.

Results

Ten of 22 genotyped family members were *PSEN1 A79V* MCs (45% carrier rate). All individuals were part of a single multigenerational family of European ancestry living in the United States. All spoke English as their primary language. MCs underwent a median of 2.5 [1–9] annual research evaluations, across 0 to 11.6 years. Seven of the MCs developed

progressive cognitive impairment due to AD dementia, with a median AAO of 75.0 [63–77] years. The remaining 3 MCs (all 60 years-old at their last assessment) still were cognitively normal (CDR 0) by December 31, 2015. Clinical information from 1115 participants with LOAD was obtained from the NACC for comparison. Participants with LOAD had a median AAO of 74 [60–101] years. Considerable overlap was observed in AAO, disease duration, and annualized rate of dementia progression between *PSEN1 A79V* MCs and individuals with LOAD (Figure 1).

Demographic characteristics; dementia features; associated symptoms, signs and comorbidities; and *APOE* allele status are reported for individuals with ADAD and LOAD (Table 1). Only educational attainment was lower in the ADAD cohort. Dementia most commonly presented insidiously, with a gradually progressive course, featuring memory loss as the presenting symptom in the vast majority of individuals. The early emergence of hallucinations and delusions distinguished *PSEN1 A79V* MCs from individuals with LOAD, occurring in 57% (4/7) of MCs with very mild or mild AD dementia, but in only 19% (137/706) of individuals with LOAD (p=.03). In 3 MCs, mild psychoses was noted concurrent with presenting symptoms of memory loss, manifesting with paranoid delusions in two individuals (suspicions that others were stealing money or food, in two MCs), and non-threatening complex auditory hallucinations of a baby crying in one MC. The remaining affected MC developed psychosis 3 years following dementia onset, manifesting with a non-threatening delusion that someone else was in the room. An additional affected MC experienced severe agitation/aggression requiring hospitalization and titration of antipsychotic medications 3 years after dementia onset. The remainder of clinical features were similarly distributed between populations, including depressive symptoms, language deficits, visuospatial impairment, parkinsonism and seizures. There were no differences in the frequency of *APOE ε4* carriers between groups, and a survival analysis showed no effect of *APOE ε4* carrier status and dementia AAO in *PSEN1 A79V* MCs.

Histopathological analyses revealed an intermediate (n=1) or high (n=4) level of AD neuropathologic change in the 5 MCs who came to autopsy (Table 2). Aβ plaques and neurofibrillary tangles were prominent in cortical association areas including the medial temporal lobe. A lower density of neuritic pathology was noted in deep gray nuclei. Mild to moderate cerebral amyloid angiopathy was a consistent finding. Lewy bodies limited to the substantia nigra pars compacta were present in one case (Case E). Arteriolosclerosis with lacunar infarcts were present in two cases (B and E). "Cotton wool" plaques[27] were absent.

Three of 12 (25%) genotyped noncarrier family members developed dementia (CDR 0.5) in the 8th to 9th decades of life. One noncarrier was diagnosed with symptomatic AD and had neuropathologic AD confirmed at autopsy (lacunar infarcts also were present). One individual with parkinsonism developed dementia with visual and auditory hallucinations with paranoid delusions; the neuropathologic assessment met criteria for AD with cortical Lewy bodies. The third noncarrier was diagnosed with normal pressure hydrocephalus at age 70 and managed with ventriculoperitoneal shunting.

Discussion

We report a generally comparable clinical phenotype between MCs from a family with late-onset ADAD due to a *PSEN1 A79V* mutation, and individuals with LOAD. Similar AAO; duration of dementia; rates of progression; and associated symptoms, signs and comorbidities were found for this ADAD family and LOAD. Hallucinations and delusions were reported more frequently in *PSEN1 A79V* MCs from this family, as has been noted previously in individuals with ADAD.[44,45] These findings demonstrate that the clinical phenotypes of late-onset ADAD and LOAD can overlap, and suggest that previously reported clinical (e.g., seizures, early myoclonus, spastic paraparesis, dysarthria, and rapid decline[9–18]) and neuropathological differences (e.g., altered cerebral $A\beta_{42}$ and neurofibrillary tangle deposition, increased prevalence of cerebral amyloid angiopathy, and formation of "cotton wool" plaques[6,12,16,19–27]) may reflect age- or mutation-dependent effects.

The factors contributing to the later dementia AAO in this *PSEN1 A79V* family remain unknown. AAO was not influenced by *APOE* allele carrier status, suggesting that additional, as of yet unexplained, genetic, epigenetic or host factors must account for the late AAO, consistent with reports that family history and mutation type account for a significant proportion of the variance in AAO across a broad range of ADAD families.[7] Within *PSEN1* families, this variance may be influenced by $A\beta$-independent effects resulting from disruption of other functions of *PSEN1*, including its role as an endoplasmic reticulum calcium leak channel.[46] These $A\beta$-independent effects could contribute to both the observed variability in AAO and phenotypic discordance between *PSEN1* ADAD and LOAD. *A79V* is unusual among *PSEN1* mutations as it was the only one of six screened *PSEN1* mutations that did not impact *PSEN1*-related calcium channel function, as measured by calcium imaging experiments using presenilin-null mouse embryonic fibroblasts.[46] The limited secondary effects on cellular calcium homeostasis associated with the *PSEN1 A79V* mutation may contribute to the later AAO reported in this cohort and others.[16,33] Additionally, variability may reflect alterations in the metabolism of other known *PSEN1* cleavage substrates, including Notch, a transmembrane receptor involved in neuronal development and function.[47] *PSEN1 A79V* mutations have been shown to alter $A\beta_{42}$ levels and $A\beta_{42/40}$ ratio in cell culture, and MCs from the family described herein were previously found to have high CSF $A\beta_{42}$ and $A\beta_{42/40}$ ratios: findings that suggest gamma-secretase function may be altered in *PSEN1 A79V* MCs within this family.[31] To our knowledge, the effect of *PSEN1 A79V* mutations on gamma-secretase-mediated Notch cleavage has not been previously investigated. However, the finding that many other pathogenic *PSEN1* mutations which alter $A\beta_{42}$ production also impact Notch cleavage,[48] suggests that *PSEN1 A79V* mutations could have a similar effect. Future studies are required to address this issue, and to explore other molecular mechanisms through which the *PSEN1 A79V* mutation may impact disease phenotype.

Because of the late AAO, family members were enrolled in research studies with presumptive LOAD until the unexpected discovery of a pathogenic mutation in an affected family member.[31] That the *PSEN1 A79V* mutation was responsible for symptoms in 7 of 10 family members who developed dementia late in life suggests that it may be necessary to

reconsider the criteria used to select individuals with symptomatic AD for genetic testing. Testing for ADAD-associated mutations is considered for individuals with both early-onset AD and 2 affected family members (third-degree relatives or closer).[49] These criteria are seldom applied to individuals with LOAD given the higher baseline prevalence of sporadic AD in this population.

Previous reports suggest that the early expression of prominent behavioral and psychiatric symptoms may represent a clinical marker for *PSEN1* families.[44,45] Although psychiatric symptoms and signs were observed more frequently in *PSEN1 A79V* MCs within this family, the specificity of this finding is expected to be low when all causes of dementia are considered across a broader population of patients. Indeed, visual hallucinations were reported in one noncarrier family-member with pathologically-proven AD and Lewy bodies. Absent a specific marker of late-onset ADAD, therefore, we support the recommendation that genetic counselling be considered in symptomatic individuals from families with 4 or more affected individuals with LOAD.[50] The emergence of psychosis early in the course of dementia in such family members may further justify testing. This recommendation has potentially important implications for clinical practice, where the emphasis on genetic evaluation in individuals with early-onset AD has likely obscured prevalence estimates of late-onset ADAD, and identification of associated mutations.

The present work is subject to several limitations, including the small number of affected individuals available for study, and potential variability in reporting of clinical results across the multiple Alzheimer Disease Centers that contribute to the NACC. Lack of power may have affected our ability to quantify differences between individuals with ADAD and LOAD, and to investigate the clinical factors that may have contributed to the later-than-expected dementia AAO in *PSEN1 A79V* MCs. Similarly, the modest number of *PSEN1 A79V* cases reviewed at autopsy limited the ability to perform a quantitative comparison of neuropathological findings between this cohort and LOAD cases. Finally, we present clinical information from three *PSEN1 A79V* MCs who remain cognitively normal beyond the 7th decade of life. This finding may raise questions concerning whether amyloidogenic mutations invariably lead to AD, although all 3 asymptomatic MCs remain well within the expected range of onset of symptomatic AD observed within affected family members and may yet develop AD dementia. This issue will be further clarified through continued prospective follow-up.

At least for this *PSEN1 A79V* family an amyloidogenic mutation largely recapitulates the clinicopathological attributes of sporadic LOAD. This recapitulation indirectly supports the concept that ADAD and LOAD arise from parallel pathways, and suggests that at least some research findings involving individuals with ADAD may be extended to individuals with LOAD. The degree to which variability in the severity of amyloidogenic mutations, host genetic, epigenetic and environmental factors contribute to the AAO within and between *PSEN1 A79V* families should be further considered through adequately powered prospective observational studies.

Acknowledgments

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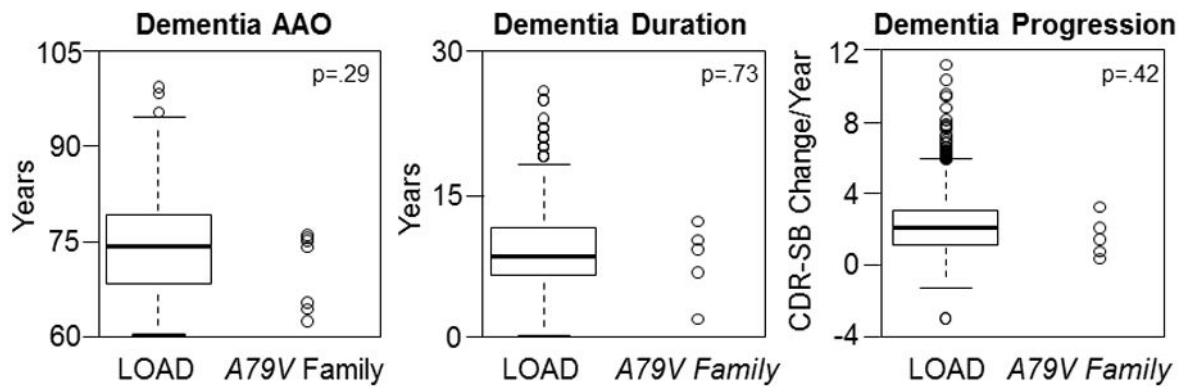
Figure 1.
Age at symptomatic onset (AAO), duration of symptomatic dementia, and rate of dementia progression in sporadic late-onset Alzheimer disease (LOAD) and *A79V* family members with dementia. Control data from participants in the National Alzheimer's Coordinating Center is shown as boxplots (N=1115 for Dementia AAO and Disease Duration; N=837 for Dementia Progression). The distribution of dementia AAO, disease duration (years), and rate of dementia progression (annualized change in CDR sum of boxes) are shown through scatterplots for individual cases (N=7 for Dementia AAO; N=5 for Dementia Duration and Progression).

Table 1

Summary of clinical information for individuals with LOAD and *PSEN1 A79V* mutation carriers with ADAD

| | Family members with dementia | | | |
	PSEN1 A79V carriers	Noncarriers	LOAD	p value, carriers versus LOAD
Demographic details	N=7	N=3	N=1115	
Median age at symptomatic onset (range), years	75.0 (63–77)	76.0	74.0 (60–101)	.29
Female gender (%)	4 (57)	2 (67)	529 (47)	.71
Median education (range), years	12 (8–15)	12 (8–15)	16 (2–24)	.01
Dementia features				
Mode of onset of dementia: insidious onset, gradual progression (%)	7 (100)	3 (100)	1105 (99)	>.99
Presenting symptom of dementia, memory loss (%)	7 (100)	3 (100)	958/1063 (90)	>.99
Median duration of dementia (range), years	9.9[+] (2.3–12.8)	5.1[+] (<10 years)	9.0 (1–27.0)	.73
Rate of dementia progression				
Change in CDR sum of box scores/year (range)	1.2 (0.1–3.3) N=5	1.64 (1.04–1.68) N=3	1.9 (−3.5–11.9) N=837	.42
Associated symptoms, signs and comorbidities early in the disease course (CDR 1)				
Depressive symptoms (low mood; %)	3 (43)	3 (100)	309/706 (44)	>.99
Psychiatric symptoms/signs	5 (71)	1 (33)	163/706 (24)	.01
Hallucinations or delusions, %	4/7 (57)	1 (33)	137/706 (19)	.03
Severe agitation, %	1/7 (14)	0 (0)	42/706 (6)	.35
Language deficit (%)	3 (43)	0	454/706 (58)	.26
Visuospatial impairment (%)	4 (57)	0	413/706 (64)	>.99
Parkinsonism (%)	2 (29)	1 (33)	64/706 (9)	.13
Seizures (active; %)	0 (0)	0	4/706 (1)	>.99
APOE allele status				
APOE ε4 carrier (%)	5/7 (71)	2 (67)	568 (51)	.45
- Unknown	1/7 (14)	0	167 (15)	>.99

[+]Calculation limited to participants in whom complete duration was known

Table 2

Neuropathological findings in *PSEN1 A79V* carriers

Case	Age at death (decade)	Brain weight (g)	ABC score for AD neuropathologic change (NIA-AA)[39]				Other
			A (Aβ plaques)	B (neurofibrillary tangles)	C (neuritic plaques)	Level of AD neuropathologic change	
A	9th	875	3	3	3	High	-
B	8th	1,050	3	2	2	Intermediate	CVD: lacunar infarcts in thalamus and basal ganglia
D	9th	940	3	3	3	High	-
E*	8th	960	3	3	3	High	CVD: lacunar infarcts in inferior parietal gyrus LBD: brainstem-predominant
F	9th	1,250	3	3	3	High	-

NIA-AA, National Institute on Aging-Alzheimer's Association criteria for the neuropathologic assessment of AD

*
Information extracted from autopsy report issued by outside center; CVD, cerebrovascular disease; LBD, Lewy body disease.