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Confirming Pathogenicity of the F386L *PSEN1* Variant in a South Asian Family With Early-Onset Alzheimer Disease

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Abstract

Objectives

The F386L *PSEN1* variant has been reported in 1 Japanese family with limited clinical information. We aimed to prove that F386L is pathogenic by demonstrating that it segregates with early-onset Alzheimer disease (AD).

Methods

Eight individuals in a South Asian family provided DNA for genetic testing and underwent a neurologic examination.

Results

The female proband was diagnosed with AD at age 45 years and died at age 49 years. She had a CSF biomarker profile consistent with AD, and her florbetaben PET scan was amyloid positive with high uptake in the striatum. Her MRI showed no prominent white matter disease. Her affected relatives had an age at onset range of 38–57 years and had imaging and biomarker profiles similar to hers.

Discussion

The results presented here, in conjunction with the prior report, confirm the pathogenicity of F386L. Furthermore, our study highlights the importance of studying families from underrepresented populations to identify or confirm the pathogenicity of rare variants that may be specific to certain genetic ancestries.

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Alzheimer disease (AD) primarily affects individuals older than 65 years, but autosomal dominant variants in presenilin-1 (*PSEN1*) have been found to cause early-onset AD (EOAD).[1] The missense *PSEN1* variant c.1158C>A, which substitutes a leucine for a phenylalanine at codon 386 (p.F386L), has been reported in 2 Japanese siblings with EOAD.[2] We provide definitive pathogenic evidence for F386L in a large family originally from the southeastern coastal state Andhra Pradesh in India.

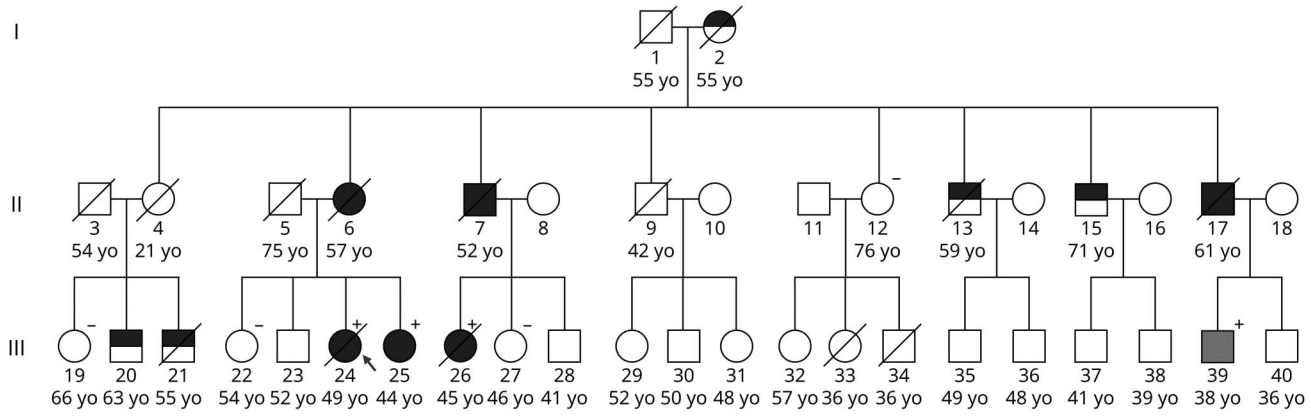
Methods and Results

The proband (III-24, Figure 1) was a woman whose memory began declining at age 44 years. Her early symptoms included repeating questions and leaving the stove on and the refrigerator door open, followed by word-finding difficulty and visuospatial issues requiring her to stop driving. At age 45 years, she was diagnosed with AD. On examination, she demonstrated phonemic paraphasic errors, difficulty following complex commands, slight symmetric cogwheeling at the wrists, mildly increased lower extremity tone, brisk patellar reflexes, slightly unstable gait, decreased left arm swing, and postural instability with retropulsion. She scored 13/30 on the Mini-Mental State Examination (MMSE). Florbetaben PET/MRI scan revealed prominent posterior parietal and medial temporal atrophy, no substantial white matter hyperintensities, and high tracer uptake in the striatum (Figure 2A). Her PET scan was amyloid positive. Her CSF biomarker profile, performed by Athena Diagnostics, was consistent with AD (Aβ-42 = 296 pg/mL, t-tau = 617 pg/mL, p-tau = 96 pg/mL, and amyloid tau index = 0.31); Athena only provides cutoffs for p-tau (abnormal above 68 pg/mL) and the amyloid tau index (abnormal below 0.8). She died at age 49 years. Clinical genetic testing confirmed that she carried F386L. Her mother and uncle (II-6, II-7; Figure 1) were diagnosed with dementia in their forties and died in their fifties but did not undergo genetic testing. Three additional family members carried F386L. The younger sister (III-25, Figure 1) was diagnosed with AD at age 43 years after presenting with progressive memory impairment for 1–2 years followed by trouble with executive function. She scored 10/30 on the Montreal Cognitive Assessment. Her neurologic examination was otherwise normal. The female cousin (III-26, Figure 1) began misplacing items, became dependent on writing things down, and was leaving the stove on at age 38 years. She became disoriented in her own neighborhood, was missing appointments, and was asked to resign from her job at age 41 years. She scored 24/30 on the MMSE. CSF showed reduced Aβ-42, elevated total tau, and elevated phospho-tau. MRI showed mild, symmetric frontoparietal atrophy, and SPECT showed frontal and mediotemporal hypoperfusion. At age 43 years, she scored 14/30 on the MMSE, developed left-sided parkinsonism with increased tone, reduced reflexes, intermittent upper extremity myoclonic jerks, and polyminimyoclonus. She died at age 45 years. The male cousin (III-39, Figure 1) was cognitively unimpaired at age 36 years and had a normal neurologic examination. His florbetaben PET scan was amyloid positive and showed pronounced striatal uptake (Figure 2B, see also eFigure 1, links.lww.com/NXG/A504). On neurological examination, the proband's 54-year-old older sister, 76-year-old aunt, 66-year-old female cousin, and 46-year-old female cousin (III-22, II-12, III-19, and III-27, respectively; Figure 1) were cognitively normal, and none carried F386L.

Standard Protocol Approvals, Registrations, and Patient Consents

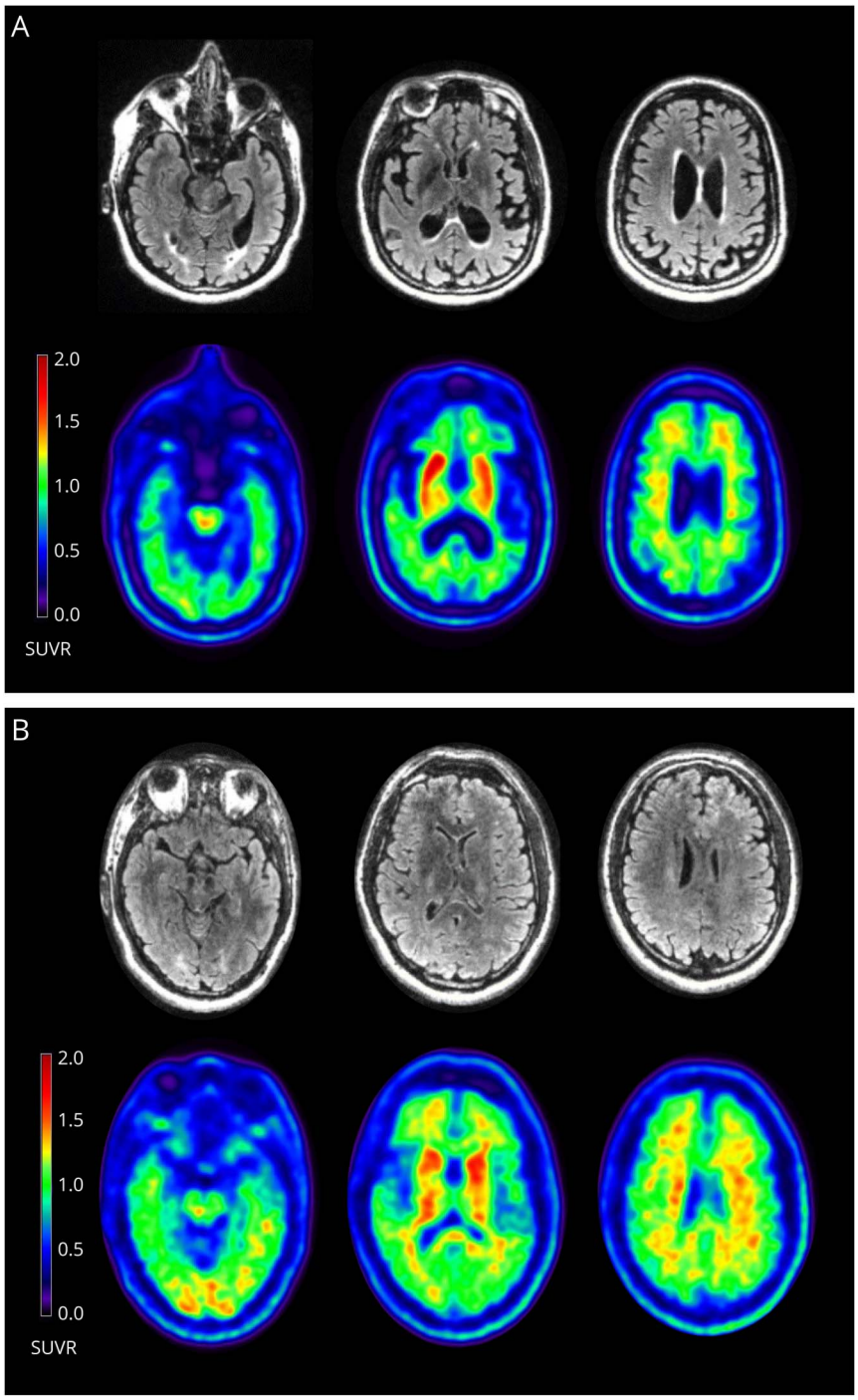
The Stanford Institutional Review Board (IRB00004593) and the Melbourne Health Human Research Ethics Committee (2013.295) approved the study. We obtained informed consent and consent to disclose from participants (or their caregivers).

Figure 1 Family Pedigree Demonstrating F386L Segregates With Early-Onset AD



III-24 (arrow) is the proband. III-39 (gray symbol) is cognitively normal but amyloid PET positive. A solid black symbol indicates that the individual was either clinically diagnosed with AD by the authors or the family provided sufficient medical record detail of the diagnosis. A half-black symbol indicates that the individual was suspected by the family to have been affected but was not formally diagnosed. Additional clinical and anecdotal information is included in eAppendix 2, links.lww.com/NXG/A504. Plus (+) and minus (−) signs indicate F386L carrier or noncarrier status (genetic testing described in eAppendix 3, links.lww.com/NXG/A504). Females are depicted as circles and males as squares. Ages represent age at death (for those marked as deceased with a diagonal line through the symbol) or current age.

Figure 2 Simultaneous MRI and Amyloid PET in (A) the Proband at Age 45 Years and (B) the Male Cousin at Age 36 Years



(A) The proband's FLAIR images (first row) demonstrate only trace periventricular white matter changes. The florbetaben PET images (second row) are positive for cortical amyloid and show prominent amyloid deposition in the striatum. The brainstem was used as the reference region for the standardized uptake value ratios (SUVRs). (B) The unaffected male cousin's FLAIR images (third row) are normal. His florbetaben PET images (fourth row) are positive and display similar striatal deposition to (A) that is not seen in older unrelated noncarriers (see eAppendix 4, links.lww.com/NXG/A504).

Data Availability

Anonymized data not published here will be made available by request from any qualified investigator.

Discussion

In addition to F386S and F386I (see eAppendix 1, links.lww.com/NXG/A504), we have shown that F386L is also pathogenic. We report initial symptoms and an age at onset range of 38–57 years, comparable to the Japanese siblings.[2] In this family, we note a fairly wide variability of disease duration (ranging from 4 to 19+ years). The proband (III-24) and male cousin (III-39) showed high striatal amyloid deposition, typical of some *PSEN1* variant carriers.[3] Their lack of prominent early motor symptoms supports the growing consensus that regional amyloid plaque has little to no bearing on

regional dysfunction.[4,5] None of the carriers with MRI scans (III-24, III-26, and III-39) had significant white matter involvement, which is inconsistent with the hypothesis that *PSEN1* variants beyond codon 200 increase predisposition to leukoencephalopathy.[6] We were unable to sequence DNA from any second-generation cases. We have shown that F386L segregates with disease (and/or amyloid positivity) in 8 individuals (3 affected, 1 unaffected but amyloid positive, and 4 unaffected) in a pedigree with autosomal dominant EOAD. In searching for other reported *PSEN1* variants detected in Indian ancestry families, we found 1 additional study,[7] emphasizing the need to expand the ancestral diversity of genetic research.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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