Supplementary Data

eAppendix 1. Functional Importance of the F386 Amino Acid.

Three *in silico* prediction tools, Polyphen-2[e1], Sorting Intolerant from Tolerant (SIFT)[e2] and Mutation Taster[e3] classify F386L as probably damaging, deleterious and disease causing, respectively. The variant is highly conserved along homolog PSEN1 proteins in several vertebrate and nonvertebrate species, which implies that the F386 site is integral for proper PSEN1 functionality. Furthermore, two other variants at the same codon have evidence of co-segregation with EOAD. Carriers of F386S have a reported age at onset of between 34-58 years, as well reports of spastic paraparesis and seizures[e4–6]. Neuropathology showed cotton wool plaques and severe cerebral amyloid angiopathy[e5]. F386I has been identified in a Chinese family with an age at onset ranging from 45-60 years of age. Brain MRI for two affected carriers showed bilateral hippocampal atrophy[e7].

eAppendix 2. Extended Pedigree Report.

I-2: A woman who developed dementia prior to her death at age 55, according to the family.

II-6: A woman whose cognitive symptoms began in her mid-forties, was diagnosed with AD in her fifties and ultimately developed leg weakness and gait issues. She died at age 57.

II-7: A man who became increasingly forgetful and withdrawn in his early forties, was diagnosed with dementia at age 47 and died at age 52.

II-13: A man suspected by the family to have developed dementia prior to his death at age 59.

II-15: A 71-year-old man who has been bedridden for several years. The family reported his age at onset as 52 years old.

III-20: A 63-year-old bedridden man. The family reported his age at onset as 57 years old.

III-26: A 45-year-old woman who carried F386L. At age 41, she scored four standard deviations below normal in the memory domain on the Neuropsychiatry Unit Cognitive Assessment Tool[e8].

III-27: A 46-year-old woman who does not carry F386L. At age 42, she had no memory or cognitive complaints. She is a tertiary educated professional. She scored 95/100 on the Addenbrooke's Cognitive Examination-III[e9], a validated cognitive test that assesses attention, memory, verbal fluency, language and

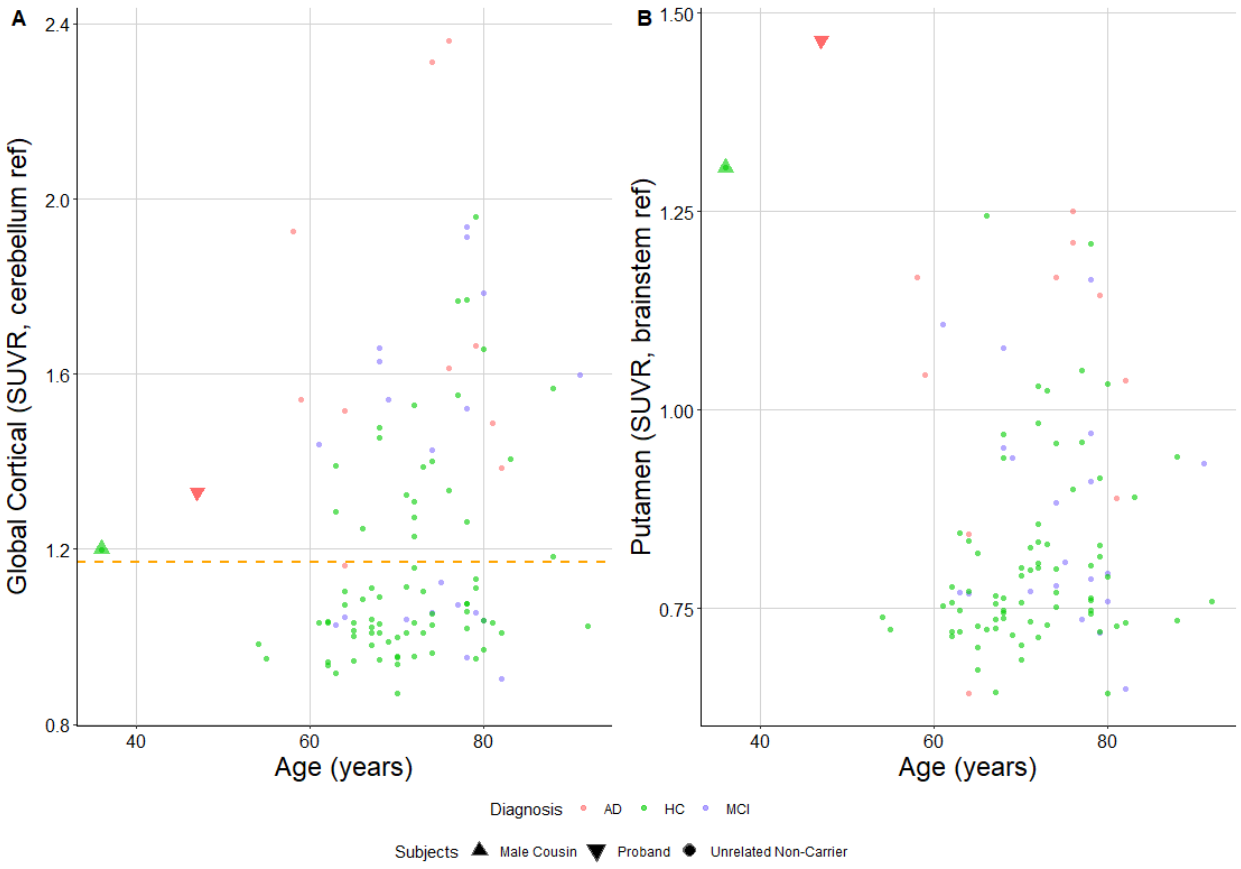
visuospatial abilities (mean score +/- SD for controls is 95.4 +/- 3.3). Neurological examination and brain MRI were normal.

eAppendix 3. Genetic Testing.

Clinical genetic testing for *PSEN1*, *PSEN2*, and *APP* variants (https://www.athenadiagnostics.com) showed the proband (III-24) was heterozygous for *PSEN1* F386L. III-26, III-27 and III-39 also underwent clinical testing. Five individuals provided whole blood samples for research whole-genome sequencing (WGS). WGS data was processed using the Best Practices GATK (v.4) pipeline[e10]. Variant calling confirmed clinical test results for III-24 and III-39 and determined that III-25 was also a carrier. II-12, III-19, and III-22 were found not to carry the variant. No other known pathogenic variants were found among any individuals. Relatedness of these six individuals was determined using GENESIS (R v4.1.0)[e11]. Kinship coefficients were consistent with reported first, second and third degrees of relatedness.

eAppendix 4. Amyloid Deposition in F386L Carriers.

The proband (III-24) and the male cousin (III-39) were both classified as amyloid positive by a neuroradiologist. Additionally, all florbetaben PET scans collected at the Stanford Alzheimer's Disease Research Center (ADRC) were dichotomized as positive or negative using a Gaussian Mixture Model (GMM). III-24 and III-39 were both above the GMM global cortical SUVR threshold (**eFigure 1A**). **eFigure 1B** demonstrates that the two carriers' putaminal uptake (seen in **Figure 2**) is clearly higher than the uptake for older healthy controls and individuals with mild cognitive impairment or AD.


A
B
Global Cortical (SUVR, cerebellum ref)
Putamen (SUVR, brainstem ref)
Age (years)
Age (years)
2.4
2.0
1.6
1.2
0.8
1.50
1.25
1.00
0.75
40
60
80
Diagnosis AD HC MCI
Subjects Male Cousin Proband Unrelated Non-Carrier

60

eReferences

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