Supplementary Methods

The FLorida Autopsied Multi-Ethnic (FLAME) cohort was queried for neuropathologically diagnosed Alzheimer's disease (AD) cases with an age at onset younger than 65 (i.e., young-onset AD) and a positive family history of cognitive decline. We excluded 1163 cases that were not neuropathologically characterized as having AD, 101 cases that lacked tangle data, and 42 cases with a Braak stage <V. We excluded 20 cases with known autosomal dominant AD mutations. We excluded 276 cases with limited availability of clinical history. Of the remaining cases, 242 were excluded for unevaluated family history, and a further 458 cases were excluded for negative family history of cognitive decline. Out of the remaining 507 AD cases, we excluded 21 cases for missing age at onset and 378 cases that were classed as late-onset AD. Of the 108 remaining cases, five were excluded for unavailable brain tissue and/or DNA. Thus, our final cohort consisted of 103 young-onset AD cases with a positive family history of cognitive decline.

Standardized neuropathologic procedures were performed by a single board-certified neuropathologist (DWD), as previously defined.[1] The 5-µm thick sections were cut from formalin-fixed, paraffin-embedded tissue blocks and mounted onto glass slides. Thioflavin-S fluorescent microscopy was used to assess AD neuropathologic changes and assign a Braak tangle stage,[2] Thal amyloid phase,[3] and AD subtype.[4] Lewy body pathology was diagnosed using the NACP antibody (1:3000)[5] and assigned a subtype according to the fourth dementia Lewy body consortium.[6] Hippocampal sclerosis of a TDP-43 etiology (MC2085, 1:2500)[7] was diagnosed when the neuronal loss in the CA1 or subiculum of the hippocampus exceeded that of the extent of tangle pathology observed.[8] Significant cerebrovascular disease was included in the neuropathologic diagnosis if two or more of the following pathologies were observed: large infarct, lacunar infarct, microinfarct, white matter infarct, moderate-to-severe white matter rarefaction, hippocampal sclerosis of a vascular etiology, or severe cerebral amyloid angiopathy.