



Probing Cognitive Function Across the Lifespan in Marmosets with Genetic Risk for Alzheimer’s disease

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INTRODUCTION

•The ability to predict and translate clinical benefit for cognitive function as well as identify mechanisms underlying cognitive dysfunction related to Alzheimer’s disease (AD) progression remains unresolved.

•Non-human primate models are conducive to studying the long prodromal phase in which cognitive decline begins to emerge prior to frank neuropathology.

•As part of our MARMO-AD consortium, we established a comprehensive testing battery sensitive to detecting age-dependent cognitive decline across the lifespan in our colony of aging marmosets including marmosets genetically engineered with mutations in the PSEN1 C410Y gene which confers early onset AD in humans.

METHODS

•As part of the overarching goals of MARMO-AD, in alignment with the NIA-Alzheimer’s Association diagnostic framework, we employ non-invasive, clinically-analogous measures that capture the spectrum of AD inception and progression.

•More than 150 individual marmosets are tracked longitudinally across the lifespan to enable within-subject analysis and correlate behavioral and cognitive changes with disease progression.

•As early as 6 weeks of age and then at 6-month intervals on their birthdays and half-birthdays, blood is collected for plasma biomarker analysis (MesoScale Discovery, Alamar Nulisa).

•Marmosets are trained for awake neuroimaging sessions with anatomical MRI, functional MRI and PET imaging conducted annually including 11C-PiB-PET for amyloid; 18F-MK6240-PET for Tau, 18F-FDG-PET for glucose metabolism, and 18F-SynVesT-1-PET for evaluating synapses.

•For cognitive testing, marmosets are trained using preferred rewards (marshmallow juice; 20-35% in drinking water) as positive reinforcement without food or water restriction, in daily sessions using touchscreens (Lafayette Instruments) placed on their homecages for discrete 20-30 min sessions.

•We designed a testing battery modified from CANTAB that captures a spectrum of cognitive domains including spatial working memory (delayed match to position; DMTP), behavioral flexibility and reversal learning (delayed non-match to position; DNMT), recognition memory (trial unique delayed match to sample; TU-DMS), attention (serial reaction time task; SRTT), and episodic-like memory (paired associative learning task; PAL). Marmosets advance across the different tests in the battery once they meet apriori criteria for each task; then tested longitudinally across the lifespan.

•Behavioral and cognitive function are aligned with longitudinal PET neuroimaging and blood-based biomarkers to track AD progression.

SUMMARY

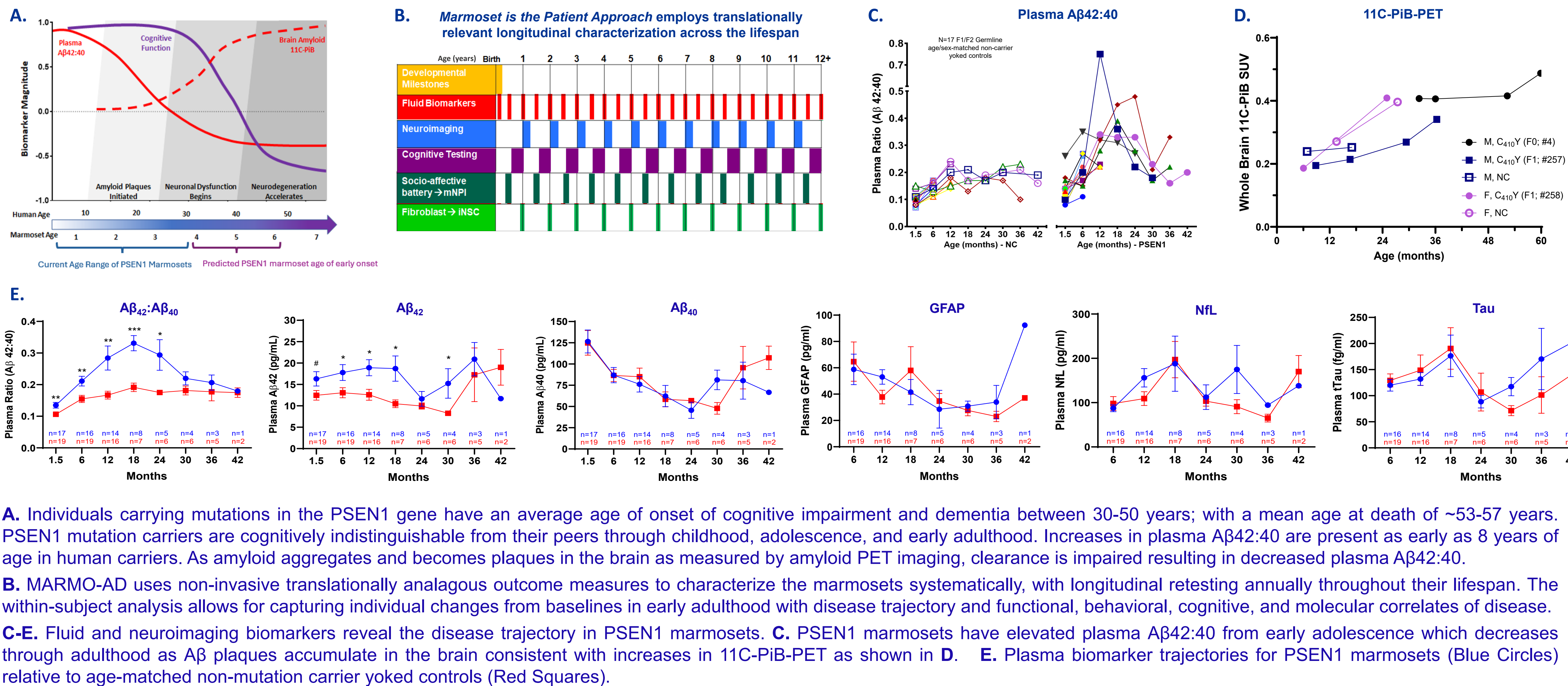
•In line with the human PSEN1 mutation carriers, PSEN1-C410Y marmosets show significantly elevated plasma A β_{42} :A β_{40} ratios relative to age-matched non-carriers in early adolescence, with a subsequent age-dependent increase in 11C-PiB retention, indicating greater A β accumulation, a hallmark of AD progression.

•Despite elevated amyloid in brain and plasma, PSEN1-C410Y are indistinguishable from age-matched non-carrier controls as indicated by similar performance across cognitive tests. The lack of cognitive alterations in PSEN1 mutation carriers in adolescence and early adulthood is consistent with human PSEN1 mutation carriers in which increases in amyloid precede cognitive decline by a decade or more.

•These studies demonstrate the validity of the PSEN1 marmoset model to recapitulate the human AD trajectory and emphasize the importance of studying genetic risk as early in life as possible, in order to identify mechanisms that precede frank neuropathology and cognitive impairment.

RESULTS

PSEN1 Marmosets Recapitulate Alzheimer’s Disease Trajectory of Human PSEN1 Patients



Marmoset Cognitive Testing Battery

