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BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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AD-causing variants that affect *PSEN1* transmembrane domains are associated with faster neurodegeneration and cognitive decline compared to those affecting cytoplasmic domains

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Abstract

Background: Rates of cognitive and biomarker change in Autosomal Dominant Alzheimer disease (ADAD) vary substantially across individuals. Prior cross-sectional work suggests that the location of the pathogenic variant within *PSEN1*, specifically whether the underlying variant affects transmembrane (TM) or cytoplasmic (CY) domains in *PSEN1*, may be a key determinant in these differential rates of progression. Here we use longitudinal data from the Dominantly Inherited Alzheimer Network observational study (DIAN-Obs) to examine whether variants affecting TM versus CY domains in *PSEN1* have differential rates of change in key cognitive and neurodegenerative markers, and whether these differences are relevant to ADAD clinical trials.

Methods: Using longitudinal clinical, cognitive, and MRI data from *PSEN1* pathogenic variant carriers [TM group N=76 and CY group N=44; **Table 1**], we assessed rates of change in Mini-Mental State Exam (MMSE), Clinical Dementia Rating® Sum of Boxes (CDR®-SOB), and hippocampal volume (HV) using linear mixed effects models accounting for disease stage (estimated years to symptom onset [EYO]). We further assessed how *PSEN1* mutation location (TM versus CY) impacts sample size and detectable

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effect size in a potential ADAD clinical trial (modeled as a 4-year trial with annual assessments; 80% power; $\alpha = 0.05$).

Results: *PSEN1* TM and *PSEN1* CY groups did not differ on baseline age, EYO, or CDR®. The *PSEN1* TM group had significantly greater rates of change on MMSE (B[SE] = -0.42[0.1], p=0.002), CDR®-SOB (B[SE] = 0.23[0.1], p=0.001), and HV atrophy (B[SE] = -58.93[14.3], p=0.0006 compared to the *PSEN1* CY group (**Fig.1**). Consistent with these differential rates of change, power analyses indicated the required sample size to detect a 30% treatment effect on MMSE or HV would be reduced by 59.6% for MMSE and 91.0% for HV for a trial population comprised of *PSEN1* TM versus CY carriers (**Fig.2**).

Conclusions: Individuals who had a variant affecting the transmembrane domains of *PSEN1* had greater rates of cognitive decline and neurodegeneration compared to those with variants affecting cytoplasmic domains. In addition to having implications for ADAD pathophysiology, these results suggest that incorporating information regarding the location of *PSEN1* variants may be beneficial in analyzing and designing stratification approaches for ADAD trials.

Characteristic	All PSEN1	PSEN1 TM (N = 76)	PSEN1 CY (N = 44)	p-value
Baseline Age, yrs	37.6 (10.2)	38.4 (10.5)	36.2 (9.8)	0.251
Baseline EYO, yrs	-7.9 (10.7)	-7.2 (10.3)	-9.2 (11.3)	0.341
Baseline Global CDR®, (0,0.5, 1+); %	55.8, 26.7, 17.5	52.7, 27.6, 19.7	61.4, 25.0, 13.6	0.327
Female; %	58.3	57.9	59.1	0.450
Education, yrs	14.4 (2.6)	14.4 (2.8)	14.4 (2.4)	0.939
Years of follow-up	3.2 (2.1)	3.3 (2.0)	3.2 (2.1)	0.899

Table 1. Background Characteristics. Mean (sd) are reported unless otherwise specified. Resulting p-value from t-test or chi-square test comparing PSEN1 TM and PSEN CY groups are reported.

TM = Transmembrane domain; CY = Cytoplasmic domain; Yrs = years; EYO = Estimated years from symptom onset; CDR® = Clinical Dementia Rating®

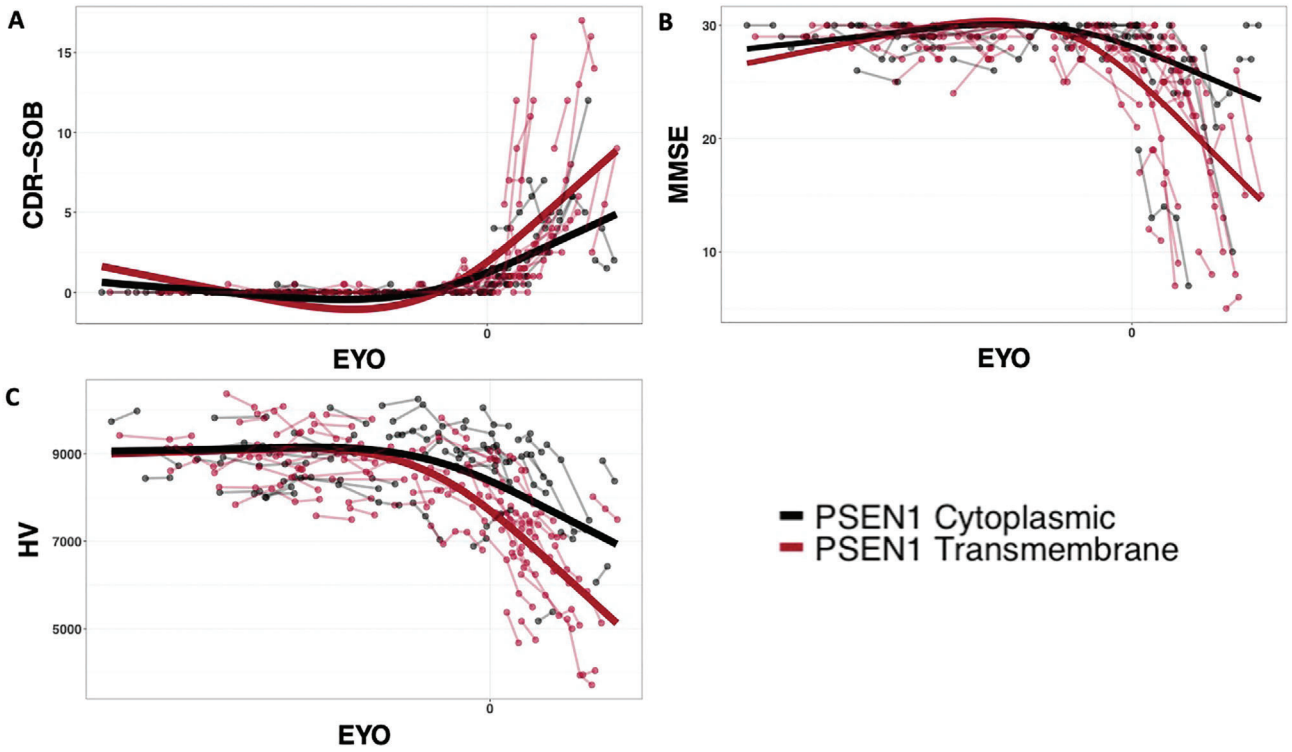

Figure 1. Differences in longitudinal trajectories of clinical, cognitive, and neurodegenerative measures between PSEN1 CY and PSEN1 TM pathogenic variant carriers. Rates of change for A) CDR®-SOB, B) MMSE, and C) HV (mm^3) are plotted, color-coded by PSEN1 grouping (PSEN1 TM in red and PSEN1 CY in black). The rate of change in each feature (i.e., CDR®-SOB, MMSE, and grey-matter atrophy) for each individual was modeled using a linear mixed effects model with random slope and intercept terms for each participant. As in prior reports to account for potential non-linear effects, EYO was modeled as a restricted cubic spline with knots at the 0.10, 0.50, and 0.90 quantiles.

MMSE = Mini mental state examination score; CDR® -SOB = Clinical Dementia Rating® - Sum of Boxes score; HV = Hippocampal volume; CY = Cytoplasmic domain; TM = Transmembrane domain; EYO = Estimated years to symptom onset.

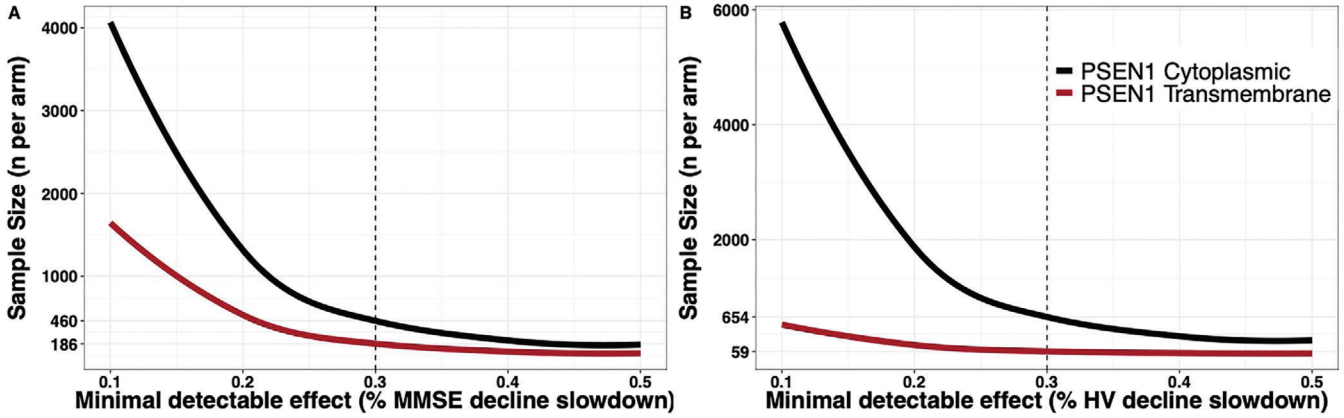

Figure 2. Sample Sizes Needed to Detect Slope Reduction in MMSE Score and HV Measures. The number of individuals per arm (y-axis) that are needed for detecting a given slope reduction on MMSE (**A**; x-axis) and HV (**B**) with an 80% power and α = 0.05 in a 4-year trial with annual assessments, using PSEN1 Cytoplasmic pathogenic variant carriers (black line) or PSEN1 Transmembrane pathogenic variant carriers (red line) as stratification criteria. The sample was restricted to individuals who have 2+ assessments starting at an estimated year of symptom onset (EYO) > - 10, consistent with recent ADAD clinical trials. Sample sizes needed to detect a 30% slope reduction are indicated by the black dotted vertical line. Estimates were based on a linear mixed effect of MMSE or HV ~ time + random intercept and random slope.

MC = Mutation carrier; MMSE = Mini Mental State Examination; HV = Hippocampal volume.