Characterizing Tau Accumulation and Amyloid-Tau Interactions in the Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease Colombia Trial and Their Implications for Advancing Drug Development

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About CPAD

- The **Critical Path for Alzheimer's Disease (CPAD)** is a global public-private partnership initiated in 2008 consisting of industry, FDA/EMA representatives, patient organizations, and academic advisors.
- The goal of CPAD is to accelerate the path to approval of therapies that improve the lives of people with Alzheimer's disease. We identify specific barriers to drug development and then create solutions to overcome those barriers.
- By sharing data, knowledge, and resources, we advance innovative drug development tools, such as biomarkers, clinical outcome assessments, and quantitative solutions like clinical trial simulator tools, that help de-risk decision making in the development and regulatory review process of novel medical products.

Background

Alzheimer's disease (AD), particularly its autosomal dominant form (ADAD), presents unique challenges for drug development. Clinical trials involving cognitively healthy individuals with ADAD can provide a useful model for sporadic Alzheimer's disease. The CPAD consortium integrates clinical trial and observational data to develop tools to accelerate drug development.

Objective

Develop a **disease trajectory model** for Autosomal Dominant Alzheimer's Disease to **support and accelerate** drug approval in AD.

API ADAD Colombia Dataset[1]

Variable	Placebo Non-Carrier (N=31)	Placebo Carrier (N=39)	CRENEZUMAB Carrier (N=44)
AGE (years)			
Mean (sd)	41.84 (8.01)	36.74 (7.30)	35.95 (5.47)
Min - Max	32.00 - 60.00	30.00 - 56.00	30.00 - 48.00
SEX			
Female	23 (74.2%)	29 (74.4%)	21 (47.7%)
Male	8 (25.8%)	10 (25.6%)	23 (52.3%)
EDUCATION (years)			
Mean (sd)	9.55 (4.43)	9.74 (4.30)	8.91 (3.93)
Min - Max	2.00 - 20.00	1.00 - 16.00	1.00 - 16.00
APOE4			
Non-Carrier	23 (74.2%)	33 (84.6%)	35 (79.5%)
Carrier	8 (25.8%)	6 (15.4%)	9 (20.5%)
Aβ group - baseline			
Negative	31 (100.0%)	19 (48.7%)	20 (45.5%)
Positive	0 (0.0%)	20 (51.3%)	24 (54.5%)

Tab. 1

- Members of the PSEN1 E280A kindred family, aged 30-60 years, who were cognitively unimpaired
- A subset of participants from the Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease Colombia Trial with available imaging biomarkers (Tab. 1) was included
- Tau PET measurements across 8 different brain regions, comparing placebo versus CRENEZUMAB treatment. Analysis included both PSEN1 E280A mutation carriers and non-carriers (Fig.1-2)
- Participants were excluded if they had significant medical, neurologic, or psychiatric conditions, extreme body weights, cognitive-impairing medications, history of strokes, or multiple microhemorrhages

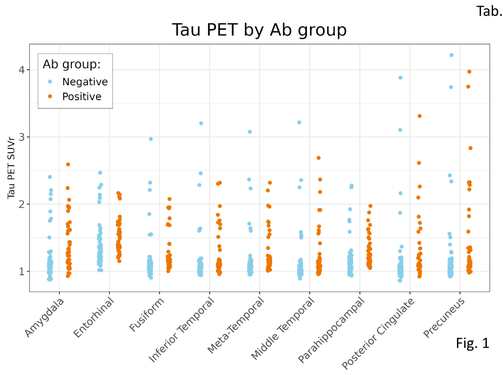

Fig. 1

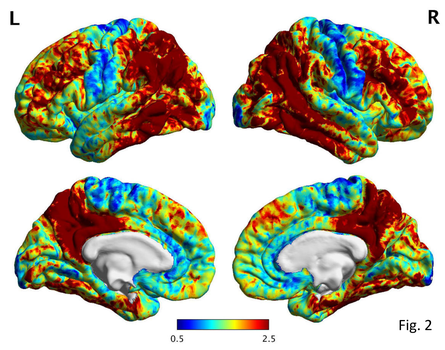

Fig. 2

Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One. 2013;8(7):e68910

Statistical Model

Linear Mixed Effect Models[2] simultaneously handle both population-level effects (fixed effect) and individual variations (random effects)

$$\text{tau} \sim \text{sex} + \text{age} + \text{educ} + \text{APOE4} + \text{ARM} + \text{time}^* A\beta\_\text{group} + (1 + \text{time} \mid \text{USUBJID})$$

- The model was applied separately to each brain region for region-specific analysis
- Variables were log-transformed to meet distributional assumptions and improve model performance (Fig. 3)
- Age and education years were standardized to enable direct comparison of effect sizes
- Cohort was categorized into three groups (Placebo Carrier, Placebo Non-Carrier, CRENEZUMAB Carrier)

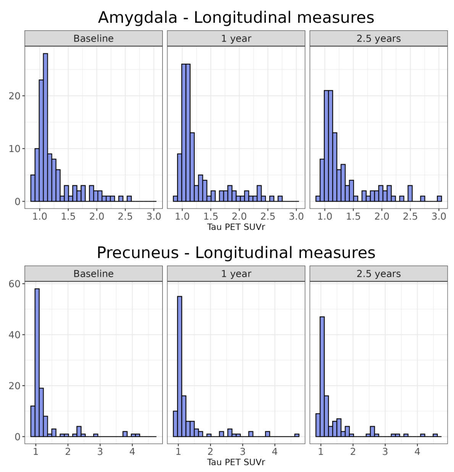

Fig. 3

Results of covariates

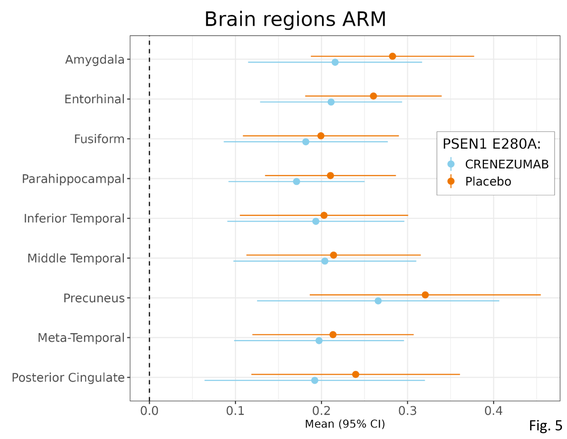

Fig. 5

- Mutation carriers demonstrated significantly elevated tau accumulation compared to non-carriers in both placebo and CRENEZUMAB treatment groups (Fig. 5)
- Most brain regions showed effect sizes ranging from 0.15-0.20. The precuneus showed the highest increase (~0.35), followed by the amygdala (~0.30) (Fig. 5)
- Age demonstrated consistent and statistically significant associations across all regions of interest, with confidence intervals that did not cross the null effect line (Fig. 6)
- APOE4 Status and years of education showed consistent non-significant effects across all examined regions (Fig. 6)
- Male sex exhibited a consistently positive effect throughout all regions, but reached statistical significance only in the entorhinal region (Fig. 6)

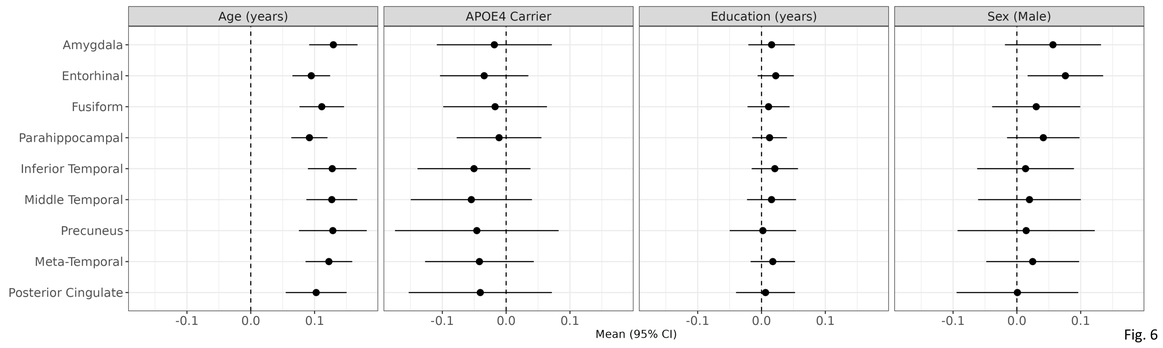

Fig. 6

Results of Longitudinal Tau PET

Longitudinal tau PET SUVr analysis across nine brain regions revealed distinct patterns between A+ and A- cohorts, with A+ individuals demonstrating elevated baseline tau burden and accelerated accumulation rates, particularly in the entorhinal cortex and precuneus regions, while A- participants maintained stable, minimal tau levels throughout the follow-up period (Fig. 4A)

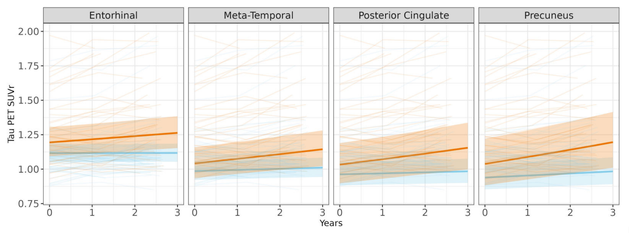

Fig. 4A

Similar longitudinal tau PET analysis in PSEN1 E280A carriers and non-carrier revealed accelerated tau accumulation with distinct regional patterns compared to sporadic Alzheimer's disease, suggesting future clinical trials should incorporate mutation-specific biomarker trajectories and tailored intervention timing to optimize therapeutic efficacy in this genetically defined population (Fig. 4B)

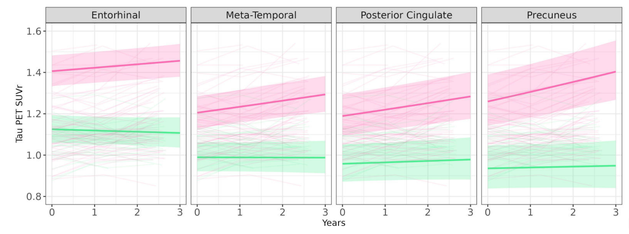

Fig. 4B

Coefficients	Amygdala	Entorhinal	Fusiform	Inferior Temporal	Meta-Temporal	Middle Temporal	Parahippocampal	Posterior Cingulate	Precuneus
Sex (Male)	0.05	0.07 (*)	0.03	0.01	0.02	0.02	0.04	0.00	0.01
Age (years)	0.13 (*)	0.09 (*)	0.11 (*)	0.13 (*)	0.12 (*)	0.12 (*)	0.09 (*)	0.10 (*)	0.13 (*)
Education (years)	0.01	0.02	0.01	0.02	0.02	0.01	0.01	0.00	0.00
APOE4 - Carrier	-0.02	-0.03	-0.02	-0.05	-0.04	-0.05	-0.01	-0.04	-0.04
Placebo - Carrier	0.28 (*)	0.26 (*)	0.20 (*)	0.20 (*)	0.21 (*)	0.21 (*)	0.21 (*)	0.24 (*)	0.32 (*)
CRENEZUMAB - Carrier	0.22 (*)	0.21 (*)	0.18 (*)	0.19 (*)	0.20 (*)	0.20 (*)	0.17 (*)	0.19 (*)	0.27 (*)
Aβ group - positive	0.10 (*)	0.06 (*)	0.04	0.04	0.05	0.06	0.05	0.07	0.10
Time (years)	0.01 (*)	0.00	0.01	0.01 (*)	0.01 (*)	0.01 (*)	0.00	0.01	0.01 (*)
Time × Aβ group	0.03 (*)	0.02 (*)	0.02 (*)	0.02 (*)	0.02 (*)	0.02 (*)	0.012(*)	0.03 (*)	0.03 (*)

Results of the fixed effect of the model for each region, the (*) means that p-value < 0.05

Tab. 2

Conclusion

We identified unique tau buildup patterns and amyloid-tau interactions in hereditary PSEN1 carriers, revealing early disease mechanics. Our model enhances both therapeutic research and understanding of neurodegeneration in hereditary and sporadic forms.

1) The Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease (ADAD) Colombia Trial, https://alzheimerspreventioninitiative.com/api-studies/adad-colombia-trial/
2) Raket, "Progression models for repeated measures: Estimating novel treatment effects in progressive diseases", Statistics in Medicine 2022
3) Ozlen et al., "Spatial Extent of Amyloid-β Levels and Associations with Tau-PET and Cognition" JAMA Neurology, 2022

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