A-T+ PET participants in preclinical AD: Clinical progression and concordance with fluid markers

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1.Background

Amyloid-negative tau-positive PET (A-T+) participants have been reported in several studies. We assessed the prevalence and characteristics of A-T+ participants in a cohort of cognitively unimpaired individuals with a first-degree family history of AD dementia.
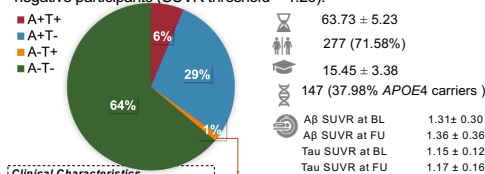
2.Methods

A total of 387 active participants from the PREVENT-AD cohort, 252 participants had baseline Aβ- and tau-PET scans.

PET thresholds

-Global [^{18}F]NAV4694-PET (Aβ) positivity (SUVR threshold = 1.27, CL = 18).

-Temporal meta-ROI regions [^{18}F]AV-1451-PET (tau) positivity were determined using a threshold of 2SD from the mean of CU Aβ negative participants (SUVR threshold = 1.29).

	A+T+	6%
	A+T-	29%
	A-T+	1%
	A-T-	64%

Age	63.73 ± 5.23
N	277 (71.58%)
Sex	15.45 ± 3.38
APOE4	147 (37.98% APOE4 carriers)
Aβ SUVR at BL	1.31± 0.30
Aβ SUVR at FU	1.36 ± 0.36
Tau SUVR at BL	1.15 ± 0.12
Tau SUVR at FU	1.17 ± 0.16

Clinical Characteristics

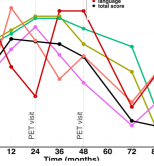|	Participant 1	Participant 2	Participant 3
Age at baseline, years	62	70	63
Sex	Male	Female	Female
Education, years (z-score)	15 (-0.13)	19 (1.05)	11 (-1.32)
APOE status	APOE4 non-carrier	APOE4 non-carrier	APOE4 carrier
PET scans (n= 252)			
Aβ-PET, BL	1.22 (- 0.33)	1.18 (-0.45)	1.25 (-0.21)
Aβ-PET, FU	-----	-----	1.33 (-0.08)
Tau-PET, BL	1.38 (1.84)	1.31 (1.29)	1.55 (3.29)
Tau-PET, FU	-----	-----	2.04 (5.41)
CSF (n = 76)			
Aβ42/40	NA	NA	0.02 (-2.22)
p-tau181 (pg/mL)	NA	NA	79.16 (1.03)
Plasma (n = 374)			
Aβ42/40	0.04 (-2.22)	0.06 (-0.51)	0.07 (-0.05)
p-tau181 (pg/mL)	3.42 (-0.68)	6.53 (-0.10)	9.08 (0.37)
NfL(pg/mL)	15.62 (-0.11)	20.47 (0.56)	20.97 (0.63)
GFAP (pg/mL)	58.09 (-0.76)	78.53 (-0.45)	336.41 (3.54)
Sleep measures (n = 230)			
PSQI	5 (-0.08)	8 (0.85)	7 (0.54)
Sleep efficiency, %	90.78 (0.7)	92.28 (0.96)	73.38 (-2.29)

3.Results
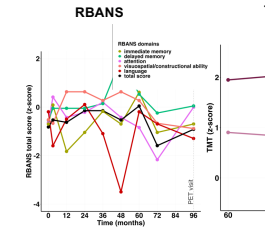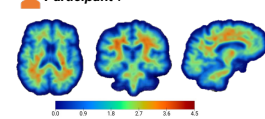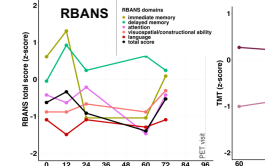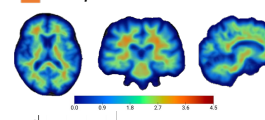
Participant 1

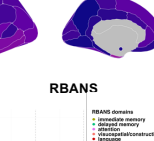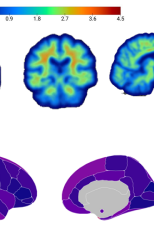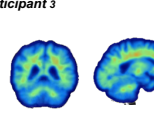
Participant 1 & 2 Aβ-PET scans were classified as quantitatively negative with relatively low tau-PET binding . Both participants showed low levels of plasma Aβ42/40. Participant 1 progressed to MCI.
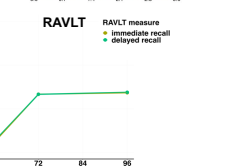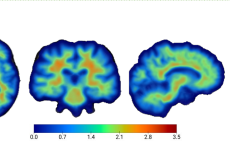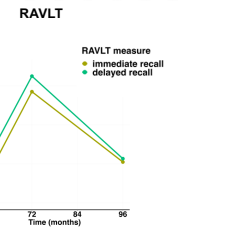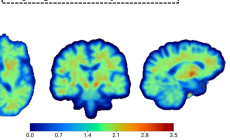
Participant 2

Participant 3

Participant 3: Aβ-PET scan was classified as positive on visual read and became quantitatively positive at follow-up. Tau-PET showed extensive unilateral tau binding at baseline that became bilateral at follow-up. The participant showed low levels of plasma and CSF Aβ42/40.Ultimately, the participant developed dementia.

4.Conclusion

A-T+ individuals are rare in the PREVENT-AD cohort (1%). The 3 A-T+ who are classified as Aβ-PET negative are positive based on fluid biomarkers. One of the 3 A-T+ individuals showed a very fast clinical progression and a tau uptake pattern atypical of AD.