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BIOMARKERS

PODIUM PRESENTATION

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NEUROIMAGING

Comparison of amyloid accumulation between Down syndrome and autosomal-dominant Alzheimer disease

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Abstract

Background: Given the triplication of chromosome 21 and the location of the amyloid precursor protein gene on chromosome 21, almost all adults with Down syndrome (DS) develop Alzheimer disease (AD)-like pathology and dementia during their lifetime. Comparing amyloid accumulation in DS to autosomal dominant AD (ADAD), another genetic form of AD, may improve our understanding of early AD pathology development.

Method: We assessed amyloid positron emission tomography (PET) imaging in 192 participants with DS and 33 sibling controls from the Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) and 265 mutation-carriers (MC) and 169 familial controls from the Dominantly Inherited Alzheimer Network (DIAN) (**Table 1**). We calculated regional standard uptake value ratios (SUVR) using a cerebellar cortex reference region and converted global amyloid burden SUVR to centiloids. We compared amyloid PET by cognitive status and estimated-years-to-symptom-onset (EYO). EYO was calculated for DIAN participants by subtracting their age from parental age of symptom onset and for ABC-DS participants by subtracting their age from 50.2 years, a published average age of symptom onset in a large sample of individuals with DS (Fortea et al., 2020). In a subset of participants, we assessed the relationship between amyloid PET and CSF Aβ42/40.

Result: The relationship between CSF Aβ42/40 and amyloid PET was similar in DS and MC participants (**Figure 1**). We did not observe significant differences between MC and DS grouped by cognitive status (**Figure 2**). However, when assessed over EYO, global amyloid burden was significantly elevated in MC at EYO $\geq$ -23 but was not elevated in DS until EYO $\geq$ -15 (**Figure 3**). We observed early cortical and subcortical amyloid PET increases in both groups, but we also measured some regional differences in amyloid PET changes between MC and DS, specifically in the medial occipital region (**Figure 4 and 5**).

Conclusion: These results demonstrate similarities in the relationship between amyloid biomarkers and the levels of amyloid accumulation in ADAD and DS. However, we also observed a 5-10 year delay and some regional differences in amyloid accumulation in DS. This is important for future clinical trials to consider when recruiting participants and determining treatment efficacy.

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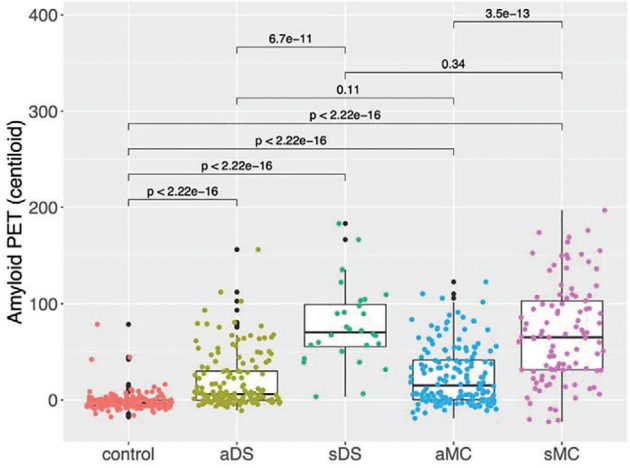
Table 1. Participant demographics

	Controls (n = 202)	Down syndrome (DS) (n = 192)	Mutation-carrier (MC) (n=265)	p-value
Age, years (mean (SD))	41·5 (10·6)	41·9 (9·1)	40·4 (9·7)	0·222
Female	123 (61%)	84 (44%)*	140 (53%)	**0·003**
Non-Hispanic white	176 (87%)	176 (92%)†	206 (78%)	**<0·001**
APOE ε4-positive	57 (28%)	38 (20%)	78 (29%)	0·059
Cognitive status				**< 0·001**
Asymptomatic	202 (100%)	155 (81%)*†	164 (62%)*	
Symptomatic	0	28 (15%)	101 (38%)	
No consensus	NA	9 (4%)	NA	
Down syndrome type				---
Full trisomy 21	--	168 (87·5%)	--	
Translocation	--	12 (6%)	--	
Mosaicism	--	6 (3%)	--	
ADAD mutation type				---
PSEN1	--	--	202 (76%)	
PSEN2	--	--	22 (8%)	
APP	--	--	41 (15%)	

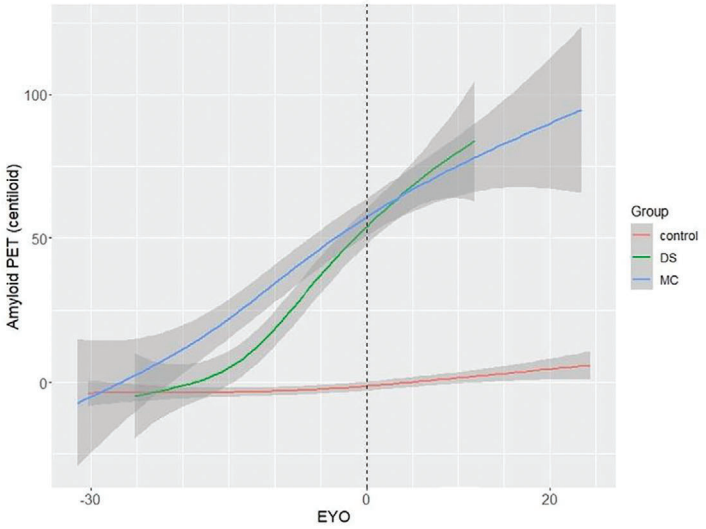
*Significantly different from controls after Benjamini-Hochberg correction for multiple comparisons ($p < 0·05$)
†Significantly different from mutation-carriers after Benjamini-Hochberg correction for multiple comparisons ($p < 0·05$)

Figure 2. Amyloid PET by cognitive status



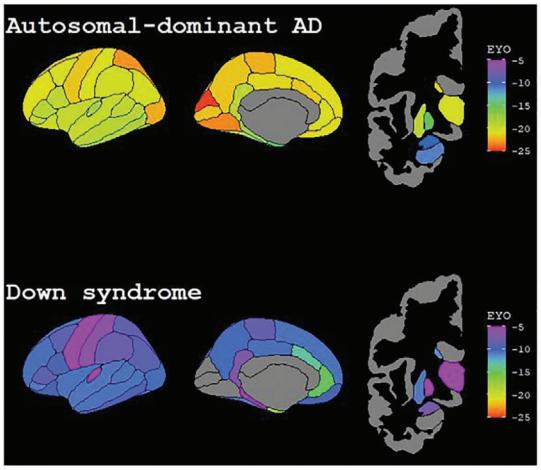
Amyloid deposition in Centiloids compared between control participants and DS and MC participants grouped by cognitive status. P-values calculated using the Wilcoxon test and adjusted for multiple comparisons using the Benjamini-Hochberg method.
Abbreviations: aDS = asymptomatic DS; aMC = asymptomatic MC; sDS = symptomatic DS; sMC = symptomatic MC; DS = participants with Down syndrome; MC = autosomal-dominant mutation carriers; PET = positron emission tomography

Figure 3. Amyloid PET as a function of EYO



Amyloid deposition in Centiloids plotted as a function of participants' EYO using a generalized additive model and fitting a spline to EYO. Abbreviations: EYO = estimated years to symptom onset; DS = participants with Down syndrome; MC = autosomal-dominant mutation carriers; PET = positron emission tomography

Figure 4. EYO at which significant regional amyloid accumulation is measured



EYO at which regional amyloid accumulation in A) autosomal-dominant AD mutation-carriers and B) individuals with DS was significantly greater than controls using a 99% confidence interval to account for multiple comparisons. Abbreviations: AD = Alzheimer's disease; EYO = estimated years to symptom onset; DS = Down syndrome

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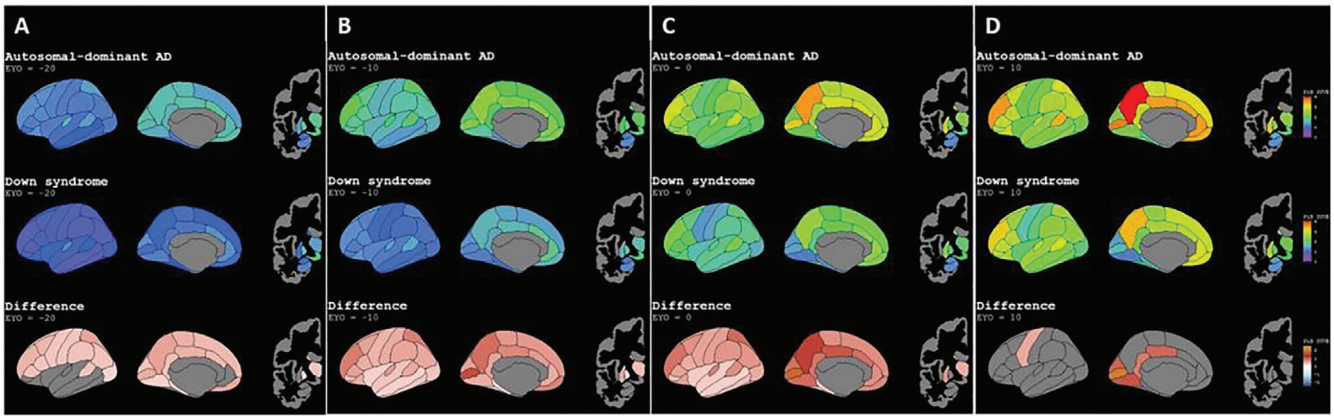
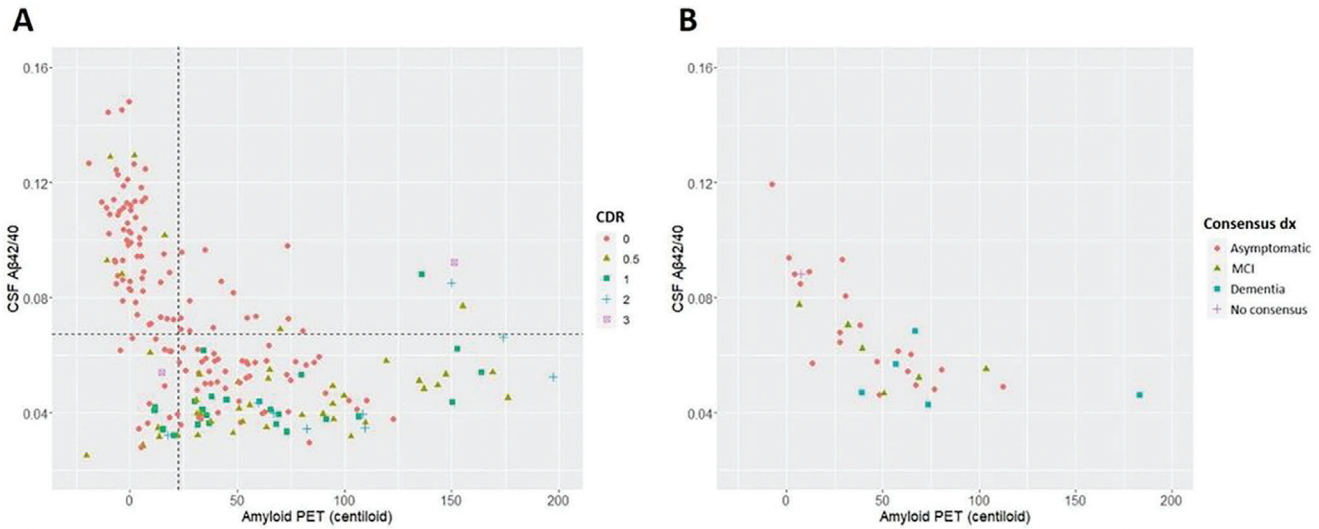
Figure 5. Regional PiB SUVR in autosomal-dominant AD versus Down syndrome



Regional PiB SUVRs at A) EYO = -20, B) EYO = -10, C) EYO = 0, and D) EYO = 10 in autosomal-dominant AD MCs, participants with DS, and the significant difference between MC and DS SUVRs using a 99% confidence interval to account for multiple comparisons. Abbreviations: AD = Alzheimer's disease; EYO = estimated years to symptom onset; DS = Down syndrome; MC = mutation-carrier; SUVR = standard uptake value ratio

Figure 1. Amyloid PET as a function of CSF amyloid ratio



Amyloid deposition in Centiloids plotted against the ratio of $A\beta_{42}/A\beta_{40}$ levels in the CSF. The dotted lines represent the previously defined amyloid-positivity cut-offs in DIAN for CSF (horizontal) and PET imaging (vertical) measures. Abbreviations: Aβ= amyloid-beta; CDR = clinical dementia rating; CSF = cerebrospinal fluid; dx = diagnosis; MCI = mild cognitive impairment; PET = positron emission tomography