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RESEARCH ARTICLE

Exploring discordant low amyloid beta and high neocortical tau positron emission tomography cases

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Abstract

Introduction: Neocortical 3R4R (3-repeat/4-repeat) tau aggregates are rarely observed in the absence of amyloid beta ($A\beta$). ^{18}F -MK6240 binds specifically to the 3R4R form of tau that is characteristic of Alzheimer's disease (AD). We report four cases with negative $A\beta$, but positive tau positron emission tomography (PET) findings.

Methods: All Australian Imaging, Biomarkers and Lifestyle study of aging (AIBL) study participants with $A\beta$ (^{18}F -NAV4694) and tau (^{18}F -MK6240) PET scans were included. Centiloid <25 defined negative $A\beta$ PET ($A\beta^-$). The presence of neocortical tau was defined quantitatively and visually.

Results: $A\beta^-$ PET was observed in 276 participants. Four of these participants (one cognitively unimpaired [CU], two mild cognitive impairment [MCI], one AD) had tau tracer retention in a pattern consistent with Braak tau stages V to VI. Fluid biomarkers supported a diagnosis of AD. In silico analysis of *APP*, *PSEN1*, *PSEN2*, and *MAPT* genes did not identify relevant functional mutations.

Discussion: Discordant cases were infrequent (1.4% of all $A\beta^-$ participants). In these cases, the $A\beta$ PET ligand may not be detecting the $A\beta$ that is present.

KEYWORDS

Alzheimer's disease, amyloid beta ($A\beta$), discordant, positron emission tomography, tau

1 | BACKGROUND

Amyloid beta ($A\beta$) plaques and tau neurofibrillary tangles (NFTs) are neuropathological hallmarks of Alzheimer's disease (AD). The amyloid-centric hypothesis posits that $A\beta$ deposition precedes tau deposition and neurodegeneration.^{1,2} The National Institute on Aging–Alzheimer's Association (NIA-AA) research framework for AD incorporates biomarkers of $A\beta$, tau, and neurodegeneration into the AT(N) classification.³ Individuals across the AD continuum have positive

$A\beta$ biomarkers, with or without abnormal tau biomarkers ($A\beta+T-$ or $A\beta+T+$).³ Combined $A\beta$ and tau positron emission tomography (PET) biomarker studies show that high neocortical tau is typically observed in association with abnormal $A\beta$.^{4–7}

In cognitively unimpaired (CU) individuals, tau aggregates restricted to the mesial temporal lobe, brainstem, basal forebrain, and olfactory areas with few or absent $A\beta$ plaques has been given the neuropathological designation of primary age-related tauopathy (PART),⁸ whereas the clinical entity of tangle-predominant dementia (TPD) is observed in

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very elderly cognitively impaired cohorts.⁹ It is common for A β - cases with high tau in the mesial temporal lobe to be considered consistent with PART or TPD. On neuropathology, tau deposition in these conditions is typically limited to Braak stages lower than IV, rarely extending to involve the neocortex beyond temporal regions.^{8,9} A β -T+ has also been proposed to represent individuals with microtubule-associated protein tau (MAPT) mutations.^{7,10,11} Carriers of MAPT mutations such as R406W and V337M produce AD-like 3-repeat/4-repeat (3R4R) cortical tau aggregates that are visually detectable using the tau PET ligand ¹⁸F-AV1451 (flortaucipir) at levels comparable to those observed in AD.¹⁰ Yet the pattern is distinct, with predominant tau PET tracer retention in the anterior temporal pole and frontal cortex,¹⁰ unlike the posterior temporoparietal pattern observed in AD. These entities do not account for discordant low A β PET retention and high tau tracer retention, extending into Braak stages V to VI, in a pattern typical for AD.

The alternative consideration in these cases is that the A β PET ligand is not detecting the A β that is present. PET studies using ¹¹C-PiB have identified a handful of cases where a low A β PET result has been observed, despite neuropathology or alternative biomarker evidence of AD.¹²⁻¹⁸

This study estimates the frequency of cases with discordant low A β PET retention and high neocortical tau tracer retention in an observational cohort, characterizes these participants, and hypothesizes that, in these instances, the A β PET ligand may not be detecting the A β present.

2 | METHODS

2.1 | Participants

Participants from the Australian Imaging Biomarkers and Lifestyle (AIBL) Flagship study of ageing and the Australian Dementia Network (ADNeT) who completed both an A β (¹⁸F-NAV4694) and a tau (¹⁸F-MK6240) PET scan before April 2020 were included in this study. Participants complete cognitive assessments every 12 to 18 months. Based on available clinical and neuropsychology assessments, a multidisciplinary clinical review panel determines whether an individual is CU or meets criteria for mild cognitive impairment (MCI) or AD dementia. An individual is deemed to be CU if they perform within 1.5 standard deviation (SD) of published norms for their age group, whereas diagnoses of MCI and AD dementia are determined in accordance with internationally agreed criteria.¹⁹ The full methodology for cohort recruitment and evaluation has been described previously.²⁰ All relevant institutional review boards have approved this study, and written informed consent was obtained from all participants.

2.2 | Image acquisition

Radiotracers were manufactured in-house (Austin Health, Melbourne, Australia). PET scans were acquired on either the Philips TF64 PET/CT

RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors reviewed the literature using PubMed, conference abstracts, and related presentations. Cases with low amyloid beta (A β) positron emission tomography (PET) signal, despite neuropathology or alternative biomarker evidence of A β , have been rarely reported.
- 2. Interpretation:** Four participants from the Australian Imaging Biomarkers and Lifestyle study of aging (AIBL) cohort had a negative A β (¹⁸F-NAV4694) PET, but quantitatively and visually high neocortical tau (¹⁸F-MK6240) tracer retention, in a pattern consistent with Braak stages V to VI. These discordant cases were rare (1.4% of all A β - participants). Fluid biomarkers supported a diagnosis of AD in these cases. Whole exome sequencing did not identify relevant *APP*, *PSEN1*, *PSEN2*, or *MAPT* mutations. These findings suggest that, similar to prior reports, the A β ligand may not be detecting the A β that is present in these cases.
- 3. Future Directions:** Post-mortem assessments of similar cases would be beneficial to better elucidate the reasons for the low A β PET signal.

or Siemens Biograph mCT. A low-dose CT was obtained for attenuation correction.

A β PET imaging involved intravenous (IV) administration of 200 MBq ($\pm 10\%$) ¹⁸F-NAV4694 with a 20-minute acquisition time, commencing 50-minutes post-injection. Tau PET imaging involved IV administration of 185 MBq ($\pm 10\%$) ¹⁸F-MK6240, with a 20-minute acquisition time, commencing 90-minutes post-injection.

2.3 | Image analysis

Centiloid values were computed from A β images using CapAIBL (<https://milxcloud.csiro.au/tools/capaibl>).²¹ Centiloid <25 was used to designate a low (negative) A β result.

Tau ¹⁸F-MK6240 PET scans were spatially normalized using the CapAIBL Principal Component Analysis (PCA)-based approach²² and scaled using the cerebellar cortex as the reference region. A gray matter inclusion mask and a meninges exclusion mask were applied. Standardized uptake value ratios (SUVR) were estimated in three composite regions-of-interest (ROIs): mesial temporal (Me) (comprising entorhinal cortex, hippocampus, parahippocampus, and amygdala); temporoparietal (Te) (comprising inferior and middle temporal gyrus, fusiform, supramarginal and angular gyri, posterior cingulate/precuneus, superior and inferior parietal, and lateral occipital cortex); and the rest of neocortex (R) (comprising the dorsolateral and ventrolateral prefrontal, orbitofrontal, gyrus rectus,

superior temporal cortex, and anterior cingulate).²³ The 95th percentile (95%ile) of $A\beta$ - CU participants was used to discriminate between high (+) and low (-) tau burden in each ROI (SUVR thresholds: 1.18 Me, 1.24 Te, and 1.08 R). A peri-threshold region, comprising between the 90%ile and 99%ile, was also established, resulting in an upper bound of the peri-threshold range of 1.29 for Me, 1.33 for Te, and 1.17 for R.

For scans where tau tracer retention was above the upper bound of the peri-threshold range in Te or R, one expert reader (CCR), blind to participant characteristics and quantitative results, visually read the scans using MedImage Software with MedView (version 12) displayed in a white-black scale. Scans were visually rated for the presence of tau in mesial temporal, temporal, parietal, occipital, posterior cingulate, precuneus, and frontal cortices.

Cases of high neocortical tau were those that had both quantitatively high neocortical tau (tracer retention above the upper bound of the peri-threshold range in Te and/or R) and were visualized to have tau in neocortical regions.

2.4 | Apolipoprotein E (APOE) genotyping

Apolipoprotein E (APOE) genotype was determined from whole blood-extracted DNA as per methodology previously described.²⁴

2.5 | Whole exome sequencing

Whole exome sequencing was performed for participants for whom a blood sample was available (participants 1, 3, and 4). Samples were sequenced on an Illumina NovaSeq platform (150 bp paired-end reads) using the IDT xGen Exome Research Panel v2 and the Illumina bcl2fastq 2.20.0.422 pipeline to generate the sequence data. Sequence alignment was via the Burrows-Wheeler Aligner Tool (BWA mem) and variant calls were made with HaplotypeCaller by GATK version 4.0.4.0. Targeted analysis was then undertaken to identify the presence of potential deleterious and functionally relevant genetic variation within the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and *MAPT* genes. Sorting Intolerant From Tolerant (SIFT)²⁵ and Polymorphism Phenotyping version 2 (PolyPhen-2)²⁶ programs were used as predictive tools to determine whether any identified amino acid substitutions in a protein-coding region were likely to affect its function.

3 | RESULTS

Of the 452 participants who had both an $A\beta$ and tau PET scan, 276 had a low $A\beta$ PET result ($A\beta$ -). Of those with a low $A\beta$ PET result, 23 (8% of all $A\beta$ -) were above the tau Te cut-off (with 9 above the upper bound of the peri-threshold) and 22 (8% of all $A\beta$ -) were above the tau R cutoff (with 7 above the upper bound). Thus 12 participants (4.3% of all $A\beta$ -) were above the tau upper bound cutoff in Te ($n = 5$) or R ($n = 3$), or both

Te and R (4). Of these, four participants (1.4% of all $A\beta$ -) were observed to have substantial and unequivocal neocortical tau on visual inspection (Figure 1). Table 1 outlines the demographics and characteristics of these four participants, whereas Table 2 provides the fluid biomarker results for these participants.

The referring diagnosis for participant 2 was MCI due to AD. An ¹⁸F-FDG (fluorodeoxyglucose) -PET scan performed for clinical diagnostic purposes showed hypometabolism in the posterior cingulate, precuneus, and bilateral temporoparietal cortices, with relative sparing of the sensorimotor cortices consistent with AD (Figure 2).

3.1 | Whole exome sequencing results

For the three participants for whom whole exome sequencing was performed (participants 1, 3, and 4), no allelic variants identified in *APP*, *PSEN1*, and *PSEN2* were predicted to be deleterious or damaging using SIFT and PolyPhen-2. Participant 4 had two missense variants in the *MAPT* gene (chromosome 17), with a C→T substitution at both rs17651549 and rs63750222. Both variants are predicted to be “deleterious” using SIFT and “probably damaging” using PolyPhen-2. However, both of these alternative alleles are observed in 24% of the European population.³³ No *MAPT* mutations were identified for participants 1 and 3.

4 | DISCUSSION

In this cohort of 452 participants, 4 participants (0.88%) (or 4/276, 1.4% of all $A\beta$ - participants) had low $A\beta$ PET and high neocortical tau PET tracer retention, quantitatively and visually. This aligns with prior reports suggesting that high neocortical tau tracer retention is rare in the absence of an abnormal $A\beta$ PET.⁴⁻⁷

The four participants with low $A\beta$ PET and high neocortical tau PET tracer retention had a tau distribution pattern consistent with that typically observed in $A\beta$ + individuals with AD. Participant 1, who was CU, had mesial temporal and asymmetric, right temporoparietal cortical ¹⁸F-MK6240 tracer retention, whereas the other three participants (two classified as having amnesic MCI and one with AD dementia) had high ¹⁸F-MK6240 tracer retention in mesial temporal, posterior cingulate, precuneus, lateral temporal, lateral parietal, lateral occipital, and prefrontal cortices, characteristic of AD Braak stages V to VI.²⁹ This pattern is consistent with the regions of high ¹⁸F-MK6240 binding reported previously for $A\beta$ + individuals across the AD continuum.³⁰ The distribution of ¹⁸F-MK6240 binding has been shown to match the post-mortem regional distribution of tau NFT, as observed for two individuals with AD dementia in a prior study.³¹ Autoradiography has also shown that ¹⁸F-MK6240 has a very high affinity for mixed 3R4R tau isoforms in AD over 3R or 4R isoforms present in non-AD tauopathies.³² Although whole exome sequencing identified two missense mutations in the *MAPT* gene in participant 4, these alternative alleles are observed not infrequently in European populations. The absence of these missense mutations in the other participants and

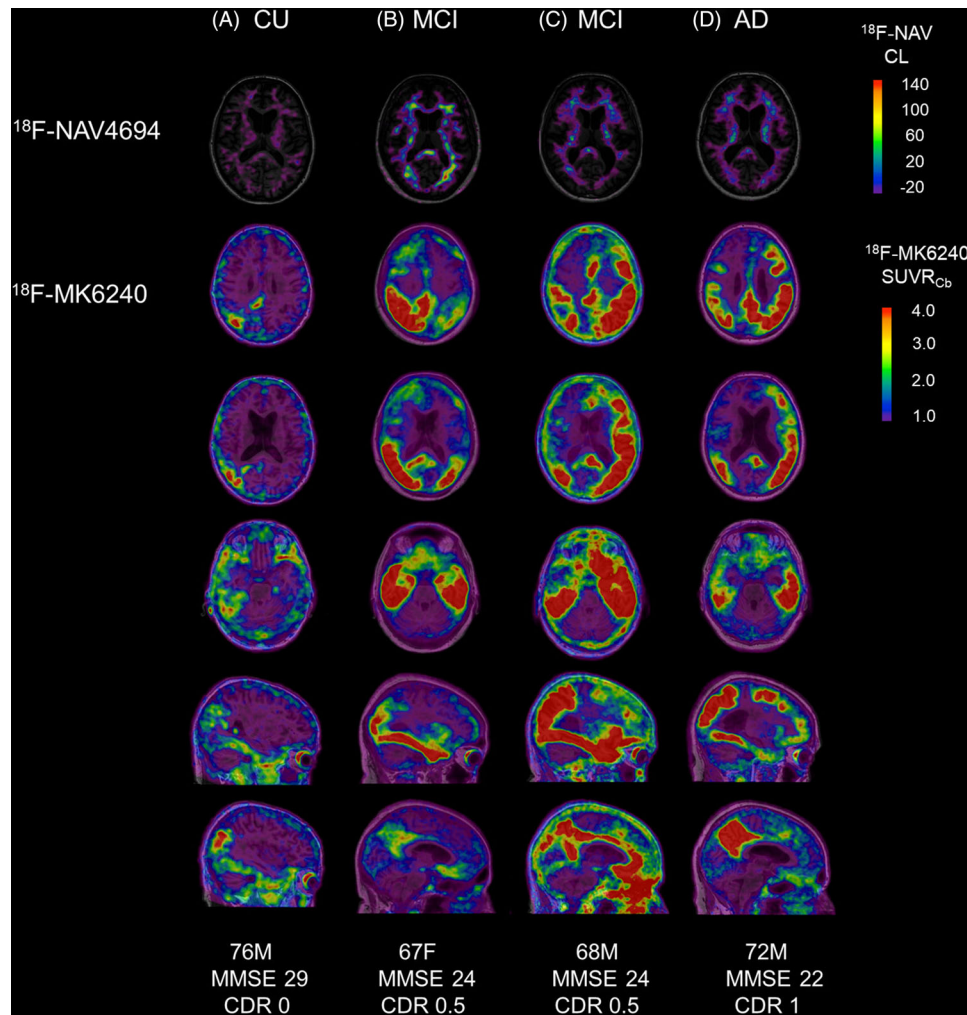


FIGURE 1 Amyloid beta ($A\beta$) and tau positron emission tomography (PET) scans of participants 1-4. $A\beta$ (^{18}F -NAV4694) (top row) and tau (^{18}F -MK6240) PET scans (bottom five rows) for participants 1-4, co-registered onto a T1-weighted magnetic resonance imaging (MRI) template. CU, cognitively unimpaired; MCI, mild cognitive impairment; AD, Alzheimer's disease; M, male; F, female; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating scale; CL, Centiloid; SUVR, standardized uptake value ratio

their moderately high minor allele frequency in the general population suggest that they are unlikely to be the driver of the observed discordance. However, it cannot be ruled out that these missense variants may contribute to the observed discordance, in combination with variants in other genes that were not investigated. Of note, whole exome sequencing did not identify known mutations in the *MAPT* gene (such as R406W), which have been associated with the formation of mixed 3R4R tau aggregates.

In this study, participants with low $A\beta$ PET and high neocortical tau PET were examined specifically to explore potential explanations for this combination of biomarker results. In primary age related tauopathy and tangle predominant dementia (PART/TPD), the distribution of tau involves the mesial temporal cortex, and can extend into the temporal lobes. We, along with other investigators, have documented elevated mesial temporal tau in the absence of $A\beta$, which may reflect PART.³⁴⁻³⁷ However, this study is restricted to participants with extensive cortical tau deposition, well beyond that typical of PART, and more consistent with AD. The extent of neocortical tracer retention and rela-

tively younger age of these participants suggest that these cases do not simply reflect PART/TPD.

$A\beta$ tracer ^{18}F -NAV4694 has a binding profile comparable to that of ^{11}C -PiB.³⁸ $A\beta$ burden in this study was measured in Centiloids, and participants 1 to 3 had Centiloid values ranging from -2.5 to 1.8. A Centiloid value of zero represents the mean $A\beta$ burden derived from scans of young healthy individuals,³⁹ and Centiloid values less than 10 have been observed to reflect the absence of any neuritic plaques at post-mortem.⁴⁰ Although the Centiloid value approached the pre-specified threshold for participant 4, the low $A\beta$ burden was in relative discordance with the extensive neocortical tau PET retention observed. We have observed recently that widespread tau deposition in the neocortex on PET occurs primarily above an $A\beta$ burden of 40 Centiloid.⁶

The four participants with discordant $A\beta$ and tau PET results had alternative biomarker findings that were supportive of a diagnosis of AD, despite the low $A\beta$ PET results. Participant 1 had a plasma $A\beta$ result available, measured using a combined immunoprecipitation and mass

TABLE 1 Characteristics of participants with low A β PET and high neocortical tau PET tracer retention

	Participant 1	Participant 2	Participant 3	Participant 4
Age	76	67	68	72
Sex	M	F	M	M
Diagnosis	CU	MCI	MCI	AD
Centiloid	-2.50	1.43	1.82	18.40
APOE	E3/E3	-	E3/E3	E4/E3
Me SUVR	1.14	2.73 ^a	3.27 ^a	1.27
Te SUVR	1.37 ^a	3.59 ^a	4.01 ^a	3.04 ^a
R SUVR	0.96	1.89 ^a	2.01 ^a	1.68 ^a
MTL atrophy ^b	0	0	2 (1 right, 3 left)	2.5 (2 right, 3 left)
PVWMH ^c	0	2	10	2
DWMH ^c	1	2	0	1
MMSE	29	24	24	22
CDR	0	0.5	0.5	1

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CDR, Clinical Dementia Rating scale; CU, cognitively unimpaired; DMWHs, deep white matter hyperintensities; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MTL, mesial temporal lobe; PVMWHs, peri-ventricular white matter hyperintensities; SUVR, standardized uptake value ratio; Me, mesial temporal; Te, temporo-parietal; R, rest of brain.

^a = above the upper bound of the peri-threshold range for the specified region of interest (ROI).

^b = average (right and left) mesial temporal lobe atrophy scores, as previously described.²⁷

^c = Fazekas' score for the visual assessment of white matter hyperintensities, as previously described.²⁸

TABLE 2 Additional biomarker results for participants with low A β PET and high neocortical tau PET tracer retention

Biomarker		Participant 1	Participant 2	Participant 3	Participant 4
CSF	CSF A β_{1-42}	-	386pg/mL (low) ^a	-	-
	CSF p-tau	-	89pg/mL (high) ^a	-	-
	CSF t-tau	-	553pg/mL (high) ^a	-	-
Plasma	Plasma A β^b	1.69 (abnormal)	-	-	-
Plasma	Plasma p217+tau ^c	High	-	High	High

^a = reference range for CSF A β_{1-42} >656 pg/mL, p-tau <59 pg/mL, t-tau <304 pg/mL, where the age-adjusted reference ranges were generated based on an AIBL healthy control cohort (>60 years).²⁹ Sample collected was tinged pink, with a red blood cell count of 1600/ μ L.

^b = AIBL composite value from a combined immunoprecipitation and mass spectrometry method previously described,³⁰ a measure validated in the AIBL cohort.

^c = plasma p217+tau assay was performed on a SIMOA platform, using a method previously described,³¹ and has been evaluated in the AIBL cohort.³² Participant 2 did not have a blood sample available for testing.

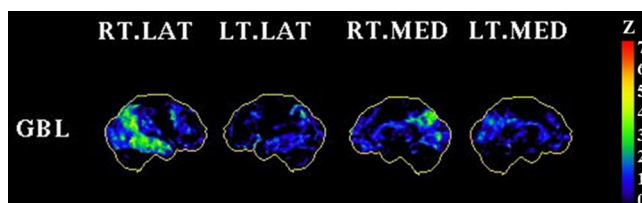


FIGURE 2 ¹⁸F-FDG (fluorodeoxyglucose) PET (positron emission tomography) scan for participant 2. This figure shows a Z-score map (displayed in NeuroStat 3D-SSP) of glucose metabolism generated by comparing the ¹⁸F-FDG PET scan of participant 2 against 20 A β negative healthy controls with a mean age of 72. The results were normalized to a global (whole brain) reference region

spectrometry method, which has been evaluated in the AIBL cohort.⁴¹ An AIBL composite result (described previously)⁴¹ was consistent with this individual being A β positive. Participants 1, 3, and 4 had high plasma p217+tau. Plasma p217+tau is a recently developed biomarker that detects tau phosphorylation at epitopes 217 and 212,⁴² and evaluation in the AIBL cohort has shown that a high level of p217+tau has good concordance with both abnormal A β and tau PET.⁴³ Participant 2 had both an ¹⁸F-FDG PET scan and cerebrospinal fluid (CSF) analysis. The observed ¹⁸F-FDG PET pattern of glucose hypometabolism in the posterior cingulate, precuneus, and bilateral temporoparietal cortices with relative sparing of the sensorimotor cortices is consistent with the pattern of hypometabolism observed in AD. This participant's

low CSF $A\beta_{1-42}$ and elevated CSF phosphorylated tau (p-tau) and total tau (t-tau) is also characteristic of AD. However, it should be noted that the CSF sample was tinged pink and had a red cell count of 1600/ μ L. Blood contamination has been observed to decrease CSF $A\beta_{1-42}$ and $A\beta_{40}$ levels, proportional to the amount of blood present.⁴⁴ Of note, blood contamination <5000 red blood cells/ μ L, as in our case, has been observed to have a negligible impact on $A\beta_{1-42}$ levels.⁴⁵ The impact on p-tau and t-tau is less clear. With these caveats, CSF results for participant 2 may also suggest a diagnosis of AD.

The patterns of tau tracer retention, relative discordance between the $A\beta$ and tau PET findings, and alternative biomarker evidence suggesting a diagnosis of AD in these four participants raises the possibility that these participants have $A\beta$ deposits undetected by the PET ligand. To our knowledge, there are no reports of this occurring with 18 F-NAV4694; however, a handful of cases have been reported using 11 C-PiB,¹²⁻¹⁸ and it has been reported in a multi-center study in which participants were scanned using 11 C-PiB, as well as $A\beta$ ligands 18 F-Florbetapir and 18 F-Florbetaben.⁴⁶ Similar to the current study, participants with low $A\beta$ and high tau in a meta-temporal composite ROI in this latter multi-center study were young (mean age of 66.2), four of seven were *APOE* ϵ 4 negative, and had a tau (18 F-Flortaucipir) PET pattern consistent with a pattern typically observed in AD in the majority of cases reported, but in contrast to this study, four of seven participants had an atypical clinical phenotype.⁴⁶

There may be different $A\beta$ conformations that are undetected by the ligand, and this has been observed in non-human primates that have the same amino acid sequence as human $A\beta$, but the aggregates have a different conformation.^{47,48} In one report, a patient was found to lack high-affinity binding sites for 3H-PiB, despite detection of extensive $A\beta$ deposition.¹⁵ A few prior reports using 11 C-PiB identified *APP* mutations associated with low 11 C-PiB signal.^{13,18} *APP* mutation E693Delta, for example, was observed to result in alternative $A\beta$ processing, leading to a propensity toward formation of oligomers over fibrillar $A\beta$.¹³ In this study, for the three participants for whom a blood sample was available for processing, whole exome sequencing did not identify any known *APP*, *PSEN1*, or *PSEN2* mutations. An undetected novel mutation in these individuals cannot be excluded. Post-mortem assessments of these cases would be beneficial to better elucidate the reasons for the low $A\beta$ PET signal.

The limitations of this study are the lack of availability of a more comprehensive panel of validated non- $A\beta$ /non-tau PET AD biomarkers, the lack of an available blood sample for participant 2, and the absence of post-mortem correlation. Although blood-based biomarkers for AD (plasma $A\beta$ and p-tau) are very promising, these biomarkers are not yet as established as CSF AD biomarkers.

5 | CONCLUSION

In this cohort, high neocortical tau PET retention in combination with low $A\beta$ PET was rare (1.4% of all $A\beta$ - individuals). The four participants with unequivocal discordant PET findings had alternative biomarker findings that supported a diagnosis AD, suggesting that similar to prior

reports, the $A\beta$ PET ligand may not be detecting the $A\beta$ present in these cases.

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CONFLICT OF INTERESTS

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