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RESEARCH ARTICLE

Genome-wide association of tau neuroimaging and plasma biomarkers in adults with Down syndrome

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Abstract

INTRODUCTION: Plasma biomarkers in Down syndrome (DS) accurately detect Alzheimer's disease (AD) pathology. This study aimed to identify genetic loci associated with plasma tau biomarkers (phosphorylated tau [p-tau]181, p-tau217, total tau [t-tau]) and tau positron emission tomography (PET) in DS.

METHODS: We examined 375 people with DS from the Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS) with data on all four tau biomarkers, and 133 subjects from another study of DS with plasma t-tau. Single-trait and multi-trait genetic association analyses were conducted. AD polygenic risk scores (PRSs) were tested with tau biomarkers.

RESULTS: Three genome-wide significant associations were identified for p-tau181: *TUBAP*/rs76523946, $P = 2.21E-08$; *CTNND2*/rs142510573, $P = 3.04E-08$; *CLSTN2*/rs112448655, $P = 3.04E-08$, and one for t-tau (*JHY*/rs77264104, $P = 2.84E-$

Kang-Hsien Fan and Ruyu Shi contributed equally to this study.

P50AG008702, P30AG062421, P50AG16537, P50AG005133, P50AG005681, P30AG062715, P30AG066519

08). AD PRS was associated with higher concentrations of tau PET (β = 0.30, P = 6.57E-04), p-tau217 (β = 0.11, P = 4.10E-02), and t-tau (β = 0.12, P = 3.60E-02).

DISCUSSION: These data indicate the presence of novel genetic loci in DS affecting plasma tau biomarkers and that AD risk PRS may modify tau neuroimaging and plasma biomarkers in DS.

KEYWORDS
Alzheimer's disease, Down syndrome, genome-wide association study, novel genetic loci, tau biomarkers, trisomy 21

Highlights

- Four loci were linked to plasma total tau (t-tau) or phosphorylated tau (p-tau)181 with genome-wide significance.
- *JHY*/rs77264104 stays genome-wide significant for plasma t-tau in a meta genome-wide association study (GWAS).
- Alzheimer's disease (AD) polygenic risk score is associated with tau positron emission tomography (PET), regardless of apolipoprotein E genotype and region.
- Tau-PET genes in Down syndrome (DS) are enriched in the cerebrospinal fluid phosphorylated tau Alzheimer's disease dementia GWAS catalog.
- T-tau genes in DS are enriched in a verbal memory GWAS catalog within a mild cognitive impairment cohort.

1 | BACKGROUND

Down syndrome (DS) is a chromosomal disorder associated with intellectual disability.[1] Individuals with DS have an extra copy of chromosome 21, leading to a lifelong overproduction of several genes on this chromosome, including the amyloid precursor protein (*APP*) gene. This genetic alteration results in increased production of amyloid beta (Aβ) plaques, one of the core neuropathological hallmarks of Alzheimer's disease (AD).[2] Another hallmark of AD is the accumulation of intracellular hyperphosphorylated tau tangles. *DYRK1A* (dual specificity tyrosine-phosphorylation-regulated kinase 1A), also located on chromosome 21, is associated with tau phosphorylation and is upregulated in the DS-AD and AD *post mortem* brains.[3,4] Individuals with DS are at high risk of developing AD at an early age, typically around 40 years, due to the early accumulation of these AD pathologies.[5]

Positron emission tomography (PET) imaging and blood biomarkers are recognized as reliable indicators for screening AD, with quantitative tau-PET proving to be a particularly dependable marker for clinical progression to dementia.[6–8] Plasma tau phosphorylated at threonine 181 (p-tau181) and 217 (p-tau217), and total tau (t-tau) are accurate blood-based biomarkers for both tau and Aβ pathological brain changes in DS.[9,10] Identifying genetic variants associated with these biomarkers through genome-wide association studies (GWASs) in the DS population can provide valuable insights into deciphering the genetic architecture of AD pathology in DS. To date, meta-analyses of large GWASs identify > 95 genetic risk loci linked to AD.[11,12] These genes are associated with Aβ production and clearance processes, lipid metabolism, immunomodulation, and synaptic function, which are heavily influenced by Aβ and tau proteins. GWASs have identified novel genetic loci for cerebrospinal fluid (CSF) tau and tau-PET,[13–15] and recent data indicate that plasma tau also has substantial heritability.[16,17] Given the near-universal occurrence of AD neuropathology in DS and the evidence that they have a genetic basis, this study aimed to perform GWASs to identify unique loci associated with tau plasma (t-tau, p-tau181, p-tau217) and neuroimaging (tau-PET) biomarkers in DS participants. By exploring these biomarkers, we sought to better understand the shared and unique genetic underpinnings of tau pathology in DS.

2 | METHODS

2.1 | Study cohorts

The subjects were derived from two DS studies: the Alzheimer Biomarkers Consortium–Down Syndrome (ABC-DS)[18] and the Multiomic Studies of Alzheimer's Disease in Adults with Down Syndrome (omicsADDS).[19–21]

2.1.1 | ABC-DS

The ABC-DS is a multi-site, longitudinal observational study focused on investigating AD-related biomarkers, along with clinical and genetic

factors in adults with DS aged ≥ 25.[18] People were eligible for ABC-DS enrollment if participants/their family members/correspondents consented to participate. Each participant was at least 25 and had genetic confirmation of DS. A total of 375 non-Hispanic White (NHW) participants with DS were available for this study. Of 375 subjects, genome-wide array data were available on 361 and apolipoprotein E (*APOE*) genotype data on 370 for genetic analyses.

2.1.2 | omicsADDS

The omicsADDS includes a subset of participants from a larger, single-site, longitudinal observational study of 612 adults with cytogenetically confirmed DS.[19–21] Adults with DS were considered eligible if (1) the participant was at least 30 years of age, (2) a family member or correspondent provided informed consent, and (3) the participant provided assent. This study included 133 NHW DS individuals, for whom only plasma t-tau was measured among the four aforementioned tau biomarkers, and these subjects were not part of the ABC-DS cohort (Table S1 in supporting information).

2.2 | Plasma tau biomarkers and processing

Measurement of plasma t-tau, obtained from both ABC-DS and omicsADDS, and p-tau181, obtained from ABC-DS, were conducted at the University of North Texas Health Science Center using commercially available single-molecule array (Simoa) technology on the HD-1 analyzer with commercial kits from Quanterix according to the manufacturer's instructions.[22] Pooled plasma control samples were included on each Simoa plate. All assays were conducted in duplicate. Coefficients of variance, lower limits of detection, and higher limits of detection for each marker have been previously reported.[6] The biomarker measures from the earliest available blood sample for each participant were selected for analysis.[22] Plasma p-tau217 was measured using immunoassays on a Meso Scale Discovery platform developed by Lily Research Laboratories.[10] Briefly, biotinylated-IBA493 was used as a capture antibody and SULFO-TAG-4G10-E2 (anti-tau) as the detector, and samples were diluted 1:2. The assay was calibrated with a synthetic p-tau217 peptide.

2.3 | Tau PET imaging and processing

ABC-DS participants underwent tau-PET imaging using ^{18}F-flortaucipir (also known as ^{18}F-AV1451), as previously described.[10] Derived outcome measures of standardized uptake volume ratio (SUVR) were used to index tau burden in the brain. Brain regions of interest were obtained from FreeSurfer (v5.3) parcellations of the co-registered T1-weighted magnetic resonance imaging (MRI). The tau SUVR index was then calculated from the PET data by dividing the signal from the tau-specific regions (entorhinal cortex, parahippocampal cortex, amygdala, middle- and inferior-temporal cortex) by the cerebellar gray matter reference region signal.[23]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature on tau biomarkers in the Down syndrome (DS) population via PubMed. While the pathophysiology of Alzheimer's disease (AD) in DS is less studied, recent publications have addressed this topic. These relevant citations are appropriately referenced.
2. **Interpretation**: Our genome-wide association study of plasma and imaging tau biomarkers in the DS population reveals several potential novel genetic risk factors, highlighting the unique genetic architecture of AD pathology in DS. The observed differences between DS and non-DS cohorts emphasize the importance of conducting population-specific analyses to investigate the distinct mechanisms underlying AD pathology in DS.
3. **Future directions**: With the findings reported in this article, future research of the DS cohort could investigate (a) the genetic factors influencing longitudinal changes in tau biomarkers, (b) shared genetic factors that contribute to both amyloid beta and tau pathologies, and (c) the genetic profile of DS-specific AD pathology by incorporating additional biomarkers.

2.4 | Genotyping, imputation, and quality control

Genome-wide microarray data were generated using the Illumina Infinium Global Screen Array (GSA) version 2.0 and were obtained from the Laboratory of NeuroImaging (LONI) website (https://ida.loni.usc.edu/). Imputation was performed on autosomal chromosomes (excluding chromosome 21) using the TOPMed Imputation Server with the TOPMed reference panel (version r2) to enhance the resolution of the genomic information.[24–26] Variants with imputation quality scores (R^2) > 0.3 were retained, resulting in 22,466,993 variants. All variants were mapped to the GRCh38 assembly.

For quality control (QC), participants with a call rate < 95% were excluded, as were single nucleotide polymorphisms (SNPs) that were not in Hardy–Weinberg equilibrium (HWE; P < 1E-05). SNPs with an imputation quality score R^2 > 0.3, and a minor allele frequency (MAF) ≥ 1% were retained for downstream analyses.

Population stratification was evaluated using PLINK (version 1.9),[27] focusing on common variants (MAF > 5%) that passed QC (N = 6,160,269 SNPs). Principal components (PCs) were calculated using a sliding window approach, with a window size of 2000 base pairs and 200 variants.

2.5 | Chr21 genotyping

Chromosome 21 variants were called as the copy number variations (CNVs) using the cnvPartition CNV analysis (version 3.2.0, Illumina) plug-in in GenomeStudio 2.0 with the Genotyping module. A total of 9785 and 8446 variants were called on GSAv2 and GSAv3, respectively. Consistent with standard practice, the p-arm of chromosome 21 was excluded from analysis due to its highly heterochromatic nature, which contains numerous repetitive sequences. This feature led to a high frequency of disomic variant calls in individuals with DS in our data and inconsistencies between duplicate samples in this region. To ensure data accuracy and reliability, all genotyped variants on the p-arm were omitted from the analysis.

2.6 | *APOE* genotyping

APOE genotypes for rs429358 (*APOE4*) and rs7412 (*APOE2*) SNPs were determined using the KASP genotyping platform provided by LGC Genomics.[28] Of 375 subjects, *APOE* genotype data were available on 370.

2.7 | Statistical analyses

2.7.1 | Phenotype construction

We applied rank-based inverse normal transformation (INT) to all tau biomarkers in R (version 4.4.0) to ensure normality. Covariates included age at the biomarker collection, sex, baseline dementia status, and ancestry's top four PCs. For both ABC-DS and omicsADDS participants, clinical dementia status was determined through a clinical consensus process involving expert DS clinicians, study coordinators, and highly trained and experienced staff. This process used medical, clinical, and cognitive testing data. The consensus conference team was unaware of any biomarker or genetic findings. The consensus diagnosis was based on cognitive and functional status, categorized as cognitively stable (no decline, CS), mild cognitive impairment (decline beyond healthy aging but not meeting dementia criteria, MCI-DS), and dementia (persistent memory loss and functional decline with no other mimicking causes, AD-DS). Those without a clear diagnosis were labeled "unable to determine." For analysis, we combined MCI-DS and AD-DS cases as "dementia" cases and excluded five participants without a valid diagnosis.[18]

2.7.2 | Association of the *APOE* polymorphism

Of the 370 participants with *APOE* genotyping available, participants were categorized into six *APOE* genotypes (2/2, 2/3, 2/4, 3/3, 3/4, and 4/4), defined by *APOE2*, *APOE3*, and *APOE4* alleles. Nine participants with the *APOE 2/4* genotypes were excluded from the analysis because of the opposite effects of these alleles on AD risk and biomarkers. Based on biomarker availability, linear regression analyses were performed to estimate the dosage effects of the *APOE2* and *APOE4* alleles on biomarker levels, including 270 subjects with plasma p-tau181, 269 with p-tau217, 283 with t-tau, and 128 with tau-PET neuroimaging data. Models were adjusted for sex, age at the biomarker collection, and baseline dementia status.

2.7.3 | Single-trait biomarker GWAS

We conducted single-trait association tests for four inverse rank-normalized tau phenotypes using an additive model in PLINK (version 1.9)[27]. Chromosome 21 SNPs were analyzed using MatrixEQTL (version 2.3)[29] with an additive effect model to account for trisomy 21, in which each SNP can have up to four genotype calls. The analysis included the same covariates used in the *APOE* polymorphism associations, with the addition of the top four PCs. Sample sizes varied based on genome-wide genotype and biomarkers data, including 261 individuals for plasma p-tau181, 259 for p-tau217, 275 for t-tau, and 126 for tau-PET neuroimaging. Manhattan and QQ plots were generated after combining GWAS outputs from all chromosomes using the R packages qqman (version 0.1.9)[30] and Haplin (version 7.3.2).[31] Variant-level visualization was performed using LDlinkR package (version 1.4.0).[32]

2.7.4 | Multi-trait biomarker GWAS

A multi-trait GWAS was performed with GEMMA software (version 0.94)[33] on a subset of 76 individuals with complete data for four tau biomarkers. The analysis employed a linear mixed model with default parameters, incorporating a centered relatedness matrix to account for relatedness. The same covariates used in the single-trait GWAS were also applied here.

2.7.5 | Meta-analysis

A meta-analysis of plasma t-tau levels was conducted on 408 individuals on overlapping variants across the ABC-DS and omicsADDS cohorts using METAL (version 2011-03-25) with a standard error–based weighted model adjusted for the genomic inflation factors.

2.7.6 | Dementia status GWAS in ABC-DS

We performed a logistic regression analysis between 92 dementia cases and 238 cognitively stable controls with DS in the ABC-DS cohort using PLINK (version 1.9).[27] Demographic details are presented in Table S2 in supporting information. The group with dementia had a mean age of 53.74 years, while the cognitively stable group had a mean age of 41.83. Both groups exhibited a higher proportion of males, with 60.87% in the dementia group and 52.10% in the cognitively stable group. The analysis adjusted for sex, age at the biomarker

collection, and the top four PCs. Chr21 was excluded from the analysis due to technical problems in performing logistic regression on CNV. Top variants identified for tau biomarkers in DS were assessed for their associations with dementia risk in the DS cohort.

2.7.7 | Polygenic risk score analysis

To examine the association of reported AD risk variants with tau biomarkers in the DS population, we used PRSice-2[34] to calculate the AD polygenic risk score (PRS) from the largest clinical NHW AD case–control study ($N = 788{,}898$).[12] The PRS was calculated as the weighted sum of the risk alleles overlapped in our DS cohort. We applied the standard clumping and *P* value thresholding (C+T) approach on genome-wide significant (GWS) variants. We calculated PRS for the GWS variants on the linkage disequilibrium (LD) clumped SNPs after excluding the variants on chromosome 21. LD clumping excludes variants with $R^2 > 0.1$ in a 250 kb window and keeps the variants with the most significant *P* values in the region. The PRS is standardized to the mean of the population.

We applied linear regression adjusting for key covariates, including age at the biomarker collection, sex, and PCs 1 to 4 to account for population stratification. Additionally, adjustments were made for the *APOE4* and *APOE2* carrier status, which are well-established genetic modifiers of AD risk in non-DS populations. Last, we excluded the *APOE* region (GRCh38, Chr19:43,907,927-45,908,821) to examine the contribution of AD-associated non-*APOE* genome to tau biomarkers in DS. By incorporating these adjustments, we aimed to isolate the contribution of other genetic variants to tau phenotypes while minimizing confounding effects from these known risk factors and demographic variables.

2.7.8 | Comparison of tau-associated variants in DS with non-DS populations

We assessed the tau-associated variants in DS at $P < 1E\text{-}03$ with the summary statistics of the following non-DS data sets: (1) the largest clinically NHW AD case–control data in non-DS,[12] (2) the reported 99 top AD-associated SNPs in non-DS,[11,12] (3) plasma p-tau181 in 1186 subjects and plasma t-tau in 563 subjects,[35] and (4) tau-PET in 1446 participants from seven cohorts.[36]

2.7.9 | Functional annotations

SNPs with available rsIDs which achieved suggestive significance ($P \leq 1E\text{-}05$) were annotated using FUMA-GWAS (https://fuma.ctglab.nl/). Lead SNPs were defined further from these independent significant SNPs if pairwise SNPs had $R^2 < 0.1$. Genomic risk loci were identified in which SNPs were in LD ($R^2 > 0.6$) with independent significant SNPs. The maximum distance for merging LD blocks into a genomic locus was 250 kb. SNPs in LD with independent significant SNPs were defined as tagged SNPs. The genetic data of European populations in the 1000 Genomes phase 3 dataset were used as reference data for LD analyses. FUMA-identified candidate SNPs were functionally annotated with their Combined Annotation Dependent Deletion (CADD) scores, RegulomeDB (RDB) ranks, and chromatin states. GWS variants were further queried with QTLBase for additional quantitative trait loci (QTL) information.[37]

Additionally, variants surpassing the suggestive threshold ($P \leq 1E\text{-}05$) or those in LD ($R^2 > 0.6$) with independent variants were mapped to genes using positional (up to 10 kb), expression QTL (eQTL; with brain datasets as reference), chromatin mapping in FUMA, default false discovery rate (FDR) is applied. Gene-set enrichment analysis was performed using the GENE2FUNC function in FUMA, with gene sets from the Molecular Signatures Database (MSigDB) and the GWAS catalog. The Benjamini–Hochberg[38] method was used for multiple corrections, and an adjusted FDR of 0.05 was used as the significance threshold. A minimum of two input genes overlapping with predefined gene sets was required for gene-enrichment analysis.

3 | RESULTS

3.1 | Participant demographics

The 375 ABC-DS participants included in the analyses are NHWs aged 25 to 81 (54% male; Table 1). Of the 375, 69% were cognitively stable, and 26% had dementia at the time of the blood collection. *APOE4* carriers were more prevalent in the dementia group compared to the cognitively stable group (36.08% vs. 19.69%; $P = 0.001$). Genome-wide genotype data were available on 330 subjects. The number of participants with available baseline plasma tau biomarker data also varied among genome-wide genotyped subjects, ranging from 126 with tau-PET to 275 with plasma t-tau. Only 76 subjects had all four biomarkers and genotypes available in this study cohort. The levels of tau biomarkers were significantly higher in ABC-DS participants having dementia versus no dementia ($P_{\text{p-Tau181}} = 1.93E\text{-}17$, $P_{\text{p-Tau217}} = 1.46E\text{-}14$, $P_{\text{t-Tau}} = 3.53E\text{-}08$, $P_{\text{Tau-PET}} = 4.40E\text{-}05$; Figure S1 in supporting information). A replication sample of 133 DS participants (4% with dementia) having only plasma t-tau was derived from the omicsADDS cohort.

3.2 | Associations of *APOE* polymorphisms

We assessed the relationship between *APOE2* and *APOE4* alleles and tau biomarkers in 361 DS participants after excluding 9 *APOE 2/4* participants (Table 2). While *APOE4* was not associated with any biomarker, *APOE2* showed the expected association with a lower concentration of plasma p-tau217 ($P = 0.023$, $\beta = -0.31$), which remained significant after the additional adjustment for PCs in genome-wide association (GWA) analysis ($P = 0.011$, $\beta = -0.34$). The borderline association of *APOE2* with tau-PET became significant in GWA analysis after the additional adjustment for PCs ($P = 0.015$, $\beta = -0.55$).

TABLE 1 Demographic characteristics of the ABC-DS participants with DS.

	Total (*N* = 375)	p-tau181 (*N* = 261)	p-tau217 (*N* = 259)	t-tau (*N* = 275)	Tau-PET (*N* = 126)	All tau biomarkers[b] (*N* = 76)
Age (mean ± SD)	45.13 ± 9.89	45.25 ± 9.65	44.97 ± 9.80	44.96 ± 9.84	38.59 ± 7.89	40.37 ± 7.97
Sex (*N*, %)						
Male	204 (54.40%)	138 (52.87%)	138 (53.28%)	148 (53.82%)	64 (50.79%)	35 (46.05%)
Female	171 (45.60%)	123 (47.13%)	121 (46.72%)	127 (46.18%)	62 (49.21%)	41 (53.95%)
APOE genotype (*N*, %)						
2/2	2 (0.53%)	2 (0.77%)	2 (0.77%)	2 (0.73%)	2 (1.59%)	2 (2.63%)
2/3	47 (12.50%)	38 (14.56%)	33 (12.74%)	37 (13.45%)	16 (12.70%)	13 (17.11%)
2/4	9 (2.40%)	7 (2.68%)	6 (2.32%)	7 (2.55%)	2 (1.59%)	1 (1.32%)
3/3	232 (61.90%)	155 (59.39%)	163 (62.93%)	170 (61.82%)	80 (63.49%)	47 (61.84%)
3/4	73 (19.47%)	53 (20.31%)	50 (19.31%)	53 (19.27%)	21 (16.67%)	12 (15.79%)
4/4	7 (1.87%)	6 (2.30%)	5 (1.93%)	6 (2.18%)	5 (3.97%)	1 (1.32%)
Not available	5 (1.33%)					
Dementia status[a] (*N*, %)						
Cognitively stable	259 (69.07%)	192 (73.56%)	192 (74.13%)	204 (74.18%)	116 (92.06%)	69 (90.79%)
APOE4 carriers (*N*, %)	51 (19.69%)	39 (20.31%)	36 (18.75%)	40 (19.61%)	25 (21.55%)	12 (17.39%)
Dementia	97 (25.87%)	69 (26.44%)	67 (25.87%)	71 (25.82%)	10 (7.94%)	7 (9.21%)
APOE4 carriers (*N*, %)	35 (36.08%)	27 (39.13%)	25 (37.31%)	26 (36.62%)	3 (30.0%)	2 (28.57%)
Not available	19 (5.07%)					

Abbreviations: ABC-DS, Alzheimer's Biomarker Consortium–Down Syndrome; *APOE*, apolipoprotein E; p-tau181, plasma tau phosphorylated at threonine 181; p-tau217, plasma tau phosphorylated at threonine 217; SD, standard deviation; t-tau, plasma total tau.
[a]Dementia categories were determined through clinical consensus by a team that included a psychologist, physician, and at least two other specialists in Alzheimer's disease dementia in Down syndrome (DS), based on medical, clinical, and cognitive testing data. Participants with DS were classified as cognitively stable (CS; "cognitively stable"), having a mild cognitive impairment (MCI-DS) or dementia; MCI-DS and dementia were combined as "dementia." Cases in which a diagnosis could not be determined were included as "not available."
[b]Total 76 DS subjects with all four tau biomarkers available.

TABLE 2 Association of *APOE2* (rs7412) and *APOE4* (rs429358) polymorphisms and tau biomarkers in a DS population.

AD biomarker	Summary statistics (Mean ± SD)	*N*	*APOE4* (rs429358)		*APOE2* (rs7412)	
			β	*P*	*β*	*P*
p-tau181	3.83 ± 2.6	270	0.03	0.758	−0.10	0.420
p-tau217	0.73 ± 0.6	269	0.03	0.821	−0.31	**0.023***
t-tau	2.65 ± 1.8	283	−0.07	0.561	−0.04	0.779
Tau-PET	1.17 ± 0.2	128	0.02	0.923	−0.38	0.079†

Note: *P*-value was obtained using an additive model adjusted for sex and age at biomarker collection; *$P < 0.05$.
Abbreviations: *APOE*, apolipoprotein E; GWA, genome-wide association; PC, principal component; p-tau181, plasma tau phosphorylated at threonine 181; p-Tau217, plasma tau phosphorylated at threonine 217; SD, standard deviation; tau PET, brain phosphorylated tau measured through positron emission tomography scan; t-tau, plasma total tau.
N = Total number of participants with the *APOE* genotype and tau biomarkers data.
*$P = 0.011$, $\beta = -0.34$ in GWA analysis after the additional adjustments for PCs
†$P = 0.015$, $\beta = -0.55$ in GWA analysis after the additional adjustments for PCs.

3.3 | Single-trait GWAS

We conducted individual single-trait GWAS analyses on all four tau biomarkers. Chr21 was analyzed separately with the same model assuming additive effect and then combined with other chromosomes for visualization. No genomic inflation was detected (Figures S2–S3 in supporting information). Tables S3–S6 in supporting information detail suggestive SNPs with $P \leq 1E\text{-}05$ for each tau biomarker, respectively. Four GWS signals were identified, including three for p-tau181 and one for t-tau (Figures 1–2, Table 3). Notably, one GWS

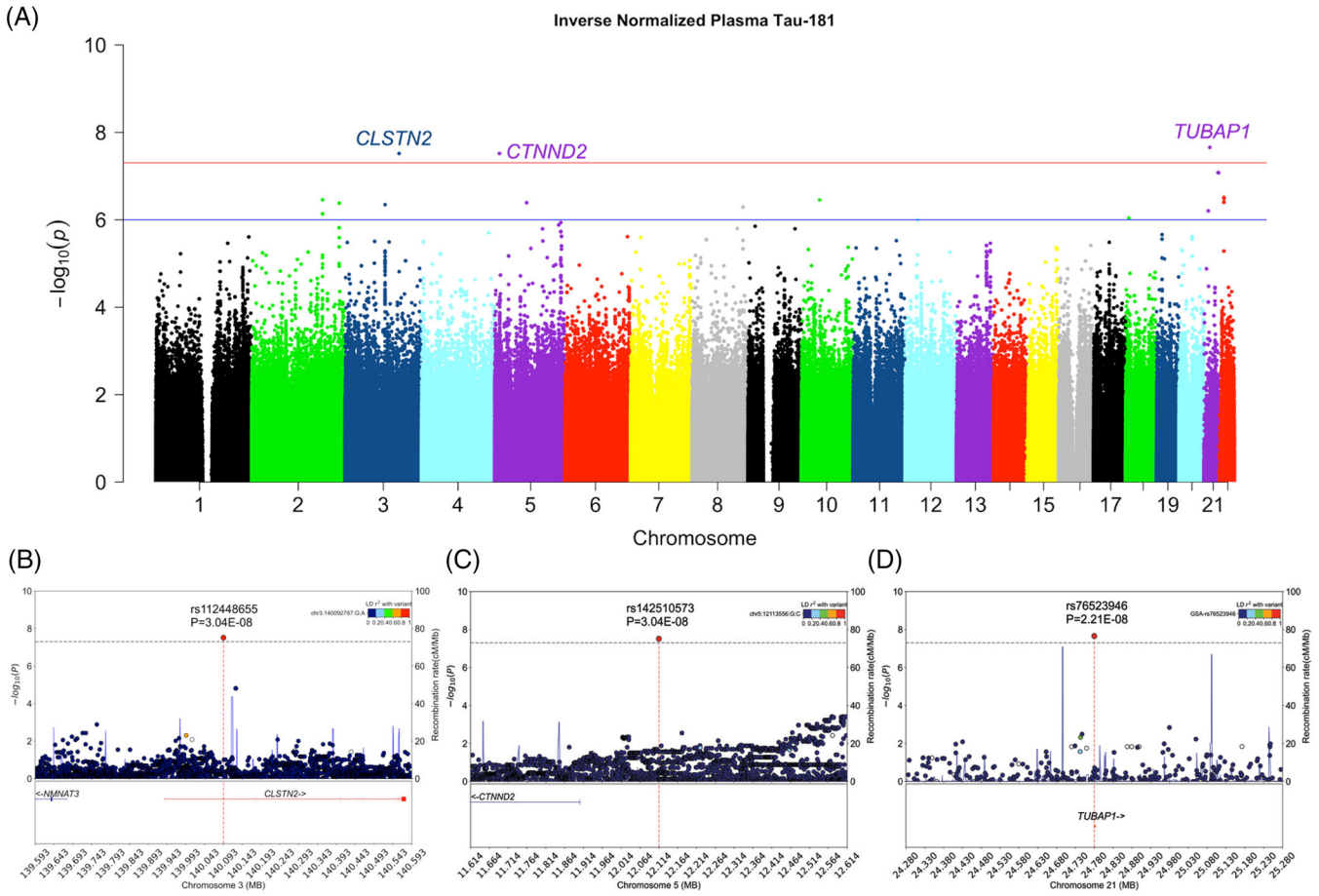

FIGURE 1 Manhattan plot and regional plots of inverse-normalized p-tau181. A, Manhattan plot showing the *P* values in the single-trait GWAS. The blue and red lines represent the suggestive ($P = 1E-06$) and genome-wide significant thresholds ($P = 5E-08$), respectively. Variants that reached the genome-wide threshold are displayed in the plot; (B–D) regional plots for genome-wide significant variants located in the Chr2, Chr5, and Chr21. The relative location of genes and the direction of transcription are shown in the lower portion of the regional plot. GWAS, genome-wide association study; p-tau, phosphorylated tau.

association of p-tau181 was observed on Chr21 in the tubulin alpha pseudogene 1 (*TUBAP1*/rs76523946, MAF = 0.042, $P = 2.21E-08$, $\beta = 0.61$). Carriers of the effect allele of this SNP also showed the same trend of association with tau-PET, although it did not reach the nominal significant threshold ($P = 0.068$, $\beta = 0.19$). The next two loci associated with p-tau181 are located on Chr3 (*CLSTN2*/rs112448655, MAF = 0.012, $P = 3.04E-08$, $\beta = -3.99$) and Chr5 (*CTNND2*/rs142510573, MAF = 0.010, $P = 3.04E-08$, $\beta = -3.99$). The top signal for t-tau was detected in an intron of *JHY* on Chr11 (rs77264104, MAF = 0.017, $P = 1.75E-08$, $\beta = -1.52$). Although this SNP was not statistically significant in the replication omicsADDS cohort having the t-tau data, it showed the same directional association (MAF = 0.015, $P = 0.417$, $\beta = -0.42$), and the meta-*P* is slightly improved ($P_{meta} = 2.91E-08$, $\beta = -1.29$, Table S7 in supporting information). *JHY*/rs77264104 also demonstrated near-nominal association with p-tau217 in the same direction ($P = 0.060$, $\beta = -0.45$). The meta-analysis of plasma t-tau also identified four suggestive associations: *TBLXR1*/rs113681535 on Chr3 ($P_{meta} = 4.91E-07$, $\beta = -0.81$), *MTUS1*/rs3930694 on Chr8 ($P_{meta} = 6.23E-07$, $\beta = -0.41$), *ITCH*/rs145727609 on Chr20 ($P_{meta} = 9.35E-07$, $\beta = 1.27$), and *CBX7*/rs117125511 on Chr22 ($P_{meta} = 9.93E-07$, $\beta = -0.99$). Those suggestive variants also show consistent directional effect in the replication cohort (Table S7).

For p-tau217, the top signal in an intron of *MRC1* on Chr10 achieved nearly genome-wide significance (rs692025, MAF = 0.068, $P = 5.65E-08$, $\beta = -0.77$; Figure 3). For tau-PET, four suggestive associations were observed with a *P* range from 7.83E-07 to 3.14E-07 (Figure 4). Interestingly, one suggestive signal for tau-PET on Chr7 (*CRYGN*,*RHEB*/rs12538040, MAF = 0.196, $P = 3.80E-07$, $\beta = -0.84$) was also nominally significant with the same direction for p-tau217 ($P = 0.032$, $\beta = -0.21$).

3.4 | Mult-trait GWAS

Multi-trait GWAS was performed on a subset of 76 participants from ABC-DS with all four tau biomarker measurements available, aiming to identify pleiotropic loci that simultaneously contribute to all tau

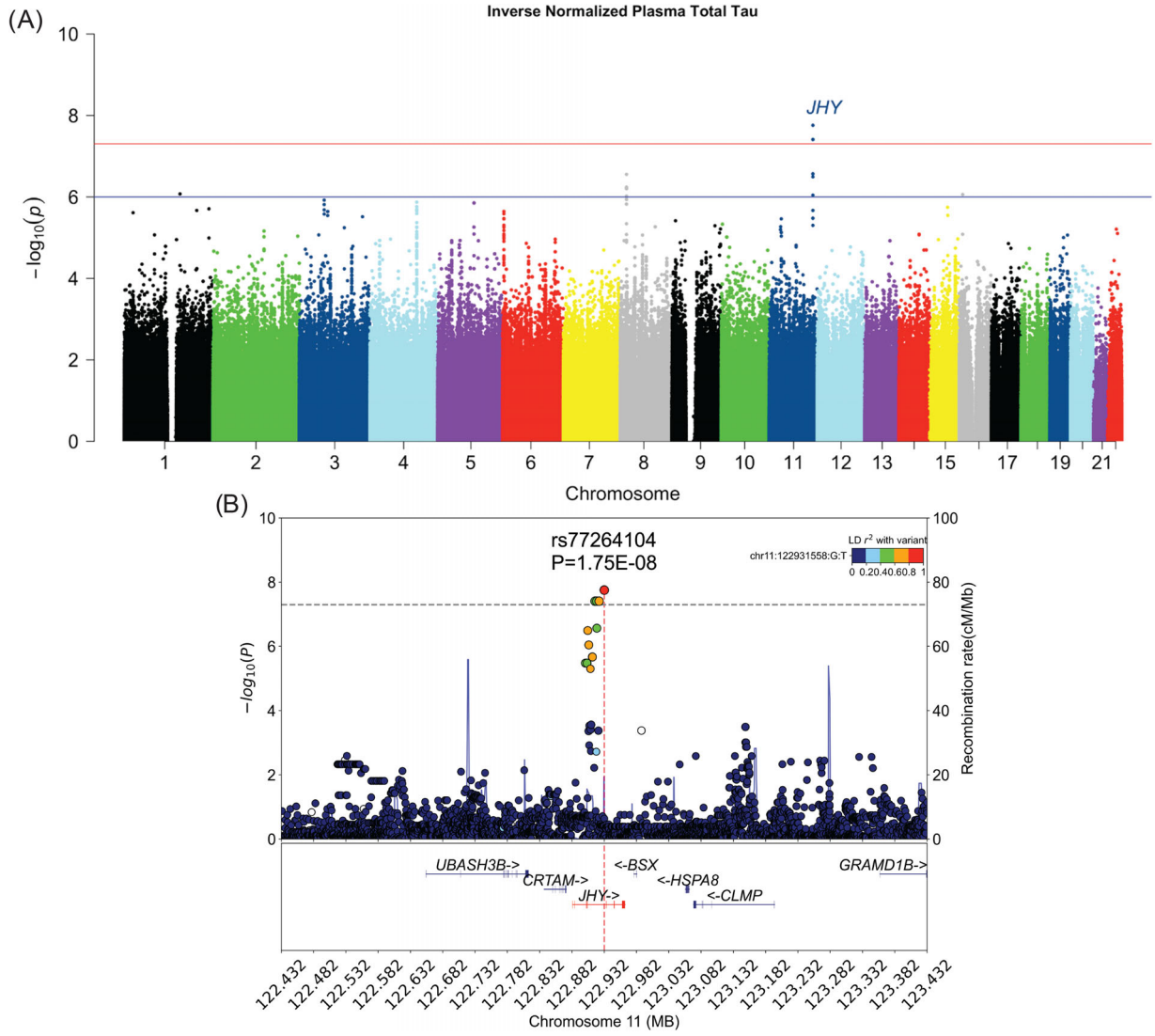

FIGURE 2 Manhattan plot and regional plots of inverse-normalized t-tau. A, Manhattan plot showing the *P* values in the single-trait GWAS. The blue and red lines represent the suggestive ($P = 1E-06$) and genome-wide significant thresholds ($P = 5E-08$), respectively. Variant that reached genome-wide threshold of $P = 5E-08$ is displayed in the plot; (B) regional plot for the top SNP on Chr11. The relative location of genes and the direction of transcription are shown in the lower portion of the regional plot. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; t-tau, total tau.

biomarkers. There was a relatively high positive correlation between p-tau181 and p-tau217 (Pearson $r = 0.65$, $P < 2E-16$) followed by a moderate to low correlation of tau-PET with p-tau181 (Pearson $r = 0.44$, $P = 3.88E-06$) and p-tau217 (Pearson $r = 0.38$, $P = 3.26E-05$), respectively (Figure S4 in supporting information). In contrast, t-tau showed a relatively weaker correlation with p-tau181 (Pearson $r = 0.33$, $P = 4.66E-07$), p-tau217 (Pearson $r = 0.35$, $P = 4.43E-08$), and tau-PET (Pearson $r = 0.24$, $P = 7.54E-03$) (Figure S4). The multi-trait GWAS on four tau biomarkers identified 37 suggestive associations at $P \leq 1E-05$ (Table S8 in supporting information), but none overlapped with the top SNPs for individual biomarkers. Among the top six variants (*P* range from 3.96E-07 to 1.04E-07), three linked common variants (rs3106346, rs369963387, rs1849188; MAF = 0.329, $P = 3.96E-07$) define a locus on Chr17 near the *ARL17A* and *NSF* genes, a region previously implicated in protecting against the risk of AD among non-*APOE4* carriers.[39,40] A fourth common missense SNP (rs1863115, p.Phe1141Leu; MAF = 0.303, $P = 4.13E-06$) located in a nearby *LRRC37A2* gene, which is in LD with the above-mentioned three variants ($R^2 = 0.858$ to 0.874, Table S9a in supporting information), is also part of this association and may be a functional variant (Figure 5). However, the association of these SNPs with tau biomarkers is independent of the reported AD association with *NSF*/rs199533 ($R^2 = 0.045$ to 0.047, Table S9a). These significant SNPs are ≈ 500 to 600 kb downstream from the *MAPT* gene that codes for tau found in neurofibrillary tangles.

Next, we examined if genetic variation in *MAPT* is associated with tau biomarkers and dementia risk in DS. As shown in Table S9b, six intronic SNPs in *MAPT* are nominally associated with lowering levels

TABLE 3 Top variants for each tau biomarker in single-trait GWAS analyses.

								p-tau181 (*N* = 261)		t-tau (*N* = 275)		p-tau217 (*N* = 259)		Tau-PET (*N* = 126)	
CHR	BP	SNP	A1	A2	LOC	GENE	MAF	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
21	24779993	rs76523946[a]	C	T		*TUBAP1*	0.042[b]	0.61	**2.21E-08**	−0.01	0.921	0.17	0.164	0.19	0.068
3	140092787	rs112448655	A	G	intronic	*CLSTN2*	0.012	−3.99	**3.04E-08**	0.59	0.141	0.07	0.825	−0.71	0.330
5	12113556	rs142510573	C	G	intergenic	*CTNND2*	0.010	−3.99	**3.04E-08**	0.90	0.058	0.39	0.419	0.56	0.411
11	122931558	rs77264104	T	G	intronic	*JHY*	0.017	−0.41	0.148	−1.52	**1.75E-08**	−0.45	0.060	−0.77	0.268
10	17855464	rs692025	A	G	intronic	*MRC1*	0.068	0.01	0.960	−0.22	0.175	−0.77	**5.65E-08**	−0.29	0.200
17	280358	rs117287880	A	T	intronic	*RPH3AL*	0.035	−0.05	0.783	−0.28	0.153	−0.13	0.525	−1.70	**3.14E-07**
7	151446370	rs12538040	G	T	intergenic	*CRYGN*, *RHEB*	0.196	−0.09	0.294	−0.08	0.462	−0.21	0.032	−0.84	**3.80E-07**
6	119611710	rs9481947	A	G	intergenic	*MAN1N1*	0.030	0.02	0.927	−0.45	0.066	−0.04	0.846	−1.79	**4.60E-07**
9	136244118	rs76574146	G	T	intronic	*QSOX2*	0.093	−0.07	0.533	0.11	0.430	−0.09	0.468	1.90	**7.83E-07**

Abbreviations: A1, effect allele; A2, reference allele; BP, base pair; CHR, chromosome; LOC, location; MAF, minor allele frequency; p-tau181, plasma tau phosphorylated at threonine 181; p-tau217, plasma tau phosphorylated at threonine 217; SNP, single nucleotide polymorphism; Tau-PET, brain phosphorylated tau measured through positron emission tomography scan; t-tau, plasma total tau.

[a]The variant is genotyped.

[b]The minor allele frequency for chr21 SNPs was calculated using three alleles.

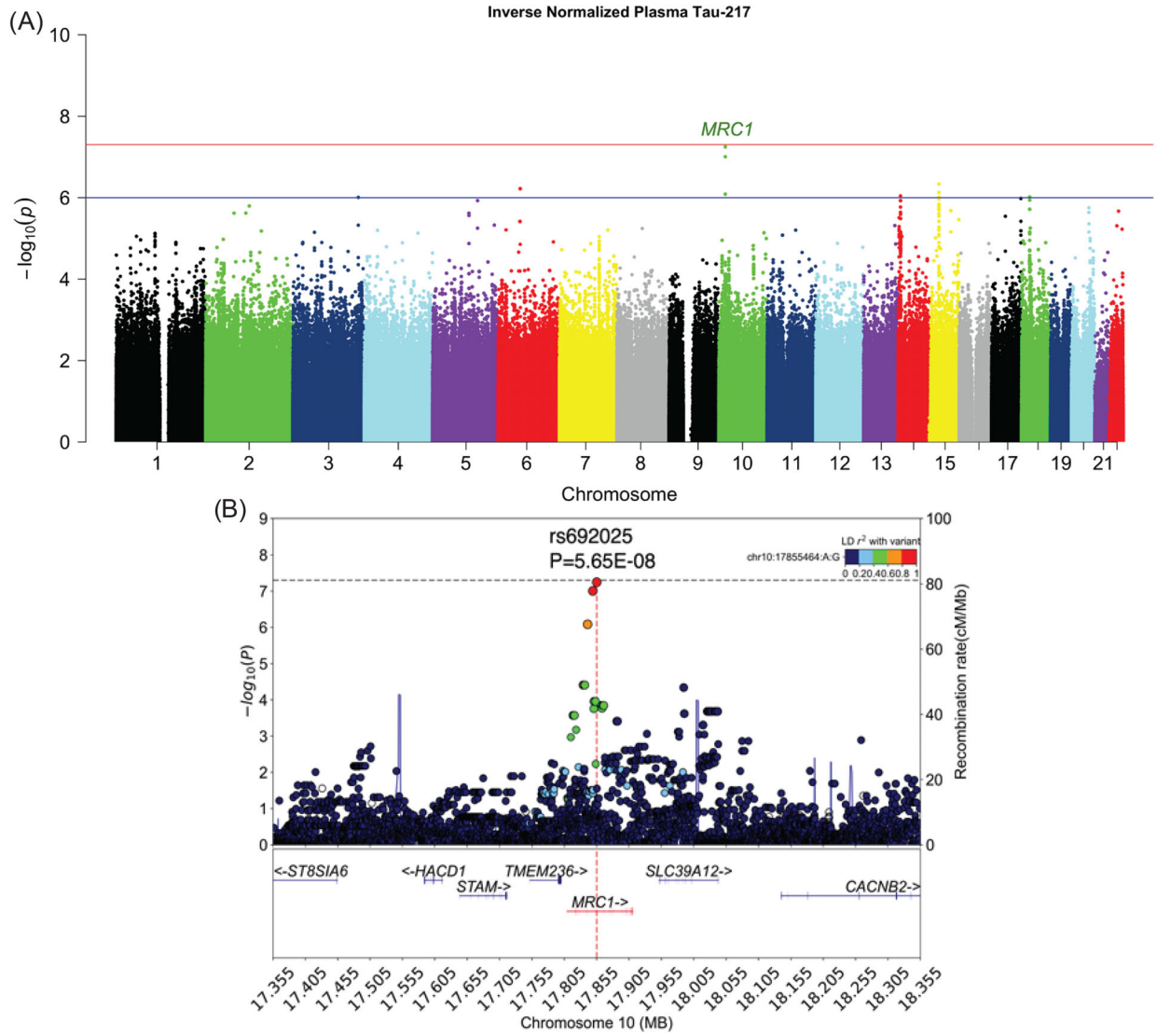

FIGURE 3 Manhattan plot and regional plots of inverse-normalized p-tau217. A, Manhattan plot showing the *P* values in the single-trait GWAS. Variant that reached subthreshold genome-wide threshold of $P = 5E\text{-}08$ is displayed in the plot; (B) regional plot for the top SNP on Chr10. The relative location of genes and the direction of transcription are shown in the lower portion of the regional plot. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; p-tau, phosphorylated tau.

of p-tau181 or tau-PET and reduced risk against dementia in DS and they are not in LD with the above four SNPs. However, four of six *MAPT* SNPs (rs8078967, rs1001945, rs9904290, rs8080903) are in LD ($R^2 = 0.992$ to 0.998, Table S9c) and thus represent a single association with a lowering effect on p-tau181 and reduced risk of dementia. The other two SNPs, *MAPT*/rs8067056 and *MAPT*/rs2435203, are independently associated with lower tau-PET levels in the brain and correspondingly lower dementia risk in DS (Table S9c).

3.5 | Comparison of DS tau-associated SNPs with non-DS populations

To explore the potential overlapping and differential genetic underpinnings of tau biomarkers in DS and non-DS populations, we compared tau-associated variants in DS ($P < 1E\text{-}03$) to the GWAS summary statistics of the corresponding tau biomarkers in non-DS and vice versa.[35,36] We only found one overlapping variant for t-tau and another three for p-tau181 (Table S10 in supporting information). The limited overlap indicates that while some genetic factors may be shared, the genetic architecture driving tau pathology may differ significantly between DS and non-DS populations.

Furthermore, we examined the top tau-associated variants in DS with AD risk in both DS and non-DS populations (Table S11 in supporting information). Seven intronic SNPs in *NOVA1* are associated with elevating plasma p-tau217 levels and represent a single association on Chr14 due to LD between them; they are also risk factors for dementia in DS (odds ratio [OR] = 1.70; $P = 3.80E\text{-}02$). On the other hand, three intergenic SNPs on Chr18, which also represent a single association and lower p-tau217, are protective against dementia in DS

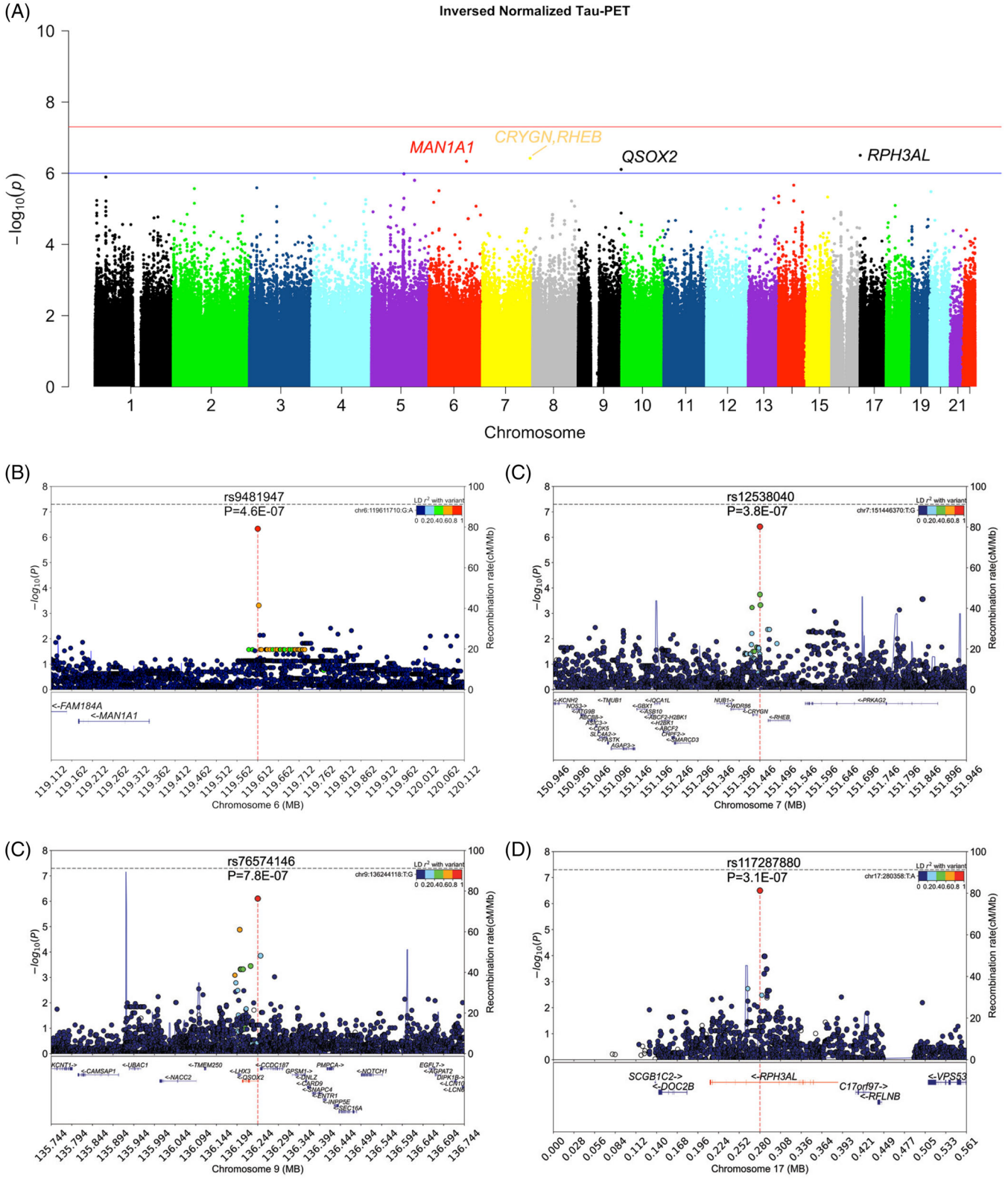

FIGURE 4 Manhattan plot and regional plots of inverse-normalized tau-PET. (A) Manhattan plot showing the *P* values in the single-trait GWAS. The blue and red lines represent the suggestive ($P = 1E-06$) and genome-wide significance thresholds ($P = 5E-08$), respectively. Variant that reached genome-wide suggestive threshold of $P = 1E-06$ is displayed in the plot; (B)–(E) regional plot for the top SNP on Chr6, Chr9, Chr11, and Chr17. The relative location of genes and the direction of transcription are shown in the lower portion of the regional plot. GWAS, genome-wide association study; PET, positron emission tomography; SNP, single-nucleotide polymorphism.

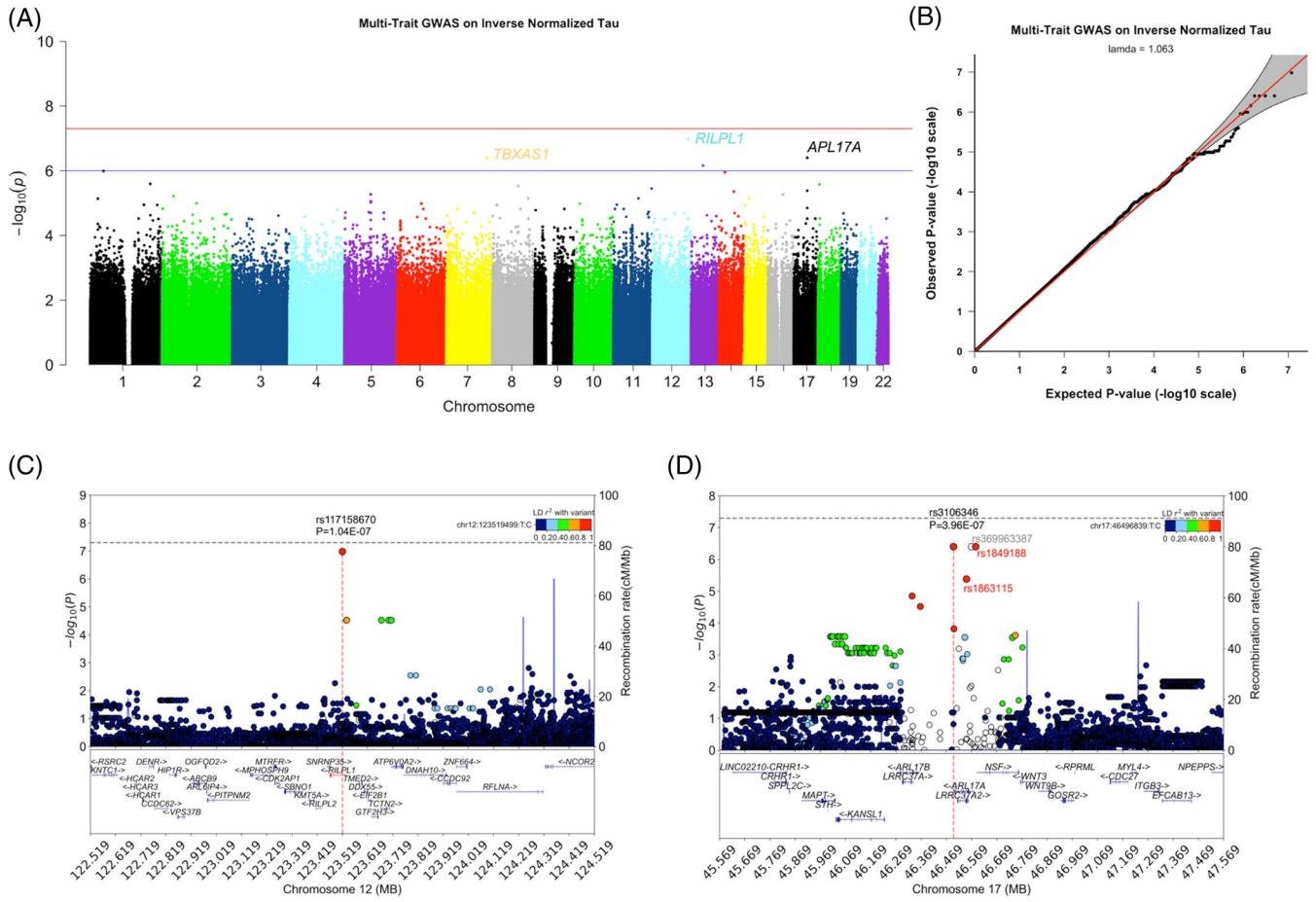

FIGURE 5 Manhattan plot and regional plots of multi-trait GWAS on all tau biomarkers. A, Manhattan plot showing the *P* values in the single-trait GWAS. The blue and red lines represent the suggestive (*P* = 1E-06) and genome-wide significant thresholds (*P* = 5E-08), respectively. Variant that reached genome-wide suggestive threshold of *P* = 1E-06 is displayed in the plot; (B) quantile–quantile plot for the multi-trait GWAS results on all four tau biomarkers; (C)–(D) regional plot for the top SNP on Chr12 and Chr17. The relative location of genes and the direction of transcription are shown in the lower portion of the regional plot. GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

(OR = 0.62; *P* = 3.30E-02). A similar lowering effect of SNPs on Chr22 for p-tau217 and on Chr1 for t-tau are associated with protection against dementia in DS. However, this correlation of tau markers in DS did not extend to AD risk in non-DS. On the other hand, three additional loci of tau biomarkers demonstrated a correlation with AD in non-DS that was not observed in DS: *LINC01170,ZNF608*/rs183445515 on Chr5 that was associated with a lower concentration of p-tau181, also showed protection against AD risk (OR = 0.93, *P* = 1.03E-02); *GSTTP2*/rs5760072 that is part of four linked SNPs on Chr22 and associated with higher concentration p-tau181, also increased AD risk (OR = 1.02, *P* = 4.88E-02); and *ZNF608*/rs183445515 that lowered p-tau217 also lowered the AD risk (OR = 0.93, *P* = 1.03E-02).

Of the 99 previously reported AD risk variants, 77 were present in our DS cohort, and 7 of them showed nominal associations with the same directional effects (Table S12 in supporting information), including one for p-tau181 (*WWOX, MAF*/rs450674: *P* = 9.53E-03), two for p-tau217 (*ABCA1*/rs1800978: *P* = 3.46E-02; *TSPAN14*/rs1878036: *P* = 2.16E-02), one for t-tau (*SLC24A4*/rs10498633: *P* = 1.25E-02), and three for tau-PET (*DOC2A*/rs1140239: *P* = 9.89E-03; *LOC107984208,ECHDC3*/rs7920721: *P* = 3.89E-02; *CLU*/rs9331896: *P* = 3.89E-02).

3.6 | PRS analysis

The PRS for AD was positively associated with tau-PET, p-tau217, and t-tau, with the highest association with tau-PET (*P* = 6.57E-04), which remained significant after additional adjustments for *APOE4* and *APOE2* or excluding the *APOE* region (Table S13 in supporting information). The AD-PRS was negatively associated with dementia in DS (OR = 0.37), which remained significant after adjusting for *APOE2* but became non-significant when additional adjustments were made for *APOE4* or excluding the *APOE* region.

3.7 | Functional annotations

Two SNPs for the Chr17 suggestive signal in the multi-trait analysis have RDB rank of 1d (*ARL17A-NSF*/rs1849188) and 2b (*LRRC37A2*/rs1863115, p.Phe1141Leu), indicating they can affect

transcription binding and expression of a gene target. The missense variant also has a CADD score of 14.74, indicating it is potentially pathogenic. While *LRRC37A2*/rs1863115 is cis-eQTL for *ARL17A*, *ARL17B*, and *NSFP1* in the brain, *ARL17A-NSF*/rs1849188 is cis-eQTL for *ARL17B* in blood (Table S14a in supporting information). Five of the six *MAPT* SNPs showing nominal associations with tau biomarkers have a RDB rank of 1f, indicating a high degree of evidence for being a regulatory variant that can affect transcription binding and gene expression. All six *MAPT* SNPs are eQTLs for multiple genes in this region of Chr17 (Table S14b).

Among the GWS signals, we found two potential mQTLs in blood using QTLBase. The index variant for p-tau181, *TUBAP1*/rs76523946, showed evidence of negatively influencing DNA methylation levels near *SMIM20* (effect size = −0.67, P = 9.38E-08). On the other hand, the lead SNP for t-tau, *JHY*/rs77264104, demonstrated evidence of positively influencing DNA methylation levels near *AKAP11* (effect size = 0.78, P = 2.36E-08).

The mapped genes from FUMA were included in enrichment analysis for specific biological functions through MSigDB, which included Kyoto Encyclopedia of Genes and Genomes (KEGG)-, Gene Ontology (GO)-, and GWAS Catalog–reported genes (Table S15 in supporting information). For p-tau181 and tau-PET, two immune-related genes, *CXCL14* and *IL9*, were enriched in "Cerebrospinal fluid p-Tau levels in Alzheimer's disease dementia" (FDR = 5.00E-04) process from the GWAS Catalog (https://www.ebi.ac.uk/gwas/home), which directly linked our findings to AD-associated tau pathology. Additionally, five genes, including two associated with synaptic plasticity (*CAPN12* and *HNRNPL*) and three immune-associated genes (*LGALS7*, *LGALS7B*, and *LGALS4*), were enriched in "Logical memory (immediate recall) in the mild cognitive impairment" process for t-tau. In addition, we also observed several pathways of interest, including triglyceride levels and sleep duration, that are directly associated with AD and pathways associated with intermediate filaments, which have been shown in neurofibrillary tangles (NFTs), indirectly associated with AD.[41]

4 | DISCUSSION

Using single-trait and multi-trait GWAS approaches, we investigated genetic associations with tau biomarkers in two cohorts with DS. The analyses were adjusted for dementia status, given that tau biomarker levels differ significantly in their means between dementia cases and cognitively stable DS participants. GWS associations were observed for t-tau and p-tau181, and suggestive association ($P \leq$ 1E-06) for tau-PET and in multi-trait analysis.

The Chr21 variant *TUBAP1*/rs76523946 is linked to higher p-tau181 levels and may increase AD risk in individuals with DS. The extra copy of *TUBAP1* and other Chr21 genes could affect microtubule dynamics. *TUBAP1*, a pseudogene related to tubulin alpha, is a key protein of cytoskeleton,[42] which affects microtubule stability and motor protein function and can severely impair axonal transport, leading to synaptic integrity deterioration, a hallmark of AD pathology.[43] In AD, disruptions in *TUBAP1* function can destabilize microtubules, impairing intracellular transport. This, in turn, leads to abnormal tau protein phosphorylation, which promotes tau aggregation and the formation of NFTs, a hallmark of AD pathology.[44]

We observed two additional GWS variants for p-tau181: *CLSTN2*/rs112448655 on Chr3 and *CTNND2*/rs142510573 on Chr5. *CLSTN2* (calsyntenin 2) positively regulates synapse assembly and synaptic transmission, which are essential for maintaining neuronal communication, synaptic plasticity, learning, and memory.[45] Synaptic dysfunction, an early hallmark of AD, precedes other more obvious signs of neurodegeneration, such as neuronal death, and strongly correlates with the severity of cognitive decline.[46,47] Because *CLSTN2* is involved in both synapse formation and function,[48] any disruptions in its activity could exacerbate synaptic loss, contributing to the early stages of AD. *CTNND2* encodes delta-catenin 2, a protein crucial for neuronal signaling and synaptic function.[49] It disrupts E cadherin–based adherend junctions, favoring cell expansion when stimulated by hepatocyte growth factor. Alterations in *CTNND2* impact synaptic stability, connectivity, neuronal development, and critical learning and memory processes.[50–52] These alterations have been previously implicated in neurodevelopmental diseases such as autism and attention hyperactivity.[51] Interestingly, elevated levels of delta-catenin have been reported in supranuclear cataracts in both DS and AD patients due to abnormal amyloid deposition in the lens.[53] In vitro cell-based studies have also shown that delta-catenin could regulate *APP* processing by interacting with *PS1*.[54]

The Chr11 signal, rs77264104, for t-tau is in the *JHY* gene that codes for junctional cadherin complex regulator protein involved in axoneme assembly and brain development. Axoneme assembly refers to the formation of the axoneme, the structural core of cilia and flagella, composed of highly organized microtubules, which is critical for the movement of cilia on astrocytes for neuronal signaling.[55] In animal models, overexpression of *APP* causes alterations in primary cilia, and inhibition of primary cilia causes increased AD neuropathology.[56,57] The functional annotation also indicated that this variant might affect tDNA methylation patterns of *AKAP11* and *SMIM20*. Loss-of-function mutations in *AKAP11* disrupt endolysosomal homeostasis within neurons.[58] This can lead to impaired endosomal trafficking of Aβ42, typically followed by lysosomal degradation and autophagic clearance of abnormal proteins. Understanding AKAP11's specific molecular mechanisms may pave the way for targeted therapies to alleviate Aβ pathology.[59] Although the role of *SMIM20* in tau pathology or dementia remains largely unexplored, a previous study reported its associations with paired helical filament tau,[60] highlighting its potential role in tau pathology.

Meta-analysis on t-tau identified additional suggestive signals relevant to AD pathology in DS. For example, mutations in *TBL1XR1* on Chr3 (P = 4.91E-07) that codes for TBL1X/Y related 1, disrupt the balance of neuronal progenitor cells, reducing proliferation and increasing differentiation.[61] This imbalance alters cortex neuron types and dendritic arborization.[61] Such dendritic abnormalities are significant, as they are present in DS and contribute to the intellectual disabilities associated with the condition.[62] Dysregulation of *ITCH* on Chr20 (P = 9.35E-07) that codes for itchy E3 ubiquitin-protein ligase can

lead to aberrant cell cycle re-entry and neuronal apoptosis, a process observed in AD and other neurodegenerative disorders.[63]

A subthreshold GWS signal rs692025 (P = 5.65E-08) for p-tau217 on Chr10 is located in *MRC1* that encodes a mannose receptor primarily associated with the M2-like activation state of microglia, which is characterized by anti-inflammatory and tissue-repair functions.[64] Impaired function or altered expression of *MRC1* could reduce the capacity of microglia to clear Aβ,[65] leading to plaque accumulation and neurodegeneration.

Multi-trait analysis identified a suggestive locus on Chr 17 that may contribute to all tau biomarkers simultaneously. Multiple significant variants (P = 3.96E-07) define this locus and implicate the *LRRC37A2*, *ARL17A*, and *NSF* genes. However, this locus is independent of the previously implicated locus for AD in or near *NSF*.[39,40] Two nearby independent signals on Chr17q21.31 seem due to their locations in a complex genomic region containing a 900 kb inversion[66] containing two extended haplotypes (H1 and H2) which are near complete LD with the inversion phases, and SNPs for the two signals are likely to be located on opposite haplotypes. Future studies on these two extended haplotypes may help to provide the answer. These top variants did not overlap with single-trait GWA results, which may stem from several factors. While previous studies suggest that multi-trait GWAS enhances power in detecting associations among highly correlated phenotypes,[67,68] the sample size is limited.[69] Moreover, the top variants identified in single-trait GWA analyses had MAF of ≈ 1%, indicating a small number of minor allele carriers among the 76 samples. Furthermore, multi-trait GWAS aims to identify variants with pleiotropic effects, whereas all four tau biomarkers complement each other in AD diagnosis and monitoring. For example, p-tau181 showed lower diagnostic accuracy than p-tau 217, particularly in distinguishing AD from other tau pathologies.[70,71] Plasma t-tau, which showed less correlation with the other tau biomarkers in our study, is a neurodegeneration biomarker.[72] The different correlation patterns in our study (Figure S4) and prior findings on tau and other plasma biomarkers highlight the potential for leveraging different combinations in future multi-trait GWAS analyses.[73,74]

We also compared our GWAS findings of tau biomarkers to the summary statistics from recently published large-scale non-DS GWASs.[35,36] Although no variants overlapped at a genome-wide suggestive threshold ($P \leq$ 1E-05), a few variants were nominally significant in both DS and non-DS populations. While DS and non-DS individuals exhibit tau pathology, particularly the spread of misfolded phosphorylated tau, factors like age-of-onset suggest that underlying disease mechanisms may not fully overlap.[44] Although our sample size is limited, some genetic variants identified in our DS cohort may represent DS-specific loci, reflecting the unique genetic architecture of trisomy 21. Moreover, we compared our *APOE* findings in DS to summary statistics in non-DS, aiming to provide further insight into the potential differences and similarities in AD mechanisms across DS and non-DS populations. Previous studies in non-DS showed a significant association of *APOE4* with tau-PET, independent of amyloid,[13,14] and CSF p-tau (P = 9.59E-59).[15] In our AD case–control analysis in DS, *APOE4* showed only a modest association with dementia (P = 5.76E-04) and was not the top SNP, which differs from non-DS studies where it is always the top significant SNP. The AD PRS was also not associated with dementia risk in DS; rather it was protective (OR = 0.37). In our DS cohort, *APOE4* was not associated with any tau biomarkers. One non-DS study reported a GWS signal for *MAPT*/rs242557 associated with higher plasma t-tau levels (P = 4.85E-09)[75] that, although it showed a directional trend in our DS cohort, was not even nominally significant (P = 0.076). Further, we intended to examine two AD-associated top variants located on Chr21,[11] *ADAMTS1*/rs2830500 and *APP*/rs48170900, but these two and those in high LD variants were absent in our genotyped panel. With the upcoming whole-genome sequencing data in DS, we aim to address this question.

Our findings suggest that AD mechanisms may differ between DS and non-DS populations and that DS may have specific genetic variants contributing to dementia. The main limitation of this study is the small sample size, especially for the multi-trait GWAS approach. Recruiting a large cohort of people with DS for research studies is challenging due to the relatively low prevalence of DS in the general population, variability in health-care access, and the need for informed consent through caregivers. However, our study represents one of the largest DS cohorts. Additionally, for variant-level QC, we applied a MAF threshold of 1%, which may not fully account for the power needed in this small cohort, as it is based on population frequency rather than the actual number of alleles in the study sample. A possible solution for further analyses could be combining MAF with minor allele count criteria to improve the reliability of variant selection. Despite these limitations, our GWAS of plasma and imaging tau biomarkers in the DS population highlights several potential genetic risk factors, emphasizing the distinct genetic architecture in DS. The observed differences between DS and non-DS cohorts underscore the need for population-specific analyses to explore AD-related mechanisms unique to DS.

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study participants, their families, and care providers, and the ABC-DS research and support staff for their contributions to this study. This manuscript has been reviewed by ABC-DS investigators for scientific content and consistency of data interpretation with previous ABC-DS study publications. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the CPFT, the NIHR or the UK Department of Health and Social Care. National Institute on Aging (NIA), Grant/Award Number: U01 AG051406, U01 AG051412, R01 AG064877, U19 AG068054; The Alzheimer's Disease Research Centers, Grant/Award Numbers: P50 AG008702, P30 AG062421, P50 AG16537, P50 AG005133, P50 AG005681, P30 AG062715, P30 AG066519; Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers, Grant/Award Numbers: U54 HD090256, U54 HD087011, P50 HD105353; National Center for Advancing Translational Sciences, Grant/Award Numbers: UL1 TR001873, UL1 TR002373, UL1 TR001414, UL1 TR001857, UL1 TR002345; Alzheimer's Disease and Related Dementias, Grant/Award Number: U24 AG21886.

CONFLICT OF INTEREST STATEMENT

Bradley Christian receives PET precursor and compounds from Avid Radiopharmaceuticals Inc and equipment from Cerveau Technologies. Benjamin Handen receives funding from National Institute of Child Health and Human Development, Autism Speaks, Roche Pharmaceuticals, and Patient-Centered Outcomes Research Institute (PCORI). Mark Mapstone is an inventor on patents related to biomarkers of neurodegenerative diseases owned by Georgetown University and the University of Rochester. The other authors declare no conflict of interest. Author disclosures are availaible in the Supporting Information.

CONSENT STATEMENT

All participants in the ABC-DS cohort provided informed consent as required by the grant proposal and approved by the relevant institutional review board. All study procedures were performed in accordance with the Declaration of Helsinki ethical principles. Data obtained from publicly available resources did not require consent, as these datasets contain no personal information and are limited to summary statistics.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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