RESEARCH ARTICLE

# Genome-Wide Meta-Analysis of Cerebrospinal Fluid Biomarkers in Alzheimer's Disease and Parkinson's Disease Cohorts

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**ABSTRACT: Background:** Amyloid-β, phosphorylated tau (p-tau), and total tau (t-tau) in cerebrospinal fluid are established biomarkers for Alzheimer's disease (AD). In other neurodegenerative diseases, such as Parkinson's disease (PD), these biomarkers have also been found to be altered, and the molecular mechanisms responsible for these alterations are still under investigation. Moreover, the interplay between these mechanisms and the diverse underlying disease states remains to be elucidated.
**Objective:** To investigate genetic contributions to the AD biomarkers and assess the commonality and heterogeneity of the associations per underlying disease status.
**Methods:** We conducted genome-wide association studies (GWASs) for the AD biomarkers on subjects from the Parkinson's Progression Markers Initiative, the Fox Investigation for New Discovery of Biomarkers, and the Alzheimer's Disease Neuroimaging Initiative, and meta-analyzed with the largest AD GWAS. We tested heterogeneity of associations of interest between different disease statuses (AD, PD, and control).
**Results:** We observed three GWAS signals: the *APOE* locus for amyloid-β, the 3q28 locus between *GEMC1* and *OSTN* for p-tau and t-tau, and the 7p22 locus (top hit: rs60871478, an intronic variant for *DNAAF5*, also known as *HEATR2*) for p-tau. The 7p22 locus is novel and co-localized with the brain *DNAAF5* expression. Although no heterogeneity from underlying disease status was observed for the earlier GWAS signals, some disease risk loci suggested disease-specific associations with these biomarkers.
**Conclusions:** Our study identified a novel association at the intronic region of *DNAAF5* associated with increased levels of p-tau across all diseases. We also observed some disease-specific genetic associations with these biomarkers. Published 2023. This article is a U.S. Government work and is in the public domain in the USA.

**Key Words:** Parkinson's disease; Alzheimer's disease; genome-wide association study; longitudinal GWAS

## Introduction

Alzheimer's disease (AD) poses a significant social burden globally.[1,2] Cerebrospinal fluid (CSF) levels for amyloid-β (Aβ), phosphorylated Tau (p-tau), and total Tau (t-tau) are established AD biomarkers integrated into the National Institute on Aging–Alzheimer's Association research framework for AD.[3] The pathological significance of these biomarkers has been studied, and genome-wide association studies (GWASs) for these biomarkers have identified several GWAS loci associated with AD risk and progression.[4-8] CSF Aβ levels have been shown to be lower in AD cases, whereas levels of CSF p-tau are elevated compared with healthy

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subjects. Interestingly, these biomarkers were also reported to be altered in Parkinson's disease (PD).[9-11] Previous studies that directly explored the relationship between these CSF biomarkers and PD showed a decrease in levels of both CSF Aβ and p-tau in cases versus control subjects. However, the genetic background of these observations across neurodegenerative diseases has not been well investigated.

In this study, we conducted GWASs on the AD biomarkers of participants from PD-focused studies: the Parkinson's Progression Markers Initiative (PPMI)[12] and the Fox Investigation for New Discovery of Biomarkers (BioFIND). We combined these results with the largest GWAS conducted on mixed cohorts for AD and control subjects.[5] We stratified the analysis on the recruitment study arms of each cohort and assessed the overall genetic contributions across healthy control (HC) and case subjects for AD and PD groups irrespective of clinical phenotype. In addition, we investigated disease-specific genetic contributions through the genetic heterogeneity between individuals with PD, individuals with AD, and healthy volunteers using the earlier PD studies and the Alzheimer's Disease Neuroimaging Initiative (ADNI). We also assessed the genetic associations with the biomarker changes over time when longitudinal data were available.

## Subjects and Methods

### Participants

PPMI is an ongoing longitudinal observational study with multiple study arms. The current analyses included data from participants with early-stage idiopathic PD who had not yet received medication for PD at enrollment (PPMI_PD); HC subjects (PPMI_HC); those with scans without evidence of dopaminergic deficit but with parkinsonism (PPMI_SWEDD); and those with prodromal symptoms such as hyposmia, REM sleep behavior disorder, and image-confirmed dopaminergic deficit (PPMI_PRODROMAL). This study also included two genetically enriched study arms from PPMI where carriers of any high-risk or causal variant for PD (*LRRK2* G2019S, R1441C/G, *GBA1* N409S, L483P, 84GG, and *SNCA* A53T) were recruited. Both carriers with PD less than 7 years from diagnosis (PPMI_GENPD) and unaffected carriers or their first-degree family members (PPMI_GENUN) were analyzed. BioFIND was a cross-sectional study with two study arms: PD cases in moderately advanced stages (BioFIND_PD) and HC subjects (BioFIND_HC). Both of these study arms were included in this study. The protocols for these studies can be obtained from The Michael J. Fox Foundation for Parkinson's research (https://www.michaeljfox.org). We also included participants from the ADNI (https://adni.loni.usc.edu). Based on their last diagnosis, these participants were stratified as either having dementia (ADNI-Dementia), mild cognitive impairment (ADNI-MCI), or normal cognition (ADNI-NC). Although clinical diagnosis of AD can change over time, 97% of the ADNI-Dementia participants were "probable" AD by National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria according to the last record when available. Clinical data of the study participants, such as disease status, age, sex, and age at diagnosis, were obtained from the study websites on December 12, 2021. For a summary of the study design and data used across disease statuses, refer to Fig. S1. Descriptive statistics for each study are available in Table S1.

### CSF Biomarkers

For ADNI and PPMI samples, CSF concentrations of $A\beta_{1-42}$, t-tau, and p-tau at the threonine 181 position (p-tau) were measured using Elecsys electrochemiluminescence immunoassays on the cobas e 601 analysis platform (Roche Diagnostics).[13] For BioFIND samples, these biomarkers were measured by INNO-BIA AlzBio3 immunoassay.[14] The detailed procedures and quality-control process are summarized on the study websites. For GWAS analyses, biomarker values were log transformed and centered at zero to be compatible with existing summary statistics.

### Genetic Data

We used the whole-genome sequencing data provided by the ADNI repository and the Accelerating Medicines Partnership for Parkinson's disease (AMP-PD) project.[15] The samples were sequenced (≥30× coverage) and underwent the GATK best practices workflow. Additional details regarding quality control are provided on the study websites. In this analysis, we used PASS-filtered variants and analyzed only the participants with European ancestry because of insufficient power to analyze non-European ancestry groups. The ancestry was confirmed by being within ±6 SD of the first two principal components of the European samples (Northern European from Utah [CEU] and Tuscans from Italy [TSI]) in HapMap3 panel.[16] We also excluded related individuals closer than second-degree relatives from the analysis.

### Summary Statistics from the Prior GWAS

We requested the summary statistics from the largest GWAS for Aβ, t-Tau, and p-Tau from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (https://www.niagads.org/) data repository (NG00055).[5] The GWAS included 3146 individuals with and without dementia from nine different studies conducted at the Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC); Saarland University in Homburg/Saar, Germany (HB);

Mayo Clinic (MAYO); Skåne University Hospital, Sweden (SWEDEN); Perelman School of Medicine at the University of Pennsylvania (UPENN); and the University of Washington (UW); as well as ADNI (ADNI1 and ADNI2) and Predictors of Cognitive Decline Among Normal Individuals (BIOCARD). The CSF biomarkers were log transformed and centered per study followed by a single-stage association test adjusted for age, sex, measurement platform, and the first two principal components.

## Analysis

Cohort-strata-level GWASs for the AD biomarkers were conducted. For the BioFIND study, we fit a linear regression model for additive allele effect using the cross-sectional data. For the other studies where longitudinal data were available, we used the GALLOP algorithm to approximate the linear mixed effects model for both the additive allele effect (cross-sectional associations) and the additive allele × time interaction (longitudinal associations). This algorithm provides equivalent solutions to a linear mixed effects model in a computationally efficient way.[17] In both models, we adjusted for age, sex, and the first two principal components (PC1-PC2). For the GALLOP model, we further adjusted for time from the baseline measurement, interactions between time and PCs (PC1-PC2), and a random intercept and random slope for each individual. Our primary analysis was to meta-analyze the cross-sectional results with the previously reported summary statistics from the largest CSF AD biomarker GWAS[5] to identify the across-disease genetic contributions for these biomarkers. We also meta-analyzed the longitudinal associations to see whether there are any genome-wide significant loci associated with the biomarker change over time.

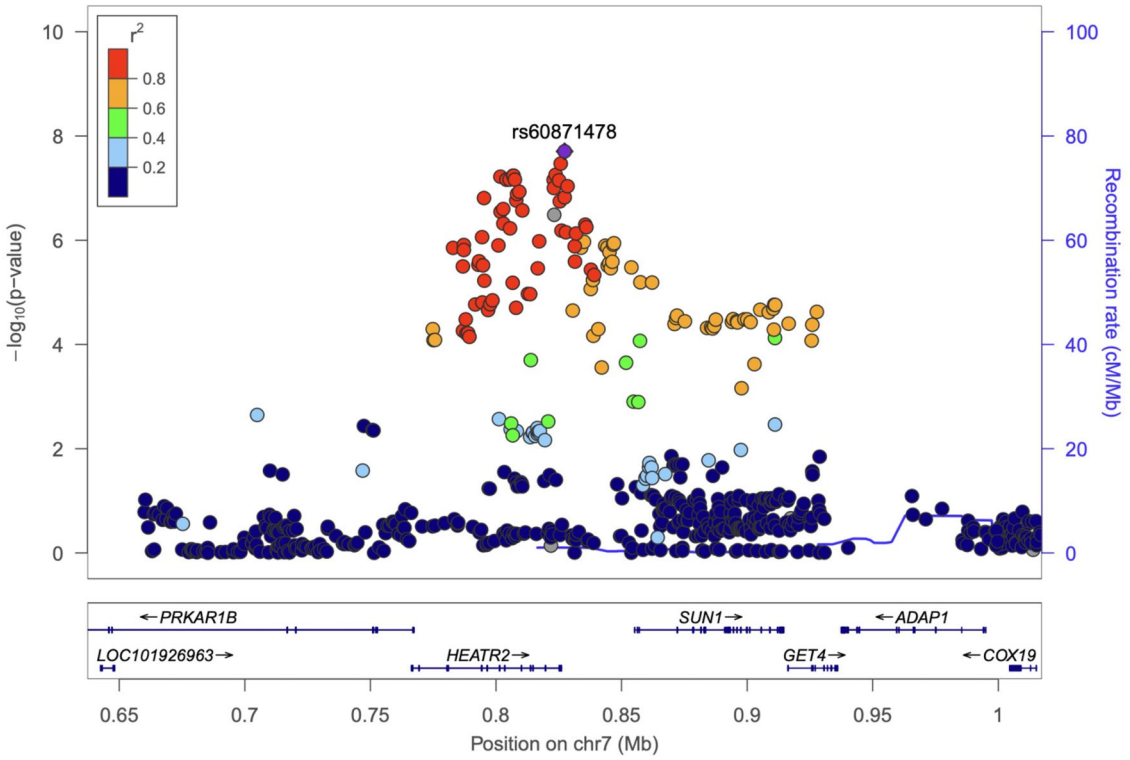
In the meta-analysis, all of the variants with a minor allele count less than five or minor allele frequency <1% among the individual studies, not reported in more than two study arms, or failed for heterogeneity assessment ($P$ value for the test of heterogeneity < 0.05 or $I^2$ > 80%) were removed from the "overall" genetic assessment for the biomarkers. For novel genome-wide significant loci, we further assessed colocalization with brain eQTLs (expression quantitative trait loci)[18] and blood eQTLs[19] using LocusCompare.[20]

For those SNPs reported in the previous study by Deming et al,[5] we assessed whether there was any evidence of heterogeneity between different disease states. We meta-analyzed GWASs from PPMI-PD, PPMI-GENPD, and BioFIND-PD to compose "PD" GWAS summary statistics. Similarly, we meta-analyzed ADNI-CN, BioFIND-HC, and PPMI-HC and PPMI-GENUN to generate "HC" GWAS results. For AD, we used the ADNI-Dementia GWAS summary statistics. The

**TABLE 1** *Genome-wide significant loci in meta-analysis with Deming et al*[5]

| Position (hg38) | Nearest Gene | rsID | Reference Allele | Effect Allele (Minor Allele) | Minor Allele Frequency | Cross-Sectional Component | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Aβ | p-tau | t-tau |
| chr3:190945768 | GEMC1 (intergenic) | rs35055419 | C | T | 0.3907 | **0.005** (0.04) $P = 0.236$ | **−0.039 (0.005)** $P = 2.169E-13$ | **−0.044 (0.006)** $P = 2.748E-15$ |
| chr7:787688 | DNAAF5 (intron) | rs60871478 | G | A | 0.2059 | **−0.009** (0.005) $P = 0.79$ | **0.037 (0.007)** $P = 1.97E-08$ | 0.034 (0.007) $P = 5.821E-07$ |
| chr19:44906745 | APOE (intronic) | rs769449 | G | A | 0.1822 | **−0.103 (0.005)** $P = 1.13E-107$ | **0.0.77 (0.006)** $P = 9.23E-34$ | **0.076 (0.007)** $P = 2.383E-30$ |

*Note:* Results from the meta-analysis of cerebrospinal fluid biomarkers from AMP-PD (The Accelerating Medicines Partnership for Parkinson's disease) and Fox Investigation for New Discovery of Biomarkers (BioFIND) cohorts with the study on Alzheimer's disease by Deming et al.[5] Genome-wide significant effect was seen in APOE for amyloid-β (Aβ), phosphorylated tau (p-tau), and total tau (t-tau); GEMC1 for p-tau and t-tau; and DNAAF5 for p-tau. MAF, Minor Allele Frequency.



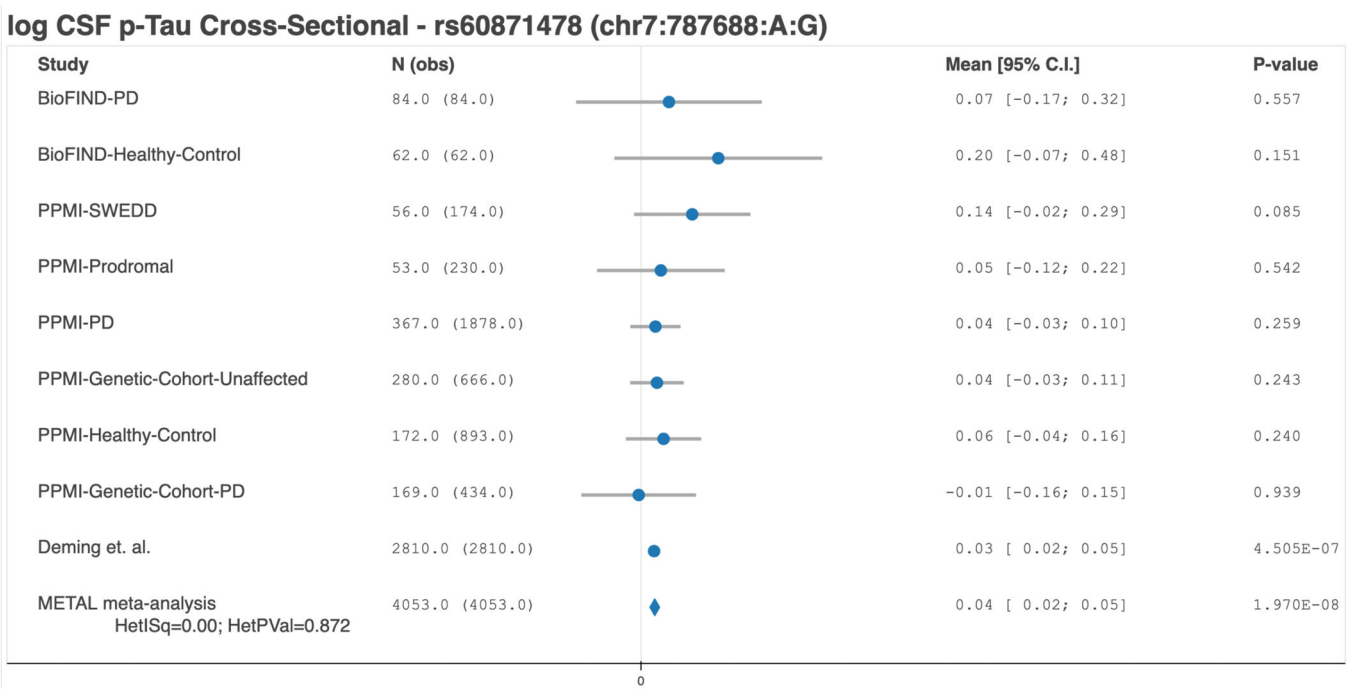




**Fig. 1.** (Top) Genome-wide association study (GWAS) hits around the rs60871478 locus with log cerebrospinal fluid (CSF) phosphorylated Tau (p-Tau) biomarker colorized by colocalization with brain and blood expression quantitative trait loci (eQTLs). (Bottom) Forest plot of cohorts in the meta-analysis of rs60871478 hit with log CSF p-tau. Cohorts from the Fox Investigation for New Discovery of Biomarkers (BioFIND) and Parkinson's Progression Markers Initiative (PPMI) studies on subjects with Parkinson's disease (PD) were meta-analyzed with the summary statistics from the Deming et al[5] study on Alzheimer's disease (AD). [Color figure can be viewed at wileyonlinelibrary.com]

heterogeneity between these disease-specific GWAS results was assessed using their $I^2$ statistics.

Finally, we assessed whether disease-specific or non-specific genetic associations with these CSF biomarkers exist for known risk loci associated with either PD or AD.[21,22] For this targeted analysis, the significance level was set at the false-positive rate ($q$ value) of 0.05 adjusting for the number of loci to be tested.

All the statistical analyses and drawings were executed using Plink version 2.0 alpha,[23] R version 3.6, and Python version 3.8. Meta-analyses were conducted using METAL software with an inverse variance weighted method with the genomic control correction applied.[24] The analysis scripts are available online at https://github.com/NIH-CARD/biomarker_longGWAS. The data were obtained from ADNI and AMP-PD.

## Results

We used data from 61 GWASs in the main meta-analyses, including previously published results: 34 GWASs for cross-sectional components and 27 GWASs for longitudinal components. The genomic inflation factors of the GWAS were reasonable, with most around 1.0, except for three between 1.1 and 1.3 (Table S2). The inflation was accounted for in the meta-analysis phase by the genomic control function in METAL.

In the meta-analysis, we observed three GWAS signals in the cross-sectional component: the *APOE* locus for Aβ; the 3q28 locus between *GEMC1* and *OSTN* for p-tau and t-tau; and the 7p22 locus (top hit: rs60871478, an intron variant for *DNAAF5*, also known as *HEATR2*) for p-tau (Table 1, Fig. 1, Figs S2 and S3). No genome-wide signals were identified in the longitudinal components (Fig. S5). The rs769449 variant on the APOE locus was identified to be significant for all three CSF biomarkers. For rs35055419, a significant association was seen for p-tau and t-tau. Both of these variants were previously reported by Cruchaga et al.[4]

The chromosome 7 locus in the *DNAAF5* gene region was not previously reported and showed a genome-wide significant *P* value for p-tau ($P = 1.97E{-}8$) and a sub-genome-wide significant *P* value for t-tau ($P = 5.82E{-}7$). When exploring the potential causal gene in this region, we identified eQTLs for *DNAAF5* that were well colocalized with the GWAS signals in both the brain and blood (Fig. S4). No other genes in this locus showed any colocalization between the QTLs and the GWAS signal.

Disease-specific genetic associations with CSF biomarkers were assessed on the significant loci reported by Deming et al[5] between AD- and PD-related dementia. A stratified meta-analysis by disease state suggested heterogeneity was present for one of the nonreplicated associations between rs12961169 (*CTDP1*) and p-tau. The ADNI-Dementia group showed a negative association ($P = 0.00182$) that was not observed in the PD and the HC groups (Figs. S6 and S7). No evidence of heterogeneity for the other nonreplicated associations was seen. One reported locus at 1p32.3 for Aβ (rs185031519, very rare) was not identified in this analysis.

Likewise, for known AD and PD risk-associated loci on CSF biomarkers, the disease-stratified meta-analysis was used to identify the genetic similarities and differences across the dementia and control groups. The *APOE* ε4 tagging allele was associated with lower CSF Aβ regardless of the disease status (Table 2). AD risk-increasing allele rs6586028_T (*TSPAN14*) was associated with the increasingly lower CSF Aβ over time in the PD group, but not in the ADNI-Dementia and the HC groups, although there was not enough evidence suggesting heterogeneity among these results. The PD risk-increasing allele, rs7134559_C (12q13.11), was associated with lower p-tau in a disease status nonspecific way.

## Discussion

In this study, we conducted GWASs on CSF levels of three known AD biomarkers. We used data from PD and AD studies and assessed multiple diseases and stages of progression. We replicated two genetic loci from the previous largest AD biomarker study[5] (*APOE* and *GEMC1*) and identified a new locus at 7p22 that reached genome-wide significance in association with p-tau. *APOE* was previously shown to have significant associations with CSF biomarkers and is a genetic risk factor for late-onset sporadic AD.[25] In PD, carriers of the *APOE*-ε4 allele were found to have both quicker cognitive decline compared with noncarriers and an increased risk of progression to dementia.[26] Prior studies have found rs9877502 on the 3q28 locus between *GEMC1* and *OSTN* to be associated with higher CSF tau levels and identified a risk variant (rs1316356) for AD that is in linkage disequilibrium with this SNP.[4,5] In addition, *GEMC1* has been recently reported to be a key molecule in multiciliated cell differentiation.[27] In the brain, these cells are involved in maintaining homeostasis and neurogenesis. The new 7p22 locus, rs60871478, was associated with increased levels of CSF p-tau regardless of the disease status and colocalized well with *DNAAF5* (also known as *HEATR2*). When exploring the potential causal gene in this region, we identified that there was good colocalization between the GWAS signal and blood and brain eQTL data for *DNAAF5*, and no correlation was seen with other genes in the locus.

This gene encodes the protein Dynein Axonemal Assembly Factor 5 and is essential for the preassembly or stability of axonemal dynein. A missense mutation in *DNAAF5* was identified in a whole-exome sequencing study of a family with primary ciliary dyskinesia, a rare autosomal recessive disease that presents with neonatal respiratory distress, sinopulmonary disease, otitis media, male infertility, and left–right laterality defects. The affected individuals showed a malfunction in airway epithelial cells.[28] The gene is expressed ubiquitously across all tissues; however, the link between p-tau and the gene is unclear.

**TABLE 2** *PD and AD risk loci associated with the AD biomarkers*

| rsID (chr: pos[hg38]) | Nearest Gene | Risk for | Risk-Increasing Allele | Biomarker | Component | Dataset | *N* | HetISq (%) | Test of Heterogeneity | Beta | SE | *P* Value | *q* Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs6586028 | TSPAN14 | AD | T | Aβ | Longitudinal | ADNI-Dementia GWAS | 175 | NA | NA | −0.0064 | 0.0253 | 0.80 | 0.917 |
| (chr10: 80494228) | | | | | | Meta-analysis of PD | 629 | 0.0 | 0.54 | −0.0167 | 0.0047 | 4.2E−04 | **0.029** |
| | | | | | | Meta-analysis of HC | 620 | 0.0 | 0.97 | 0.0001 | 0.0061 | 0.98 | 0.984 |
| | | | | | | Meta-analysis all (AD, PD, HC) | 1424 | 63.8 | 0.06 | −0.0117 | 0.0034 | 7.2E−04 | 0.052 |
| rs7134559 | SCAF1/ ARID2 | PD | C | p-tau | Cross-sectional | ADNI-Dementia GWAS: CS | 181 | NA | NA | −0.0672 | 0.0444 | 0.13 | 1.000 |
| (chr12: 46025303) | | | | | | Meta-analysis of PD: CS | 620 | 39.2 | 0.19 | −0.0776 | 0.0234 | 9.1E−04 | 0.077 |
| | | | | | | Meta-analysis of HC: CS | 680 | 53.6 | 0.09 | −0.0409 | 0.0187 | 0.03 | 0.784 |
| | | | | | | Meta-analysis all (AD, PD, HC): CS | 1481 | 0.0 | 0.46 | −0.0564 | 0.0139 | 4.8E−05 | **0.004** |
| rs429358 | APOE | AD | C | Aβ | Cross-sectional | ADNI-Dementia GWAS: CS | 175 | NA | NA | −0.2672 | 0.0461 | 7.0E−09 | **5.2E−07** |
| (chr19: 44908684) | | | | | | Meta-analysis of PD: CS | 629 | 0.0 | 0.78 | −0.1868 | 0.0347 | 7.2E−08 | **5.1E−06** |
| | | | | | | Meta-analysis of HC: CS | 620 | 0.0 | 0.85 | −0.2157 | 0.0308 | 2.7E−12 | **2.0E−10** |
| | | | | | | Meta-analysis all (AD, PD, HC): CS | 1424 | 0 | 0.38 | −0.2158 | 0.0206 | 1.2E−25 | **8.6E−24** |

*Note*: Results from meta-analysis of Parkinson's disease (PD) and Alzheimer's disease (AD) risk loci by disease states. PD cohort was composed of PD cases from AMP-PD (The Accerelating Medicines Partnership for Parkinson's disease) and Fox Investigation for New Discovery of Biomarkers (BioFIND). AD cohort was composed of dementia cases from Alzheimer's Disease Neuroimaging Initiative (ADNI). Healthy control (HC) cohort was composed of control subjects from AMP-PD, BioFIND, and ADNI. Effect is aligned to the risk allele (allele corresponding to the higher risk of the disease). The APOE risk allele rs429358 was observed to be associated with the amyloid β (Aβ) biomarker in AD, PD, and control.

HetISq, $I^2$ value for heterogeneity (if HetISq > 80 or test of heterogeneity < 0.05, then meta-analysis was not evaluated); GWAS, genome-wide association study; p-tau, phosphorylated tau. CS, cross-sectional analysis; NA, not applicable.

To assess the clinical consequence of the variant, we conducted ad hoc analyses testing associations of this locus with age at onset and Mini-Mental State Examination in the ADNI cohort (Table S3). The results suggest the loci are associated with Mini-Mental State Examination scores in the ADNI-Dementia group ($-1.07 \pm 0.48$, $P = 0.025$). A similar association was shown in the ADNI-CN group with a smaller magnitude of effect ($-0.34 \pm 0.17$, $P = 0.021$). This variant may play a role in cognitive decline related to increased tau pathology with underlying AD pathology, but the sample size is not large enough to adjust for multiple testing, and further evaluation with a larger cohort would be required. In addition, biological evaluation, such as cellular or animal AD models, may provide more information regarding progression and dementia risk associated with the locus.

Six previously reported cross-sectional associations with CSF biomarkers in AD were not replicated in this study. Of these, rs12961169 (*CTDP1*) showed high heterogeneity across diseases. For the others, it may in part be because of differences in the study designs. The previous study was focused on identifying AD-related loci using the biomarkers as endophenotypes. Thus, they conducted one-stage GWASs without adjusting for the disease status.

Interestingly, the PD risk-increasing locus rs7134559 (*SCAF11*) was associated with the lower CSF p-tau. A recent study reported that these biomarkers were indeed lower in PD when compared with HC, in contrast with the generally higher CSF p-tau in AD.[9] The reason for the difference in these biomarker profiles between the two diseases is unknown, but there are many reports suggesting the influence of AD pathology to the PD pathology or vice versa.[29-31] The current observation may be associated with some interaction between the two disease mechanisms.

Longitudinal changes are smaller compared with baseline differences in biomarker levels between disease states. Reported heterogeneity on CSF biomarker trajectories has been observed in AD risk allele carriers prior to and after the onset of dementia symptoms.[32] The need for a stratified analysis by dementia progression in addition to larger cohort sizes might improve detection of longitudinal genetic contributions.

By integrating data from PD studies, we were able to expand the knowledge of genetic–biomarker relationships that were mainly derived from AD studies previously. For some SNPs, we could differentiate disease-specific and nonspecific genetic associations. Admittedly, the size of this study, especially in regard to the disease-specific GWAS, was still small. Additional data are needed for more effective analyses in particular large datasets from diverse ancestries with longitudinal measures available. Nevertheless, we believe that the current approach would be useful to investigate underlying AD mechanisms modified by different disease status. Another limitation of this study is the potential misdiagnosis of AD and PD because the clinical diagnosis is not always accurate. In particular, misdiagnosis would affect the heterogeneity assessment. Access to additional biomarkers and increasing study sizes are both important to overcome this problem.

Also, notably, this study may have not fully accounted for the complex relationships between Aβ, p-tau, and t-tau. These biomarkers are recognized as endophenotypes, and they are highly sensitive and specific in differentiating AD and control subjects.[25,33] However, the clinical significance of these biomarkers is not equal. First, they are thought to represent different pathological processes related to AD: low CSF Aβ for aggregation of Aβ, high CSF p-Tau for neurofibrillary tangle formation, and high CSF t-Tau for neurodegeneration.[34] The timing of deviation from normal is also different, because the decrease of Aβ is observed earlier than the increase of CSF p-Tau and t-Tau.[33] In addition, the increase of t-Tau and p-Tau in the early stage of AD may be associated with faster progression of disease.[35,36] Moreover, there is a study that reported the level of p-Tau, supposedly reflecting tangle pathology, was more closely associated with amyloid PET than with tau PET.[37] To further investigate these complex relationships between the biomarkers, GWASs on various stratifications, such as disease status, other biomarker status, and imaging status, should provide important information to untangle these relationships.

In conclusion, we analyzed the CSF AD biomarker from the AD and the PD studies. We identified three associations across disease status, including one novel genome-wide significant locus, and also observed some associations suggesting the disease-specific modifications of these biomarkers at known risk loci.

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

# References


1. Dorsey ER, Elbaz A, Nichols E, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018; 17(11):939–953.
2. Nichols E, Szoeke CE, Vollset SE, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(1):88–106.
3. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14(4):535–562.
4. Cruchaga C, Kauwe JSK, Harari O, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. Neuron 2013;78(2):256–268.
5. Deming Y, Li Z, Kapoor M, et al. Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. Acta Neuropathol 2017;133(5): 839–856.
6. Han M-R, Schellenberg GD, Wang L-S, Alzheimer's Disease Neuroimaging Initiative. Genome-wide association reveals genetic effects on human Aβ42 and τ protein levels in cerebrospinal fluids: a case control study. BMC Neurol 2010;10:90.
7. Kim S, Swaminathan S, Shen L, et al. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology 2011;76(1):69–79.
8. Ramirez A, van der Flier WM, Herold C, et al. SUCLG2 identified as both a determinator of CSF Aβ1-42 levels and an attenuator of cognitive decline in Alzheimer's disease. Hum Mol Genet 2014; 23(24):6644–6658.
9. Irwin DJ, Fedler J, Coffey CS, et al. Evolution of Alzheimer's disease cerebrospinal fluid biomarkers in early Parkinson's disease. Ann Neurol 2020;88(3):574–587.
10. Kang J-H, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebrospinal fluid β-amyloid 1-42, T-tau, P-tau181, and α-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol 2013;70(10):1277–1287.
11. Zhang J, Mattison HA, Liu C, et al. Longitudinal assessment of tau and amyloid beta in cerebrospinal fluid of Parkinson disease. Acta Neuropathol 2013;126(5):671–682.
12. Marek K, Jennings D, Lasch S, et al. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011;95(4):629–635.
13. Shaw LM, Waligorska T, Fields L, et al. Derivation of cutoffs for the Elecsys amyloid β (1-42) assay in Alzheimer's disease. Alzheimers Dement 2018;10:698–705.
14. Olsson A, Vanderstichele H, Andreasen N, et al. Simultaneous measurement of beta-amyloid(1-42), total tau, and phosphorylated tau (Thr181) in cerebrospinal fluid by the xMAP technology. Clin Chem 2005;51(2):336–345.
15. Iwaki H, Leonard HL, Makarious MB, et al. Accelerating Medicines Partnership: Parkinson's Disease Genetic Resource; 2020. medRxiv 2020.11.19.20235192.
16. International HapMap 3 Consortium. Integrating common and rare genetic variation in diverse human populations. Nature 2010; 467(7311):52–58.
17. Sikorska K, Lesaffre E, Groenen PJF, Rivadeneira F, Eilers PHC. Genome-wide analysis of large-scale longitudinal outcomes using penalization-GALLOP algorithm. Sci Rep 2018;8(1):6815.
18. Allen M, Carrasquillo MM, Funk C, et al. Human whole genome genotype and transcriptome data for Alzheimer's and other neurodegenerative diseases. Sci Data 2016;3:160089.
19. Võsa U, Claringbould A, Westra H-J, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet 2021;53(9):1300–1310.
20. Liu B, Gloudemans MJ, Rao AS, Ingelsson E, Montgomery SB. Abundant associations with gene expression complicate GWAS follow-up. Nat Genet 2019;51(5):768–769.
21. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 2022;54(4):412–436.
22. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019;18(12):1091–1102.
23. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81(3):559–575.
24. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 2010; 26(17):2190–2191.
25. Blennow K. A review of fluid biomarkers for Alzheimer's disease: moving from CSF to blood. Neurol Ther 2017;6(Suppl 1):15–24.
26. Szwedo AA, Dalen I, Pedersen KF, et al. GBA and APOE impact cognitive decline in Parkinson's disease: a 10-year population-based study. Mov Disord 2022;37(5):1016–1027.
27. Lalioti M-E, Arbi M, Loukas I, et al. GemC1 governs multiciliogenesis through direct interaction with and transcriptional regulation of p73. J Cell Sci 2019;132(11):jcs228684. https://doi.org/10.1242/jcs.228684
28. Horani A, Druley TE, Zariwala MA, et al. Whole-exome capture and sequencing identifies HEATR2 mutation as a cause of primary ciliary dyskinesia. Am J Hum Genet 2012;91(4):685–693.
29. Irwin DJ, Lee VM-Y, Trojanowski JQ. Parkinson's disease dementia: convergence of α-synuclein, tau and amyloid-β pathologies. Nat Rev Neurosci 2013;14(9):626–636.
30. Sengupta U, Kayed R. Amyloid β, tau, and α-Synuclein aggregates in the pathogenesis, prognosis, and therapeutics for neurodegenerative diseases. Prog Neurobiol 2022;214:102270.
31. Wennberg AM, Whitwell JL, Tosakulwong N, et al. The influence of tau, amyloid, alpha-synuclein, TDP-43, and vascular pathology in clinically normal elderly individuals. Neurobiol Aging 2019;77:26–36.
32. Fagan AM, Xiong C, Jasielec MS, et al. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. Sci Transl Med 2014;6(226):226ra30.
33. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement 2018;14(11): 1470–1481.

34. Villemagne VL, Pike KE, Chételat G, et al. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann Neurol 2011;69(1):181–192.

35. Therriault J, Vermeiren M, Servaes S, et al. Association of phosphorylated tau biomarkers with amyloid positron emission tomography vs tau positron emission tomography. JAMA Neurol 2023;80(2):188–199.

36. Wattmo C, Blennow K, Hansson O. Cerebro-spinal fluid biomarker levels: phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer's disease. BMC Neurol 2020;20(1):10.

37. Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YAL, van Elk EJ, Scheltens P, van der Flier WM. CSF biomarkers predict rate of cognitive decline in Alzheimer disease. Neurology 2009; 73(17):1353–1358.

## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.