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Negative Results

A genome-wide association study of plasma phosphorylated tau181

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ABSTRACT

Plasma phosphorylated tau at threonine-181 (P-tau181) demonstrates promise as an accessible blood-based biomarker specific to Alzheimer's Disease (AD), with levels recently demonstrating high predictive accuracy for AD-relevant pathology. The genetic underpinnings of P-tau181 levels, however, remain elusive. This study presents the first genome-wide association study of plasma P-tau181 in a total sample of 1153 participants from 2 independent cohorts. No loci, other than those within the *APOE* genomic region (lead variant = rs429358, beta = 0.32, $p = 8.44 \times 10^{-25}$) demonstrated association with P-tau181 at genome-wide significance ($p < 5 \times 10^{-08}$), though rs60872856 on chromosome 2 came close (beta = -0.28, $p = 3.23 \times 10^{-07}$, nearest gene=CYTIP). As the *APOE* $\varepsilon 4$ allele is already a well-established genetic variant associated with AD, this study found no evidence of novel genetic associations relevant to plasma P-tau181, though presents rs60872856 on chromosome 2 as a candidate locus to be further evaluated in future larger size GWAS.

1. Introduction

Plasma phosphorylated tau181 (P-tau181) is a promising blood-based biomarker that is highly specific for Alzheimer's disease (AD) pathology. It correlates with cerebral Aβ and tau pathology (Karikari et al., 2020), is specifically associated with AD neuropathology (Lantero-Rodriguez et al., 2020) and predicts future cognitive decline (Karikari et al., 2021). It therefore has great potential for the diagnostic and prognostic evaluation of AD. Identifying genetic loci associated with plasma P-tau181 could help enhance understanding of specific components of AD pathophysiology; in particular, tau-associated pathology. To date, 2 GWAS on AD-relevant CSF endophenotypes (Cruchaga et al., 2013;

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Table 1
Lead SNPs for loci associated with P-tau181 at $p < 5 \times 10^{-07}$ within fixed-effects meta-analysis

CHR	BP	Lead SNP	A1	BETA META	SE META	PMETA	Nearest Gene	Functional relevance
2	158320559	rs60872856	G	-0.280	0.055	3.23E-07	*CYTIP*	Regulation of immune response
19	**45411941**	**rs429358**	**C**	**0.281**	**0.027**	**2.54E-25**	***APOE***	**Lipid metabolism**

SNPs associated with P-tau181 at $p < 5 \times 10^{-08}$ *are in bold*.

Deming et al., 2017) have identified 5 loci, including *APOE*, to be associated with CSF P-tau181. Recently, we investigated the relation between AD polygenic risk scores (AD-PRS) and plasma P-tau181 (Zettergren et al., 2021). No GWAS on plasma P-tau181 levels have yet, however, been performed. Here, we present the first plasma P-tau181 GWAS, aiming to identify genetic loci associated with plasma P-tau181 levels and in turn, tau-associated pathology.

2. Materials and methods

932 participants from the Alzheimer's Disease Neuroimaging initiative (ADNI) (http://www.adni-inof.org) and 228 participants from the European based AddNeuroMed (ANM) study (Lovestone et al., 2009) with available plasma P-tau181 and genotype data were utilised. Plasma P-tau181, for both ADNI and ANM cohorts, was measured using the Single-molecule array (Simoa) technology on an HD-X Analyzer (Quanterix, Billerica, MA) (Karikari et al., 2021; Simrén et al., 2021). ADNI participants were genotyped across 3 genotyping platforms (Human610-Quad, HumanOniExpress and Omni 2.5M platforms). ANM participants were genotyped using the Human610-Quad genotyping platform. All chips underwent full quality control (QC), principal components (PCs) extraction and imputation in accordance with matched pipelines outlined within Supplementary Methods. Following QC, data across ADNI's 3 genotyping platforms were merged, resulting in 2 cohorts of data – 1 from ADNI and 1 from ANM.

To maximise sample power, ADNI and ANM were each analysed separately before combining into a fixed-effects meta-analysis with betas weighted by the inverse of their variance. Plasma P-tau181 data was $\log_{10}$ transformed to approximate a normal distribution, and age, sex, and the first 7 PCs were controlled for within each study (Supplementary Methods). To correct for multiple testing, loci demonstrating evidence of an association at $p < 5 \times 10^{-08}$ were considered to show evidence of an association with P-tau181.

3. Results

Following QC, 932 ADNI and 221 ANM participants were retained (Supplementary Table 1). Meta-analysed results demonstrated a genome-wide significant association between plasma P-tau181 and the *APOE* genomic region (lead SNP: rs429358 (beta = 0.281, $p = 2.54 \times 10^{-25}$)) (Table 1, Supplementary Figure 1, Supplementary Table 4). No other loci reached genome-wide significance, though 1 chromosome 2 SNP within the *CYTIP* region (rs60872856) demonstrated an association at $p < 5 \times 10^{-07}$ (beta = 0.280, $p = 3.23 \times 10^{-07}$) (Table 1, Supplementary Figures 1-2, Supplementary Table 4).

4. Discussion

Here, we present the first GWAS of plasma P-tau181, in a sample of 1,153 individuals from ADNI and ANM. rs429358 within the *APOE* genomic region demonstrated evidence of a genome-wide significant association with plasma P-tau181 (beta = 0.281, SE =0.027, $p = 2.54 \times 10^{-25}$). No other loci reached genome-wide significance, though rs60872856 on chromosome 2 came close with a p-value of 3.23×10^{-07}. This chromosome 2 variant is located nearest to the cytohesin-interacting protein *CYTIP* region, a region involved in the regulation of immune response. None of the SNPs previously associated with CSF P-tau181 levels (Cruchaga et al., 2013; Deming et al., 2017) showed associations with plasma P-tau181 levels in this study.

The *APOE* $\varepsilon 4$ allele is a well-established AD-associated genetic variant. Moreover, it has previously been shown to associate with AD-relevant pathology such as amyloid deposition, an event which is a precursor of elevated P-tau181 levels in the blood (Karikari et al., 2021). This study therefore identifies no evidence of novel genetic associations relevant to plasma P-tau181. It does, however, present rs60872856 on chromosome 2 as a candidate which may show promise in future, well-powered GWAS (Supplementary Results). As blood P-tau181 is an easily accessible and scalable blood biomarker, large-scale GWAs studies exceeding those of CSF biomarkers will be soon feasible.

Disclosure statement

KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. HZ has served at scientific advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies and CogRx, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.04.015.

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