ARTICLE

Genome-wide association study identifies *APOE* locus influencing plasma p-tau181 levels

Yu-Yuan Huang[1]✉, Yu-Xiang Yang[1], Hui-Fu Wang[2], Xue-Ning Shen[1], Lan Tan[2], Jin-Tai Yu[1]✉ and Alzheimer's Disease Neuroimaging Initiative*

As a promising diagnostic and prognostic biomarker for Alzheimer's Disease (AD), plasma p-tau181 is robustly differentiated AD dementia from non-AD neurodegenerative diseases. We aimed to discover single nucleotide polymorphisms (SNPs) associated with plasma phosphorylated tau at threonine 181 (p-tau181) levels that affect the risk of developing AD. We carried out a genome-wide association study for plasma p-tau181 levels using participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The thresholds of $P < 5 \times 10^{-6}$ was used for suggestive associations, and thresholds of $P < 5 \times 10^{-8}$ was used for significant associations. Subsequently, we tested whether the associations remained significant in subgroup analysis and examined the impact of SNPs on the longitudinal changes in plasma p-tau181 levels. A total of 714 eligible non-Hispanic white participants with plasma p-tau181 data were included. The most significant SNP (rs769449, $P = 6.26 \times 10^{-8}$) in *APOE* gene was suggestively associated with plasma p-tau181, which is close to the genome-wide significance threshold. The minor allele (A) of rs769449 in the *APOE* was associated with higher plasma p-tau181 levels in a dose-dependent fashion. Besides, rs769449- A carriers were more likely to exhibit a greater longitudinal cognitive decline ($P = 0.03$). Our results suggest that the AD risk variant in the *APOE* gene participates in the regulation of plasma p-tau181. The plasma p-tau181 concentration could be a useful endophenotype for identifying risk for AD in elderly individuals.

Journal of Human Genetics; https://doi.org/10.1038/s10038-022-01026-z

INTRODUCTION

Tau is a core biomarker for Alzheimer's disease (AD) [1]. Overwhelming evidence indicates that total tau (t-tau) and some p-tau isoform levels of cerebrospinal fluid (CSF) are significantly increased in patients with AD. Methods for the detection of tau in blood are also available. Plasma t-tau assays can detect neuronal injury in acute brain disorders, but they work relatively poorly in AD settings [2]. The previous studies indicate that plasma tau and CSF tau levels poorly correlate with each other, introducing controversy and casting doubts on the reliability of plasma tau pathology biomarkers [1–3].

The recent breakthrough development of an ultrasensitive assay for phosphorylated tau at threonine 181 (p-tau181) in blood has allowed to study the relationship between plasma p-tau181 and AD. Numerous findings suggested highly valuable information that plasma p-tau181 is a promising blood biomarker for the detection and progression of AD pathology [4], whose levels are elevated along the AD continuum, and can differentiate AD from other neurodegenerative disorders [5]. Furthermore, plasma p-tau181 associates cross-sectionally with CSF p-tau181 [4, 5].

On the basis of this finding, our previous genome-wide association study (GWAS) for variants that modulated plasma total-tau in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort identified variants in microtubule-associated protein tau gene (*MAPT*) [6]. However, there is limited work on systematically exploring plasma p-tau181 genetic associations. In this study, we hypothesized that plasma p-tau181, similar to CSF p-tau181, may constitute a suitable endophenotype for identifying variants for AD. Within this context, we conducted a GWAS for plasma p-tau181 and identified three SNPs (rs769449 in *APOE*, rs4420638 and rs56131196 in *APOC1*) were suggestively associated with the increase in plasma p-tau181 levels.

METHODS

Participants

We used data from the multicenter ADNI study whose was designed to develop and validate neuroimaging, biological biomarkers, and clinical and neuropsychological assessment for the early detection, monitoring, and treatment. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD, has included more than 1500 participants aged 55–90 years with normal cognition (NC), mild cognitive impairment (MCI), or AD. All participants were enrolled from ADNI-1, ADNI-2, and ADNI–Grand Opportunity (GO) database (http://adni.loni.usc.edu). To reduce potential bias due to population substructure and cryptic relatedness, we checked the preliminary results with genomic

[1]Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China. [2]Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China. *Data used in preparation for 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 the analysis or writing of this report. A complete listing of ADNI investigators can be found at in the coinvestigators list at links.lww.com/WNL/B86.
✉email: huang_yuyuan@126.com; jintai_yu@fudan.edu.cn

Received: 19 January 2022 Revised: 10 February 2022 Accepted: 15 February 2022
Published online: 07 March 2022

Table 1. Plasma p-tau181 GWAS participant characteristics

	NC ($n = 243$)	MCI ($n = 428$)	AD ($n = 43$)	Total ($n = 714$)	*P*
Age (y)	77.13 (6.41)	74.01 (8.10)	75.14 (9.22)	75.14 (7.77)	<0.0001
Women, No. (%)	120 (49.38)	172 (40.19)	17 (39.53)	309 (43.28)	0.06
Education (y)	16.38 (2.68)	16.00 (2.81)	15.58 (2.68)	16.11 (2.77)	0.106
APOE ε4 carriers, No. (%)	66 (26.94)	193 (45.09)	31 (72.09)	290 (40.62)	<0.0001
CSDR-SB scores	0.34 (1.54)	2.30 (2.73)	4.63 (1.88)	1.77 (2.61)	<0.0001
Plasma p-tau 181 (pg/mL)	15.83 (8.46)	19.01 (10.58)	24.02 (6.77)	18.23 (9.92)	<0.0001

APOE Apolipoprotein E, *CDR-SB* Clinical Dementia Rating-Sum of Boxes, *NC* Normal cognition, *MCI* Mild cognitive impairment, *AD* Alzheimer's Disease.

identity-by-descent (IBD) and multidimensional scaling (MDS) components (Supplementary Fig. 1), and three participants were removed.

In this study, 714 (AD 43, MCI 428, NC 243 at baseline) non-Hispanic white individuals whose data met all quality control (QC) criteria were included from the ADNI-1/2/GO cohort. Table 1 shows the demographic data and description of the plasma p-tau181 levels in each group.

Genotyping and QC

Genotyping was conducted using blood DNA samples with the Illumina Human610-Quad BeadChip (Illumina Inc) or theIllumina HumanOmniExpressBeadChip (Illumina Inc). Genotype data underwent standard quality control with the following criteria: minimum call rate for SNPs and subjects > 95%, minimum allele frequencies (MAF) > 0.05, and Hardy–Weinberg equilibrium test $P > 0.01$. The final data set included 1, 209, 826 SNPs and 714 participants. *APOE* alleles which were defined by rs7412 and rs429358 were genotyped separately by an *APOE* genotyping kit [7]. Systematic quality control analyses were performed using PLINK (version 1.90) software (http://www.cog-genomics.org/plink2).

Plasma p-tau181 measurement

Plasma p-tau181 data from ADNI was provided by the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden. Through the Single Molecule array (Simoa) technique, plasma p-tau181 was analyzed by an in-house assay using a combination of two monoclonal antibodies to measure N-terminal to mid domain forms of p-tau181 (Tau12 and AT270) [8]. Mean (18.23 pg/ml) and standard deviations (SD, 9.92 pg/ml) of plasma p-tau181 levels were calculated. Participants who had extreme outliers (<3-fold or >3-fold SD from the mean value) were removed from the analysis.

Statistical analysis

Associations between plasma p-tau181 levels and the genetic variants were determined using PLINK (version 1.90) with the additive genetic model. Age, gender, sum-of-boxes Clinical Dementia Rating (CDR-SB), and the first three principal components from population stratification analysis were included as covariates. Conditional analysis was carried out to assess the independence of the novel associations of the genotyped SNPs. The thresholds of $P < 5 \times 10^{-8}$ was used for conservative significance associations, and the thresholds of $P < 5 \times 10^{-6}$ was used for suggestive associations. Manhattan and quantile-quantile (QQ) plots were generated using the R "qqman" package (Version 3.4.2, https://www.r-project.org/). Regional association plots were generated via LocusZoom (http://locuszoom.sph.umich.edu/locus zoom/). In addition, stratified analysis was performed by amyloid and disease status.

Stratifying by amyloid status, the participants were divided into two groups: Aβ positive (Aβ+) and Aβ negative (Aβ−) subgroup. CSF Aβ42 < 977 pg/mL [9] was used to define amyloid positive status [9, 10]. Amyloid PET data were acquired using florbetapir (AV-45) tracer, and the cutoff for categories of brain amyloid PET was set as 1.11 for florbetapir SUVR [11] as a supplement when CSF data is unavailable. A total of 328 (45.75%) were Aβ+. When, stratifying by clinical syndrome, 81 (38.21%) of the NC, 209 (54.57%) of the MCI and 38 (88.37%) of the AD dementia individuals were Aβ+. A total of 310 were Aβ− (AD: 5. MCI: 174, CN: 131).

The effects of genotypes on plasma p-tau181 were examined with a multiple linear regression implemented in R software ("arm, lme4 and lmerTest" packages) [12]. Linear mixed models were adjusted for age, gender, education years, treatment duration, and APOE status to compute longitudinal changes in cognitive performance and in plasma p-tau181 levels. From these models, we estimated the mean rates of cognitive performance and plasma p-tau181 concentrations change for the whole samples. Longitudinal changes in cognitive performance were assessed by Mini-mental State Examination (MMSE).

RESULTS

Characteristics of included subjects

After quality control and imputation, the ADNI cohort encompassed 714 unrelated individuals from the non-Hispanic white population and 1,209,826 variants (Table 1). In general, the mean age at onset was 75.14 ± 7.77 years, and 309 (43.28%) were female. Participants included a mixture of 243 cognitively normal, 428 MCI, and 43 AD subjects. Analysis of variance of each demographic variable indicated significant differences across the cohorts (Table 1). For example, age ($P < 0.0001$), CSDR-SB scores ($P < 0.0001$), percent *APOE*-positive ($P < 0.0001$) were significantly different between groups. The percentage of *APOE* carrier were higher in AD (72.09%; $n = 31$) than in MCI (45.09%; $n = 193$) or CN (26.94%; $n = 66$) participants. Likewise, significant difference was observed among the plasma p-tau181 levels of three diagnostic groups ($P < 0.0001$).

Results from genome-wide association studies

After adjusting for age, sex, and CDR-SB score along with the first three principal components, several markers on various chromosomes exhibited genome-wide significance, with the sentinel markers occurring on chromosome 19. We have identified three SNPs (rs769449, $P = 6.26 \times 10^{-8}$; rs4420638, $P = 1.72 \times 10^{-7}$; rs56131196, $P = 1.75 \times 10^{-7}$) were suggestively associated with plasma p-tau181 levels (Fig. 1A). Table 2 presents the top three SNPs ranked according to *P* value. The strongest association was observed for the rs769449, an intronic SNP in *APOE*. Manhattan and QQ plots are provided in Fig. 1B. Regional association analysis showed that no SNPs were significantly associated with plasma p-tau181 levels after controlling for rs769449, suggesting that the association was also driven by rs769449 (Fig. 1C, D).

The minor allele (A) of rs769449 was associated with higher plasma p-tau181 levels in a dose-dependent effect (Supplementary Fig. 2), especially with amyloid positive participants (328 participants, $P = 1.93 \times 10^{-3}$, Fig. 2A, Supplementary Fig. 3A), but not with amyloid negative participants (307 participants, $P > 0.05$, Fig. 2B, Supplementary Fig. 3C). As expected, rs769449 at the *APOE* locus reach a level of suggestive association in the non-dementia population (671 participants, $P = 4.68 \times 10^{-7}$, Supplementary Fig. 4).

Impact of rs769449 on longitudinal cognitive performance and plasma p-tau181 levels

In order to assess the relationship between rs769449 variants and cognitive decline over time, we performed a linear mixed effects analysis. The cognitive assessments were based on MMSE score. After controlling for genotype, follow-up duration, age, gender, education level, and *APOE* genotype, we found rs769449-A carriers were associated with accelerated decline in cognitive performance ($P = 0.03$), but not associated with long-term plasma p-tau181 accumulation ($P = 0.44$, Fig. 3).

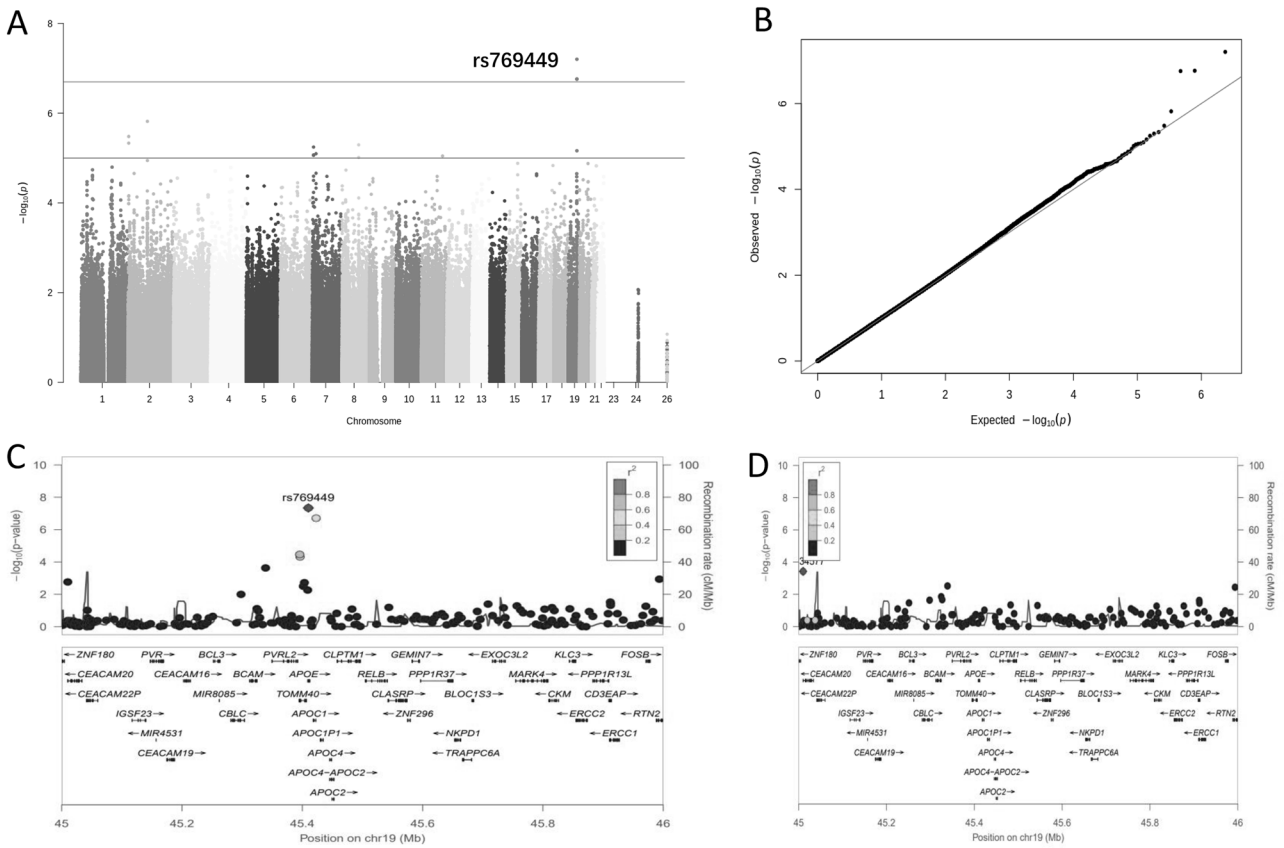

Fig. 1 Manhattan and regional plots for associations with plasma p-tau181 levels. **A** Manhattan plots for associations with plasma p-tau181 in ADNI-1/GO/2 cohorts. **B** Quantile–quantile plot. **C** Regional association results for the *APOE* region of chromosome 19. **D** Association results for chromosome 19: controlling for rs769449

Table 2. Top three SNPs associated with plasma p-tau181

SNP	Chr	BP	MAF	Gene	Function	BETA	*P*
rs769449	19	45410002	0.1828	*APOE*	intron	3.361	$6.26*10^{-8}$
rs4420638	19	45422946	0.2638	*APOC1*	downstream	2.869	$1.72*10^{-7}$
rs56131196	19	45422846	0.2620	*APOC1*	downstream	2.906	$1.75*10^{-7}$

BP Base pair (variant position), *CHR* Chromosome, *MAF* Minor allele frequency, *SNP* Single nucleotide polymorphism.

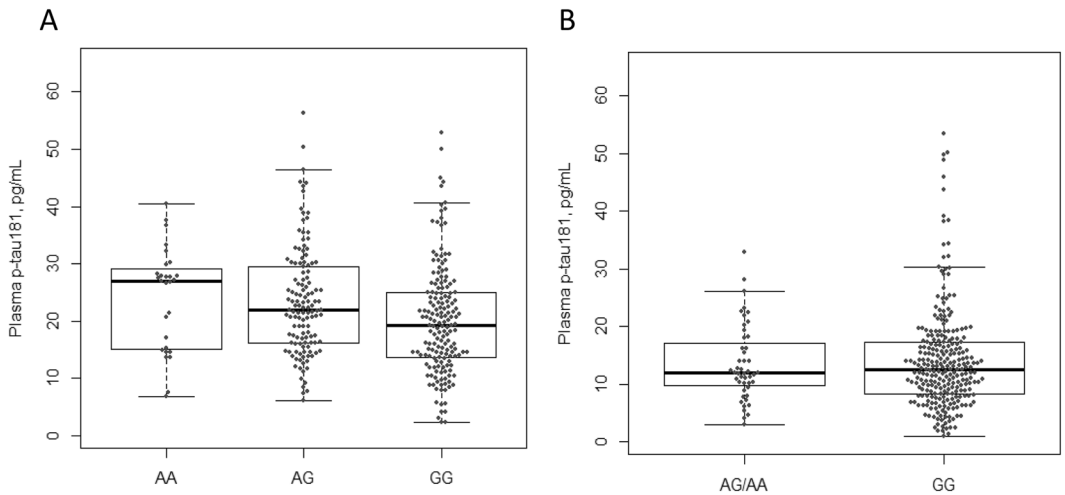

Fig. 2 Effects of rs769449 on plasma p-tau181 levels in different amyloid status groups. Plasma p-tau181 levels in different amyloid status groups and genotypes. The minor allele (**A**) of rs769449 showed significant association with higher plasma p-tau181 levels in a dose-dependent fashion in individuals with amyloid pathology (**A**), but not in amyloid negative individuals (**B**)

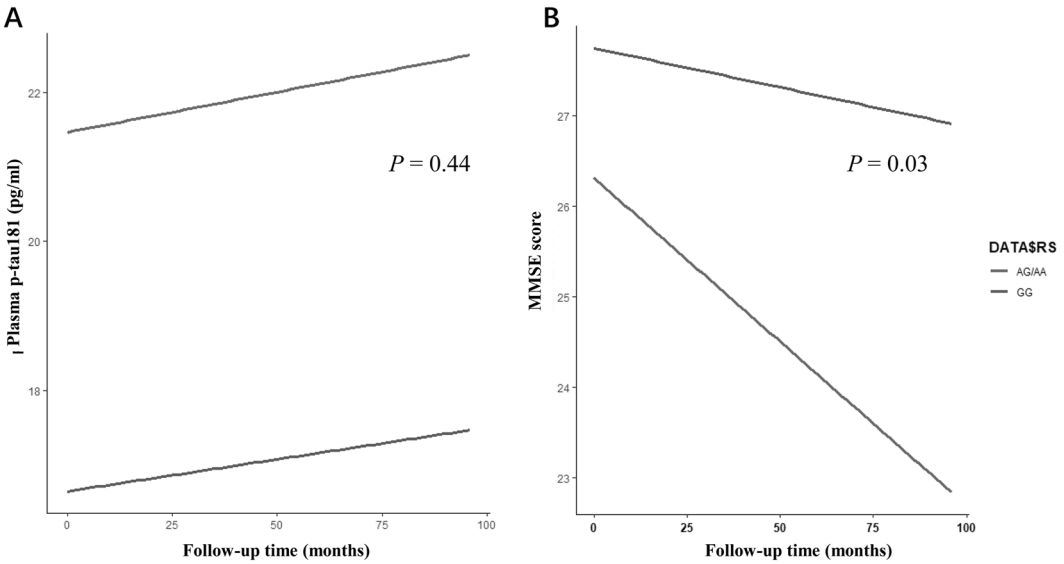

Fig. 3 Effects of rs769449 on plasma p-tau181 levels and cognitive performance over time. Associations of rs769449 with longitudinal measurements in plasma p-tau181 levels (**A**) and Mini-mental State Examination (MMSE) score (**B**) over time. The linear mixed models were adjusted for age, gender, education years, treatment duration, and *APOE* status

DISCUSSION

We carried out a genome-wide association study of plasma p-tau181 concentrations. Although we did not observe novel genome-wide significant locus, we found that *APOE* region variant was correlated with plasma p-tau181 levels and more likely to exhibit a greater longitudinal cognitive decline.

Previous studies have identified that the minor allele (A) of rs769449 associated with cognitive decline among African-Americans and European-Americans in the 19q13.32 region [13, 14]. In our study, the top SNP rs769449 located in the *APOE* region showed a suggestive association, which is close to the genome-wide significance threshold. This observation is partly consistent with earlier reports [6, 7, 15], whose results suggested that *APOE* significantly associated with CSF t-tau and CSF p-tau, but not with plasma tau levels [6]. The differences between our results and previous reports maybe derive from the development of assays for the quantification of p-tau181 in blood which can measure the endophenotype for identifying genetic risk for AD more accurately than before [16]. Further, meta-analysis study also demonstrated a genome-wide significant association between plasma P-tau181 and the *APOE* genomic region [17].

Plasma p-tau181 was associated with increased risk of AD, and correlated with CSF p-tau181, tau PET as well as Aβ accumulation standardized uptake value [5]. Noteworthiness is that the association between plasma p-tau181 and other AD pathology biomarkers was significant in amyloid positive individuals, but not in amyloid negative individuals [5], which was similar to our result. Besides, the only participants who showed an increase in CSF p-tau among AD mutation non-carriers were those who were amyloid positive [18]. These data taken together maybe explained by that the events initially contributing to elevated tau phosphorylation in AD are probably associated with aggregated Aβ pathology [18].

The mechanism by which the *APOE* increase plasma p-tau181 levels is not clear. *APOE* is the strongest genetic risk factor for late-onset AD, associated with cognitive impairment [19] and amyloid pathology [20]. *APOE* also affects tau pathology, and tau-mediated neurodegeneration in an isoform dependent manner, although the association of this observation with Aβ accumulation requires further investigation [21–23]. Numerous prior studies have investigated the role of the *APOE* on amyloid aggregation and clearance in the context of AD [24]. AD is considered a secondary tauopathy as the tau pathology is accompanied by earlier development of amyloid pathology [21]. Together, these data indicate that plasma p-tau181 might be a useful and credible endophenotype for identifying genetic risk for identifying genetic risk factors for AD.

Apolipoprotein C1 (apoC1), participates in lipid transport and metabolism. *APOC1* is in linkage disequilibrium with *APOE* on chromosome 19 [25]. Our results showed that after adjusting rs769449 or *APOE* as covariates, *APOC1* has no significant association with plasma p-tau181 concentrations. Our previous work also found that rs4420638 in the *APOC1* region were associated with rate at genome-wide significance [26]. Moreover, significant associations were found between the apolipoprotein gene cluster and cognitive impairment, longevity [27], and total cholesterol.

LIMITATIONS

This study has some limitations. Firstly, GWAS merely identify loci associated with phenotypes, and we might not have identified the causal variants. Secondly, the present analyses were restricted to individuals of non-Hispanic Caucasian ancestry; the generalizability of our findings to other racial or ancestral backgrounds is uncertain. Thirdly, due to the limited data, we didn't replicate these findings in an independent cohort. Further, the sample size for analysis was relatively small, leading to the limited power for a GWAS. The future availability of comparable data from larger samples will be necessary for replication testing and additional discovery to confirm our results. Finally, functional genomics experiments are expected in future research to characterize our novel finding.

CONCLUSION

In summary, we detected three SNPs (rs769449 in *APOE*, rs4420638 and rs56131196 in *APOC1*) suggestively associated with plasma p-tau181 concentrations measured in individuals included from ADNI-1/2/Go cohort. The results of our study indicate that the rs769449 locus in the *APOE* could be a genetic regulator related to the expression of plasma p-tau181. Our findings suggest that plasma p-tau181 concentration could be a useful endophenotype for identifying risk for AD in older individuals.

REFERENCES

1. Barthelemy NR, Horie K, Sato C, Bateman RJ Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. J Exp Med 2020; 217 : https://doi.org/10.1084/jem.20200861.
2. Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E, et al. Plasma tau in Alzheimer disease. Neurology. 2016;87:1827–35. https://doi.org/10.1212/wnl.0000000000003246
3. Zetterberg H, Wilson D, Andreasson U, Minthon L, Blennow K, Randall J, et al. Plasma tau levels in Alzheimer's disease. Alzheimers Research & Therapy. 2013;5 https://doi.org/10.1186/alzrt163.
4. Karikari TK, Benedet AL, Ashton NJ, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, et al. Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative. Mol Psychiatry. 2020; https://doi.org/10.1038/s41380-020-00923-z.
5. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nat Med. 2020;26:379-+ https://doi.org/10.1038/s41591-020-0755-1
6. Chen J, Yu JT, Wojta K, Wang HF, Zetterberg H, Blennow K, et al. Genome-wide association study identifies MAPT locus influencing human plasma tau levels. Neurology. 2017;88:669–76. https://doi.org/10.1212/wnl.0000000000003615
7. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, et al. Genome-wide association study of CSF biomarkers A beta(1-42), t-tau, and p-tau(181p) in the ADNI cohort. Neurology. 2011;76:69–79. https://doi.org/10.1212/WNL.0b013e318204a397
8. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. 2020;19:422–33. https://doi.org/10.1016/s1474-4422(20)30071-5
9. Blennow K, Shaw LM, Stomrud E, Mattsson N, Toledo JB, Buck K, et al. Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Abeta(1-42), pTau and tTau CSF immunoassays. Sci Rep. 2019;9:19024 https://doi.org/10.1038/s41598-019-54204-z
10. Jack CR Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018
11. Guo T, Landau SM, Jagust WJ, Alzheimer's Disease Neuroimaging I. Detecting earlier stages of amyloid deposition using PET in cognitively normal elderly adults. Neurology. 2020;94:e1512–e1524. https://doi.org/10.1212/WNL.0000000000009216
12. Dou KX, Zhang C, Tan CC, Xu W, Li JQ, Cao XP, et al. Genome-wide association study identifies CBFA2T3 affecting the rate of CSF Abeta42 decline in non-demented elders. Aging (Albany NY). 2019;11:5433–44. https://doi.org/10.18632/aging.102125
13. Zhang C, Pierce BL. Genetic susceptibility to accelerated cognitive decline in the US Health and Retirement Study. Neurobiol Aging. 2014;35:1512.e1511–1518. https://doi.org/10.1016/j.neurobiolaging.2013.12.021
14. Arpawong TE, Pendleton N, Mekli K, McArdle JJ, Gatz M, Armoskus C, et al. Genetic variants specific to aging-related verbal memory: Insights from GWASs in a population-based cohort. PLoS One. 2017;12:e0182448 https://doi.org/10.1371/journal.pone.0182448
15. Cruchaga C, Kauwe JSK, Harari O, Jin SC, Cai Y, Karch CM, et al. GWAS of Cerebrospinal Fluid Tau Levels Identifies Risk Variants for Alzheimer's Disease. Neuron. 2013;78:256–68. https://doi.org/10.1016/j.neuron.2013.02.026
16. Tatebe H, Kasai T, Ohmichi T, Kishi Y, Kakeya T, Waragai M, et al. Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome. Molecular Neurodegeneration 2017;12 https://doi.org/10.1186/s13024-017-0206-8.
17. Lord J, Zettergren A, Ashton NJ, Karikari TK, Benedet AL, Simrén J, et al. A genome-wide association study of plasma phosphorylated tau181. Neurobiology of aging 2021; https://doi.org/10.1016/j.neurobiolaging.2021.04.018.
18. Barthélemy NR, Li Y, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, et al. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med. 2020;26:398–407. https://doi.org/10.1038/s41591-020-0781-z
19. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JCS. Cache County Study I. Apolipoprotein E epsilon 4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility - The cache county study. Arch Gen Psychiatry. 2004;61:518–24. https://doi.org/10.1001/archpsyc.61.5.518
20. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ, et al. Prevalence of cerebral amyloid pathology in persons without dementia a meta-analysis. Jama-J Am Med Assoc. 2015;313:1924–38. https://doi.org/10.1001/jama.2015.4668
21. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019;15:501–18. https://doi.org/10.1038/s41582-019-0228-7
22. Shi Y, Yamada K, Liddelow SA, Smith ST, Zhao L, Luo W, et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. Nature. 2017;549:523–527. https://doi.org/10.1038/nature24016
23. Wang Y, Mandelkow E. Tau in physiology and pathology. Nat Rev Neurosci. 2016;17:5–21. https://doi.org/10.1038/nrn.2015.1
24. Yu JT, Tan L, Hardy J. Apolipoprotein E in Alzheimer's disease: an update. Annu Rev Neurosci. 2014;37:79–100. https://doi.org/10.1146/annurev-neuro-071013-014300
25. Fuior EV, Gafencu AV. Apolipoprotein C1: its pleiotropic effects in lipid metabolism and beyond. Int J Mol Sci 2019; 20 : https://doi.org/10.3390/ijms20235939.
26. Guo Y, Xu W, Li JQ, Ou YN, Shen XN, Huang YY, et al. Genome-wide association study of hippocampal atrophy rate in non-demented elders. Aging. 2019;11:10468–84. https://doi.org/10.18632/aging.102470
27. Beekman M, Blanché H, Perola M, Hervonen A, Bezrukov V, Sikora E, et al. Genome-wide linkage analysis for human longevity: genetics of healthy aging study. Aging Cell. 2013;12:184–93. https://doi.org/10.1111/acel.12039

AUTHOR CONTRIBUTIONS

JTY designed and organised research for this study. YYH, YXY, and HFW analysed the data. YYH wrote the first draft of the manuscript. LT and JTY interpreted the data. All authors critically revised the article for important intellectual content and approved the final version of the Article.

FUNDING

This study was supported by grants from the National Natural Science Foundation of China (82071201, 81971032), the National Key R&D Program of China (2018YFC1314700), the Research Start-up Fund of Huashan Hospital, Fudan University (2022QD002), Research Start-up Fund of Huashan Hospital (2022QD002), Excellence 2025 Talent Cultivation Program (3030277001), Shanghai Municipal Science and Technology Major Project (2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University. Data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s10038-022-01026-z.

Correspondence and requests for materials should be addressed to Yu-Yuan Huang or Jin-Tai Yu.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.