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CLINICAL STUDY

A genome-wide association study of longitudinal change in CSF tau among non-demented elderly

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ABSTRACT

OBJECTIVES: To investigate the genetic determinants affecting the rate of change in CSF total tau (t-tau).

METHODS: This study conducted a genome-wide association study (GWAS) on longitudinal CSF t-tau and genotype data from 319 non-Hispanic Caucasians within the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. The aim was to identify genetic determinants influencing the rate of change in CSF t-tau, a key biomarker in AD.

RESULTS: The GWAS identified a significant single nucleotide polymorphism (SNP), rs17149074, within the C9orf171 (CFAP77) gene region that showed significant association with changes in CSF t-tau over time. Additionally, five other SNPs–rs10916844, rs10916846, rs9425869, rs3744474, and rs8078303–were found to potentially influence CSF t-tau variability.

CONCLUSIONS: These findings not only enhance our understanding of t-tau's progression in AD but also suggest that these identified SNPs could serve as novel genetic biomarkers, potentially providing novel insights in the prognostic landscape of AD by refining the predictive value of CSF-tau measurements *(Tab. 2, Fig. 2, Ref. 31)*. Text in PDF www.elis.sk

KEY WORDS: cerebrospinal fluid, t-tau, genome-wide association study, single nucleotide polymorphism, genetic factors.

Introduction

Amyloid-β (Aβ) and tau pathology are two hallmarks of Alzheimer's disease (AD). Tau is a microtubule-binding protein that is critical to the organization and stabilization of microtubules physiologically. However, the normal function of tau can be disrupted in a variety of circumstances, including AD, tauopathies, traumatic brain injury (TBI), and stroke, which ultimately results in the development of intraneuronal neurofibrillary tangle (NFT) pathology (1). Elevated levels of both t-tau and p-tau have been observed in CSF of AD patients compared to those with normal cognitive function (2). However, p-tau is regarded as a specific biomarker of AD-related tau pathology, whereas t-tau mirrors neuronal injury in the brain not specifically to AD (3). In the last twenty years, the diagnostic performance of CSF Aβ42, t-tau, and p-tau have been assessed and confirmed in numerous studies. A meta-analysis assessing the diagnostic performance of the three core biomarkers further validated that CSF T-tau, p-tau, and Aβ42 were strongly correlated with mild cognitive impairment (MCI) due to AD and AD (2). CSF p-tau has been corroborated as a biomarker in the differentiation of AD from controls, as well as other tauopathies such as frontotemporal dementia (FTD) (4–7). Moreover, elevated CSF p-tau levels could predict cognitive decline and progression to dementia, suggesting the value of longitudinal change of p-tau in neurodegenerative processes (8). CSF total tau (t-tau) and CSF phosphorylated tau (p-tau) have been recommended as diagnostic biomarkers for AD according to the 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) research framework (3). A recently published study showed that CSF p-tau217 performed better than p-tau181 as a biomarker of AD (9). Previous GWAS for CSF t-tau and p-tau levels have identified several genetic loci (10, 11). However, no GWAS has explored the genetic loci associated with longitudinal change of CSF t-tau.

Given the sufficient evidence for the role of CSF t-tau in neurodegenerative disorders, we hypothesized that certain genetic factors might also be involved in the rate of t-tau change over time. Therefore, we performed a GWAS of longitudinal change of t-tau in CSF to identify novel genetic factors in non-demented elderly.

Methods

ADNI database

Data analyzed in the article were acquired from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership. The study gathered and analyzed thousands of brain scans, including positron emission tomography (PET) and magnetic resonance imaging (MRI), genetic profiles, and biomarkers in blood and CSF from normal older subjects, as

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well as mild cognitive impairment (MCI) and early AD patients. This study was approved by the institutional review boards of all contributing research institutions, and written informed consent was obtained from all subjects or authorized representatives. Up to date information is available at www.adni-info.org.

A total of 319 non-Hispanic Caucasians with longitudinal CSF t-tau data and genotype data were available before quality control. To reduce bias in GWAS caused by cryptic relatedness and population substructure, the preliminary results were checked with genomic identity-by-descent (IBD) and multidimensional scaling (MDS) components using the PLINK v1.07 software. Two participants who appeared cryptically related and clustering separately from the other subjects were removed in this step.

Baseline CSF samples were acquired from 317 ADNI participants. The rate of tau change was assessed with the mixed effect model implemented in R software, accounting for age, gender, APOE status and education as covariates. Participants who had a value >4 or <4 SD from the mean value were considered as extreme outliers and were removed from the analysis. No individuals were removed at this step, so there were still 317 valid samples.

Statistical analyses

GWAS was conducted using linear regression analysis under the assumption of the additive genetic model in PLINK v1.07 software. Covariates included baseline age, gender, years of education, baseline diagnosis and *APOE* status, as well as three principal component factors. We included *APOEε4* as a covariate in the GWAS for limiting the effects on *APOE*ε4 genotype. The threshold for suggestive association was set at $p < 1\times10^{-5}$ and the conservative significance threshold for genome-wide significance was $p < 5\times10^{-8}$. The Manhattan plot and Q-Q plot were generated with the qqman package in R software (Version 3.5.3). Regional association plots were obtained using the LocusZoom web tool (http://locuszoom.org/).

Results

Demographic characteristic and the rate of CSF t-tau change

The detailed demographic information of included participants is presented in **Table 1**. A total of 317 non-demented non-Hispanic participants (191 MCI and 126 cognitively normal subjects) were included in this study. No significant differences in gender (p=0.08), education level (p=0.10) and the rate of t-tau change (p=0.13) were found between the two diagnostic groups, while age and *APOE* genotype differed between groups (p<0.001).

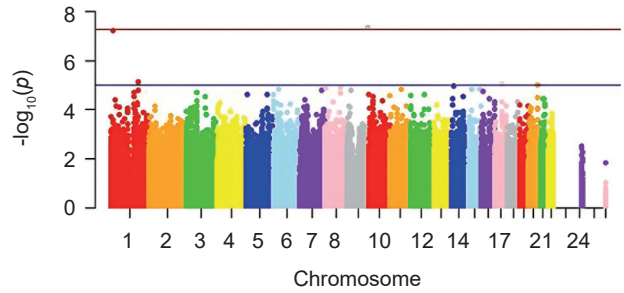

Fig. 1. Manhattan plot for the GWAS of longitudinal change of CSF t-tau. Observed -log10 P-values (y-axis) are displayed for all tested SNPs on each autosomal chromosome (x-axis), adjusting for age, gender, APOE, educational years and diagnosis as covariates. The red line is the genome-wide significant threshold at $p = 5\times10^{-8}$; the blue line is a suggestive threshold at $p = 10^{-5}$.

Loci associated with the rate of CSF t-tau change

The associations between 1231747 SNPs and the rate of t-tau change were shown in a Manhattan plot, adjusting for age, gender, APOE, years of education and diagnosis as covariates (Fig. 1). One SNP (rs17149074) reached genome-wide significance ($p=4.31\times10^{-8}$). Five SNPs (rs10916844, rs10916846, rs9425869, rs3744474, rs8078303) were identified as suggestive loci associated with the rate of t-tau change ($p<5\times10^{-5}$) (Tab. 2).

The most significant SNP and other five SNPs near the *C9orf171* gene were confirmed in linkage disequilibrium (LD, r2>0.8) (Fig. 2A). However, no correlations were detected after controlling for rs17149074 genotype, suggesting that all the correlations in this locus were driven by rs17149074 (Fig. 2B).

Tab. 1. Demographic information of participants with the longitudinal change in CSF tau.

Baseline diagnosis	CN (n=126)	MCI (n=191)
Age (mean±SD)	75.06±5.43	72.02±7.18
Education (mean±SD)	16.68±2.76	16.17±2.78
Sex(male/female)	66/60	119/72
APOE ε4 (0/1/2)	102/21/3	99/70/22
The longitudinal change rate of t-tau (mean±SD)	-0.45±1.90	0.10±2.56

CN = cognitively normal; MCI = mild cognitive impairment

Tab. 2. Top SNPs associated with longitudinal change in CSF tau.

CHR	SNP	BP	A1	MAF	Closest Gene	SNP Type	BETA	*p*
9	rs17149074	135304526	T	0.1042	C9orf171	Intron variant	2.322	4.31×10^{-8}
1	rs10916844	20983460	C	0.0487	DDOST	Intron variant	2.306	6.03×10^{-8}
	rs10916846	20986557	C	0.0691	DDOST	Intron variant	2.306	6.03×10^{-8}
	rs9425869	180112153	G	0.0897	Unknown	Intergenic	1.931	7.34×10^{-6}
17	rs3744474	43100070	C	0.1903	LOC107987243	Intron variant	1.026	8.58×10^{-6}
	rs8078303	43117813	C	0.2258	DCAKD	Intron variant	0.9861	8.75×10^{-6}

CHR = chromosome; SNP = single nucleotide polymorphism; BP = base pair; A1 = the minor allele; MAF = minor allele frequency in ADNI; SNP. Type = type of SNP; BETA = change the rate of t-tau per copy of the minor allele

Discussion

We conducted a GWAS of longitudinal change in CSF t-tau levels in the ADNI cohort. We found one SNP (rs17149074) near *C9orf171 (CFAP77)* was associated with the rates of CSF t-tau change among non-demented elderly. Moreover, SNPs near *DDOST* (rs10916844, rs10916846), *LOC107987243* (rs3744474), *DCAKD* (rs8078303) and one intergenic locus on chromosome 1 (rs9425869) were identified as suggestive loci associated with the rates of change in CSF t-tau levels. *CFAP77* (cilia and flagella associated protein 77) is involved in cell projection and protein binding. An epigenome-wide association study (EWAS) of European-American (EA) women identified one GWS DNA methylation site in gene *CFAP77* that is in association with opioid dependence (OD), and the association appears to be mostly independent of comorbid alcohol dependence (AD) and cocaine dependence (CocD) in OD subjects compared to opioid-exposed controls (13). *DDOST* is localized in chromosomal region 1p36.1 and it encodes a 48 kDa subunit of the N-glycosylation oligosaccharyltransferase (OST) complex (14). However, its biological function has yet to be fully elucidated. Evidence shows that *DDOST* could catalyze the transfer of high-mannose oligosaccharides to nascent polypeptide chains across the ER membrane (15). Besides, mutations in *DDOST* have led to reduced OST (oligosaccharyltransferase) activity and a destabilized OST complex (16, 17). A 22 bp deletion and missense mutation in *DDOST* was found in a patient with congenital disorder of glycosylation (CDG), which could affect nearly all the organs, particularly the nervous system (18, 19). Impaired *DDOST* could also result in decreased glycosylation of glycoproteins. Dysfunction of glycoproteins has been implicated in various diseases, including AD, epilepsy, diabetes, and cancer (20–26). Moreover, insertion of a sequence from intron 2 of the *DDOST* gene was found in early onset Parkinson's disease (EOPD) patients (27). Besides, mutations in DDOST were also found in esophageal squamous cell carcinoma (ESCC) (28). DCAKD codes for dephospho-CoA kinase domain-containing protein and is localized 800 kb proximal to *MAPT*. *DCAKD* showed disease-specific associations with the Parkinson disease (PD) risk SNPs. PD cases with the risk allele showed increased expression of *DCAKD*, while healthy controls with the PD risk allele showed decreased expression (29). *DCAKD* is also a member of the postsynaptic density proteins from the human neocortex (30). A study analyzed the cortical synaptic membrane proteome of juvenile postnatal days and adult mice and found that *DCAKD* was among the proteins with the highest changes, suggesting its potential role in brain development (31).

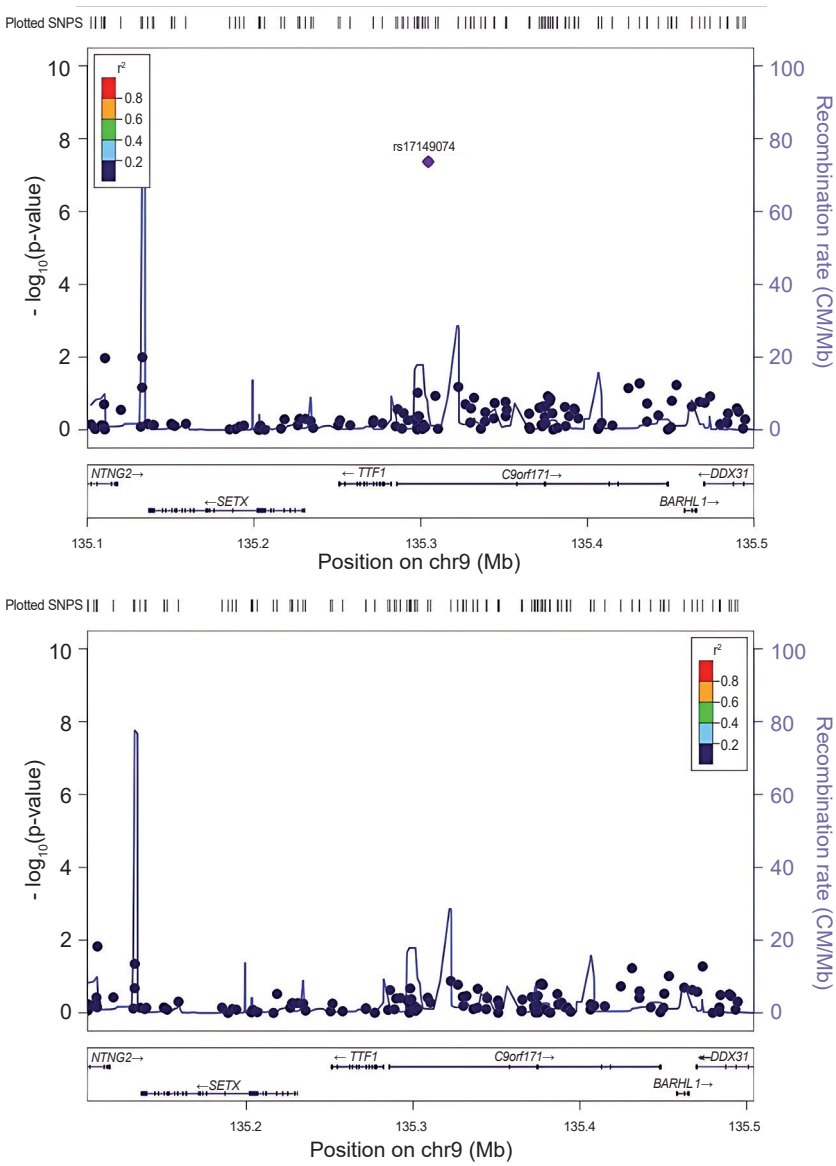

Fig. 2. Regional association plot. A) Regional association results for the C9orf171 region of chromosome 9. B) Association results for C9orf171 gene after controlling for rs17149074. No correlation was detected after controlling for rs17149074 genotype, suggesting that all the correlation in this locus was driven by rs17149074.

Our findings must be interpreted with caution, and some limitations need to be taken into consideration. Firstly, the sample size was relatively small, which could result in a limited power for a GWAS and could raise the possibility of false positive results. Moreover, ADNI participants were restricted to non-Hispanics, and replication studies across various races are necessary in

future exploration. Furthermore, we failed to conduct a replication study to confirm our findings.

In summary, we detected one genome-wide significant SNP (rs17149074) near *C9orf171* and 5 potential loci (rs10916844, rs10916846, rs3744474, rs8078303, rs9425869) associated with the rates of change in CSF t-tau among non-demented elderly. Further validation of these loci in large samples and various races is warranted in future research.

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