The impact of *GAB2* genetic variations on cerebrospinal fluid markers in Alzheimer's disease

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Background: Growth factor receptor-bound protein-associated binding protein 2 gene (*GAB2*) has been regarded as one of the susceptibility gene associated with Alzheimer's disease (AD). However, the role of *GAB2* polymorphisms on cerebrospinal fluid (CSF) proteins in AD continuum remains unclear.

Methods: We evaluated the connection between four single nucleotide polymorphisms (SNPs) of *GAB2* and AD-related CSF biomarkers including amyloid β (Aβ), total tau (T-tau) and phosphorylated tau (P-tau) level in 627 Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects.

Results: rs1385600 and rs1007837 were significantly associated with all the three biomarkers in CSF (rs1385600: Aβ Pc =0.0112, T-tau Pc =0.0356, P-tau Pc =0.0116; rs1007837: Aβ Pc =0.0058, T-tau Pc =0.0278, P-tau Pc =0.0231). rs2373115 only showed significant association with Aβ and P-tau (Aβ, Pc=0.0398, P-tau, Pc=0.0329). rs10793294 showed no significant association with all the three biomarkers.

Conclusions: Our study suggested that *GAB2* variants were significantly associated with the level of the three CSF biomarkers, which further supported that *GAB2* genetic variation modulates AD risk via the alteration of both Aβ and tau pathology.

Keywords: *GAB2*; Alzheimer's disease (AD); cerebrospinal fluid (CSF) biomarkers; single nucleotide polymorphisms (SNPs); Alzheimer's Disease Neuroimaging Initiative (ADNI)

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Introduction

Alzheimer's disease (AD) can explain about 59% of all dementia, which is deemed as the leading form of dementia among elderly (1). It is believed that genetic and environmental factors influence the incidence of the late-onset AD (LOAD) together. Growth factor receptor-bound protein-associated binding protein 2 (*GAB2*), as well as other susceptibility genes, had been confirmed to have significant associations with the LOAD by several genome wide association studies (GWAS) (2-6). *GAB2*, situated on 11q14.1, was first discovered to modify AD risk in *APOE ε4* carriers in Caucasian (7). Since then, subsequent research was continually conducted to explore the association between *GAB2* gene and the AD susceptibility in various

* 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.

Table 1 The characteristics of the ADNI subjects at baseline

Characteristics	CN (n=206)	MCI (n=377)	AD (n=44)	P*
Age (years)	74.36±5.79	74.51±5.56	75.58±9.46	–
Gender (male/female)	102/104	218/159	27/17	–
Education (years)	16.38±2.73	16.07±2.73	15.61±2.66	–
APOE ε4 (0/1/2)	157/42/7	208/136/33	13/22/9	<0.01
CDR-SB	0.03±0.14	1.40±0.85	4.45±1.64	<0.01
MMSE	29.03±1.20	28.00±1.67	22.82±1.79	<0.01
ADAS-cog	9.17±4.36	14.91±6.59	30.36±8.37	<0.01
RAVLT	45.30±9.73	35.96±10.73	22.38±8.37	<0.01

Data are given as mean ± standard deviation unless otherwise indicated. *, values for continuous variables are from one-way analysis of variance (ANOVA). P values for categorical data are from chi-square test. CN, cognitively normal; MCI, mild cognition impairment; AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Exam; ADAS-cog, Alzheimer's disease Assessment Scale Cognition; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Activities Questionnaire.

districts and ethnic groups, and controversial conclusions were obtained (8-21).

GAB2 protein belongs to the family of scaffolding and adapter proteins, and is abundantly expressed in the central nervous system (CNS) especially in prefrontal cortex and hypothalamus. It participates in many signaling pathways including cell proliferation, differentiation, survival and apoptosis (22,23). In AD, GAB2 protein is an amplifier of PI3K/AKT signaling, which is able to reduce tau phosphorylation to prevent the formation of neurofibrillary tangles (NFTs) and neuronal loss (24,25). The diminished GAB2 expression would lead to a high level of phosphorylation of tau and the formation of NFTs, which are induced by glycogen synthase kinase 3β (*Gsk-3β*). Reiman *et al.* also demonstrated small interfering RNA (siRNA)-mediated reduction of GAB2 protein increased tau phosphorylation and NFTs formation *in vitro* (7). From the evidence, *GAB2* can alter tau pathology and further mediate the susceptibility of AD. However, it is still undefined about the role of *GAB2* polymorphisms. As phosphorylated tau (P-tau), total tau (T-tau) and amyloid β (Aβ) in cerebrospinal fluid (CSF) could be effective biomarkers of AD; however, little is illustrated whether *GAB2* polymorphisms mediated the susceptibility of AD through the change of CSF biomarkers. Therefore, in our study, we research the impact of *GAB2* genetic polymorphisms on CSF biomarkers. In this way, we sought to provide clues to how *GAB2* genetic polymorphisms influence AD pathogenesis.

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset and subjects

In our paper, we used the data from the ADNI database (https://ida.loni.usc.edu/), which is a large, multicenter, longitudinal neuroimaging study. At the very beginning, ADNI aimed to identify mild cognitive impairment (MCI) and AD at earlier stages under the combination of serial magnetic resonance imaging (MRI), other biological markers, and clinical and neuropsychological assessment. The details about the ADNI cohort were described elsewhere (26,27). Our study recruited 627 individuals, including 206 cognitively normal (CN), 377 MCI patients, and 44 AD patients at baseline eventually and we downloaded their detailed demographics from the ADNI website in 2015 (*Table 1*). The ADNI study was approved by all the Institutional Ethical Review Boards of all participating centers. All participants signed written informed consent.

Single nucleotide polymorphisms (SNPs) selection

We extracted *GAB2* genotypes from the ADNI PLINK format data and performed the quality control (QC) procedures with the use of PLINK v1.07 (28).The following were the inclusion criteria: minimum call rates >90%, minimum minor allele frequencies (MAF) >0.01, Hardy-Weinberg equilibrium test $P>1\times10^{-3}$. Finally, with

the method of Haploview 4.2 platform, four targeted *GAB2* loci (rs1385600, rs1007837, rs10793294, rs2373115) were selected in our research.

CSF proteins

We downloaded all CSF data from ADNI dataset. The steps of acquisition and measurement of CSF were as follow: firstly, collected and then transferred samples into corresponding tubes; secondly, held them in dry ice for 1 hour for freezing; thirdly, transported them to corresponding laboratory at the University of Pennsylvania Medical Center for measurement; fourthly, thawed them at room temperature, prepared aliquots (0.5 mL)and reserved them at –80 ℃; finally, measured proteins with the multiplex xMAP Luminex platform and with Innogenetics immunoassay kit-based reagents (29). Full details of analytical platform are exhibited at site (http://adni.loni.ucla.edu).

Statistical analysis

We carried out all statistical analyses with R3.12 (http://www.r-project.org/) and PLINK 1.07 (http://pngu.mgh.harvard.edu/wpurcell/plink/). One-way analysis of variance (ANOVA) was used to test differences in continuous variables (age, education years, cognitive scores, volume, etc.) and chi-square test was used to examine categorical data (gender, *APOE ε4* status). We assessed possible relationship between *GAB2* SNPs and CSF biomarkers at baseline in total sample by a multiple linear regression model, in which age, gender, education years, and *APOE ε4* status were regarded as covariates. In addition, we explored the correlation between these *GAB2* SNPs and these suggestive phenotypes in the haplotype-based association analysis, and made subgroup analysis to investigate the influence of *GAB2* loci in the AD pathogenesis. We used Bonferroni correction to control the false discovery rate of multiple tests. Bonferroni-corrected Pc<0.05 was considered statistically significant.

Results

Characteristics of included subjects

We enrolled 206 CN (104 women, 74.36±5.79 years), 377 MCI (159 women, 74.51±5.56 years) and 44 AD patients (17 women, 75.58±9.46 years) in this study and *Table 1* presented the characteristics of the included subjects. Age, gender and education were matched between the three subgroups. As would be expected, the frequency of the *APOE ε4* allele is highest in AD group (45.5%) compared to the MCI (26.8%) and CN (13.6%) subjects. The cognitive function of all subjects was measured by various neuropsychological scales (*Table 1*). Unsurprisingly, the worst performance was displayed by AD patients.

CSF markers and GAB2 genotypes

We firstly confirmed relations between CSF biomarker sand *GAB2* genotypes. There were significant relations between all the three CSF biomarkers and *GAB2* loci (*Figure 1*, *Table 2*). We discovered that both rs1385600 and rs1007837 were significantly associated with all the three biomarkers in CSF (rs1385600: Aβ Pc =0.0112, T-tau Pc =0.0356, P-tau Pc =0.0116; rs1007837: Aβ Pc =0.0058, T-tau Pc =0.0278, P-tau Pc =0.0231), whereas rs2373115 only showed significant association with Aβ and P-tau (Aβ Pc =0.0398, P-tau Pc =0.0329). However, the levels of all the three biomarkers are not significantly different among the three genotypes of rs10793294.

Additionally, subgroup analysis was performed to make sure whether *GAB2* genetic polymorphisms regulated the levels of CSF markers in AD, MCI and CN subgroup (*Table 3*). After Bonferroni correction, only rs1385600 and rs1007837 showed significant associations with the expression of P-tau and T-tau in CN subgroup (rs1385600: T-tau Pc =0.0398, P-tau Pc =0.0049; rs1007837: T-tau Pc =0.0172, P-tau Pc =0.0027). However, none of these loci changed T-tau and P-tau expression in MCI and AD subgroup. Likewise, we did not observe any *GAB2* loci which altered the levels of Aβ in AD, MCI and CN subgroup (*Table 3*).

Discussion

Our study has analyzed the correlations between *GAB2* genotypes and CSF biomarkers in ADNI database. We corroborated that *GAB2* genetic variants displayed significant effects in the expression of the three CSF biomarkers.

Different with many prior findings about the involvement of *GAB2* in AD pathogenesis, our study revealed that *GAB2* loci altered the expression of Aβ, P-tau and T-tau. Among the four SNPs associated with the level of CSF proteins, rs2373115 has also been showed a significant

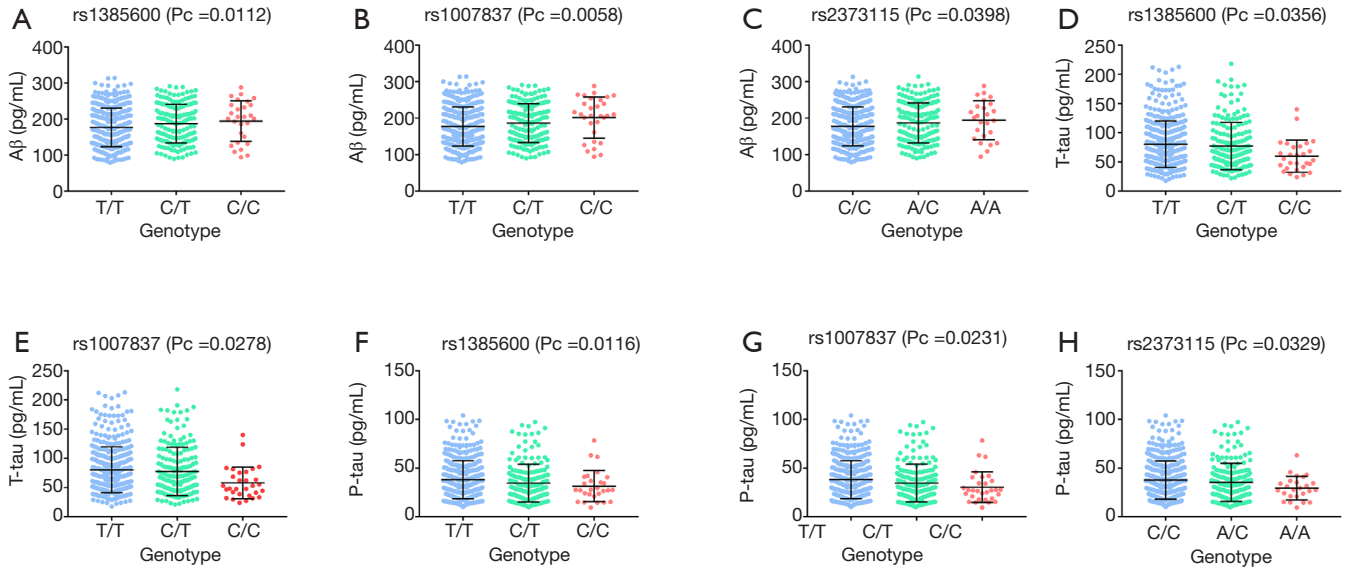

Figure 1 Presents the significant relations between all the three CSF biomarkers and GAB2 loci. (A,B,C) rs1385600, rs1007837 and rs2373115 are significantly associated with Aβ (rs1385600: Aβ Pc =0.0112; rs1007837: Aβ Pc =0.0058; rs2373115: Aβ Pc =0.0398); (D,E) rs1385600 and rs1007837 are significantly associated with T-tau (rs1385600: T-tau Pc =0.0356; rs1007837: T-tau Pc =0.0278); (F,G,H) rs1385600, rs1007837 and rs2373115 are significantly associated with P-tau (rs1385600: P-tau Pc =0.0116; rs1007837: P-tau Pc =0.0231; rs2373115: P-tau Pc =0.0329). CSF, cerebrospinal fluid; GAB2, growth factor receptor-bound protein-associated binding protein 2; Aβ, amyloid β; T-tau, total tau; P-tau, phosphorylated tau.

Table 2 The associations of *GAB2* polymorphisms with CSF proteins at baseline in entire group

CSF	SNP	Sample	P	Pc*
Aβ (pg/mL)	rs1385600	627	0.0028	0.0112
	rs1007837	627	0.0015	0.0058
	rs10793294	627	0.0403	0.1613
	rs2373115	627	0.0099	0.0398
T-tau (pg/mL)	rs1385600	620	0.0089	0.0356
	rs1007837	620	0.0070	0.0278
	rs10793294	620	0.0305	0.1221
	rs2373115	620	0.0676	0.2702
P-tau (pg/mL)	rs1385600	627	0.0029	0.0116
	rs1007837	627	0.0058	0.0231
	rs10793294	627	0.0128	0.0513
	rs2373115	627	0.0082	0.0329

*, P value after Bonferroni correction. CSF, cerebrospinal fluid; SNP, single nucleotide polymorphisms; Aβ, amyloid β; T-tau, total tau; P-tau, phosphorylated tau.

Table 3 The relations between GAB2 loci and CSF proteins in subgroup analysis at baseline

CSF	SNP	CN			MCI			AD		
		Sample	P	Pc*	Sample	P	Pc*	Sample	P	Pc*
Aβ (pg/mL)	rs1385600	206	0.0310	0.1240	377	0.0966	0.3865	44	0.5565	1
	rs1007837	206	0.0210	0.0841	377	0.1206	0.4823	44	0.5565	1
	rs10793294	206	0.1207	0.4828	377	0.3093	1	44	0.8932	1
	rs2373115	206	0.0765	0.3060	377	0.1027	0.4109	44	0.6173	1
T-tau (pg/mL)	rs1385600	205	0.0099	0.0398	374	0.1822	0.7287	41	0.8329	1
	rs1007837	205	0.0043	0.0172	374	0.2545	1	41	0.8329	1
	rs10793294	205	0.0161	0.0643	374	0.2166	0.8664	41	0.5301	1
	rs2373115	205	0.1108	0.4433	374	0.2883	1	41	0.6278	1
P-tau (pg/mL)	rs1385600	206	0.0012	0.0049	377	0.1968	0.7872	44	0.2182	0.8727
	rs1007837	206	0.0007	0.0027	377	0.4412	1	44	0.2182	0.8727
	rs10793294	206	0.0132	0.0527	377	0.2649	1	44	0.3145	1
	rs2373115	206	0.0169	0.0678	377	0.1614	0.6456	44	0.1879	0.7516

*, P value after Bonferroni correction. GAB2, growth factor receptor-bound protein-associated binding protein 2; CSF, cerebrospinal fluid; SNP, single nucleotide polymorphisms; CN, cognitively normal, MCI, mild cognition impairment, AD, Alzheimer's disease; T-tau, total tau; P-tau, phosphorylated tau.

association with AD in *APOE ε4* carriers (30). Rs2373115 is the locus that has been studied most frequently in different races followed by rs1385600 and rs1007837, and various conclusions were drawn. Interestingly, Zou *et al.* considered rs1385600 and rs2373115 as protective *GAB2* variants because they could reduce LOAD pathology via the elevated *GAB2* mRNA levels in lymphoblastoid cells in some ethnicities. Additionally, we should pay attention to that we did not confirm any association of the four SNPs with the three CSF biomarkers in MCI and AD subgroup. This might be explained by the different roles of these loci in CN individual verses those in MCI and AD.

GAB2 protein plays a vital role in the phosphorylation of kinases that involve in core neuropathogenesis of AD (7,31-33). The abnormal tau is thought as one of primary pathological factors in AD. GAB2 protein is responsible for the inhibition of tau protein phosphorylation and tangle formation known as NFTs (7). GAB2 can activate PI3K, resulting in the activation of PKB and further inactivation of *GSK-3β* (34). *GSK-3β* overexpression is involved in the phosphorylation of tau, the linkage between amyloid and tau pathology, and microglia-mediated inflammation (35,36). Therefore, it is rational to suppose that the reduced GAB2 expression and/or function would lead to the increase in tau phosphorylation. Moreover, studies *in vitro* indicated that the diminished GAB2 protein working through siRNA could increase tau phosphorylation (7). It remains unclear whether this coupling affects phosphor-ERK-1 and phosphor-ERK-2 signal transduction pathway though this mechanism in AD pathogenesis (37). In addition, GAB2 also promotes neural/glial cell proliferation to prevent the occurrence of AD via the interaction with a Rho family GTPase-activating protein (GC-GAP) which is mainly expressed in the brain (38). Collectively, GAB2 is a scaffolding protein linked with multiple signaling pathways that influence AD-related tau and cell survival or other aspects of AD pathogenesis.

Now, the genetic effects on neuroimaging and CSF markers can be depicted directly using neuroimaging phenotypes (39). So, possible mechanisms through which these genetic factors modulate the development of AD might be disclosed. The crucial strength of this study lies in quantitative traits (QTs) association studies, which have less sample size and increased statistical power requirements compared to traditional case-control designs. Moreover, ADNI database has advantages of detailed cognitive assessment agreement and diagnostic criteria, and shows relative changes across the spectrum of AD. However, we should notice that there still are some limitations. Firstly, the QT analysis reduced the sample size, because not all the

participants have all information. Secondly, we recruited only Caucasians to reduce the influence of population stratification. However, the frequency of four *GAB2* loci differs in various populations, so our results were not on behalf of other ethnicities and replication studies in other races are indispensable. Thirdly, not all candidate gene variants in *GAB2* of ADNI database were analyzed.

Collectively, our research demonstrated that *GAB2* variants were significantly associated with the expression of Aβ, T-tau and P-tau protein in CSF, which further supported that *GAB2* genetic variation modulates AD risk via the alteration of both Aβ and tau pathology. Moreover, these variants might specifically affect CN individuals, which offer new insights into the relationship between *GAB2* polymorphisms and AD. However, several limitations precluded the explanation of these findings, and future researches are wanted to figure out the detailed molecular mechanisms by which *GAB2* influence Aβ and tau protein with a longer follow-up or in other ethnicities, and an independent population is needed to replicate these findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The ADNI study was approved by all the Institutional Ethical Review Boards of all participating centers. All participants signed written informed consent.

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