

Association analysis of polymorphisms in *STARD6* and near *ECHDC3* in Alzheimer's disease patients carrying the *APOE* ϵ 4 Allele

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Background and purpose: Lipid metabolism plays an important role in Alzheimer's disease (AD), and recent evidence suggests that single nucleotide polymorphisms (SNPs) in the StAR-related lipid transfer domain 6 (*STARD6*) and near the enzyme enoyl CoA hydratase domain containing 3 (*ECHDC3*) gene are related to plasma lipid levels or lipid traits in AD.

Materials and methods: To identify whether the variants in or near the *STARD6* and *ECHDC3* genes contribute to AD susceptibility, we carried out an association analysis of *STARD6* rs10164112 and *ECHDC3* rs7920721 in combination with the apolipoprotein E (*APOE*) ϵ 4 allele in a case-control study (278 cases, 509 controls) in China.

Results: We identified that SNP rs10164112 in the *STARD6* gene was a risk factor associated with AD and the *APOE* ϵ 4 carriers (all $P < 0.05$) after Bonferroni correction. However, multivariate logistic regression analysis indicated that only the minor T allele of *STARD6* rs10164112 combined with the *APOE* ϵ 4 allele increased the risk of AD under the additive and dominant models (additive model: $P = 0.0078$, OR = 1.988, 95% CI: 1.198–3.298; dominant model: $P = 0.0172$, OR = 2.169, 95% CI: 1.147–4.102).

Conclusion: These results suggest that the rs10164112-T allele is not an independent risk factor for AD patients. However, in combination with the *APOE* ϵ 4 allele, the rs10164112-T allele has been found to be a risk factor for AD in the Han Chinese population reported in this study.

Keywords: Alzheimer's disease, *STARD6*, *ECHDC3*, *APOE*, polymorphism, association study

Introduction

Alzheimer's disease (AD) is the most common type of dementia and is characterized by the interaction of both genetic and environmental factors.¹ Amyloid- β (A β) peptide and phosphorylated Tau (p-Tau) reflect cerebral amyloid deposition and tau-related neurodegeneration, respectively, and both are potential diagnostic biomarkers for AD.

The ϵ 4 allele of the apolipoprotein E gene (*APOE* ϵ 4) is the strongest known genetic risk factor for AD, indicating that lipid metabolism may significantly contribute to AD risk and progression.^{2–6} However, the molecular mechanisms behind *APOE* ϵ 4 are not fully understood. One potential mechanism connecting AD to lipid metabolism is the fact that *APOE* also involves the aggregation and clearance of brain A β peptide, which is the main component of senile plaques.⁷ The amyloid- β protein precursors (*A β PP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*), have been shown to lead to familial forms of AD and have also been reported to influence A β metabolism.⁸ Thus, it is important that additional AD risk genes are uncovered.

In the last 2 years, studies have identified two single nucleotide polymorphisms (SNPs) that are associated with AD susceptibility, including rs7920721 (closest

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gene, *ECHDC3*; enzyme enoyl CoA hydratase domain containing 3) and rs10164112 (*STARD6*; steroidogenic acute regulatory-related lipid transfer domain 6); the genes have also been shown to be involved in plasma lipid levels or other lipid traits.^{9–11} Desikan et al⁹ demonstrated the pleiotropic effects of rs7920721 near the *ECHDC3* gene for AD, plasma C-reactive protein and lipid levels. The rs7920721 SNP is adjacent to *ECHDC3*, a gene that encodes the enzyme enoyl CoA hydratase domain containing 3; furthermore, the expression of *ECHDC3* was shown to be altered in the brains of AD patients when compared with those of the brains of controls.⁹ Subsequently, a recent, large, transethnic genome-wide association study (GWAS) identified rs7920721 to be specifically associated with persons lacking the *APOE* ϵ 4 allele.¹⁰ The risk locus rs7920721 was also identified through proxy case–control analysis and meta-analysis within a published GWAS of AD.^{12,13} In addition, increased *ECHDC3* expression was reported in patients with acute myocardial infarction, and *ECHDC3* is known to be involved in fatty acid biosynthesis in mitochondria.¹⁴ Furthermore, Kim et al¹¹ reported that *STARD6* rs10164112 was significantly correlated with AD. The steroidogenic acute regulatory (StAR)-related lipid transfer (START) domain is a conserved sequence of approximately 210 amino acids that bind lipids, including sterols.^{15,16} In humans, there are 15 START domain proteins, STARD1–STARD15, which can be classified into six subfamilies.^{17,18} START proteins are also implicated in the nonvesicular transport of lipids and sterols, lipid metabolism, and cell signaling events.^{17,18} STARD6 behaves similar to StAR proteins, which control the rate-limiting step of neurosteroid synthesis in which cholesterol is transferred from the outer mitochondrial membrane to the inner membrane.^{19,20} Accordingly, Létourneau et al²¹ published on the detailed structural and dynamical data obtained by STARD6 in steroid transport. Nevertheless, to date, no study has evaluated both SNPs rs7920721 and rs10164112 among AD patients in a Han Chinese population.

The SNPs rs7920721 and rs10164112 and the *APOE* genotypes are known to be related to lipid metabolism, which plays a central role in AD. Therefore, this study was designed to explore these two recently reported SNPs in combination with the *APOE* ϵ 4 allele in terms of the risk of AD in the Han Chinese population.

Materials and methods

Subjects

Patients with AD were recruited from the Wuxi Mental Health Center and diagnosed according to the criteria of the

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Participants with a family history of AD, neurological or psychiatric illnesses or dementia were excluded. The healthy controls without memory complaints or cognition dysfunctions were confirmed to be neurologically normal according to their medical history, general examinations and Mini-Mental State Examination (MMSE). All participants were of the Han Chinese ethnic population and were geographically from Wuxi city in Jiangsu province. According to self-reported data, individuals not born in Jiangsu or whose family members were not born in Jiangsu were excluded from the study. This study was approved by the ethics committee of the Wuxi Mental Health Center, and, prior to enrollment, signed informed consent was obtained from each participant or guardian. The study protocols were performed according to the principles of the Declaration of Helsinki.

The study sample included 278 AD patients (118 males and 160 females; mean age =72.77 years at recruitment, SD=9.09) and 509 unrelated healthy controls (249 males and 260 females; mean age =71.78 years at recruitment, SD=6.27), which were drawn from a population of people of Han descent (Table 1).

DNA extraction and SNP genotyping

Blood samples were collected from all participants using K₂EDTA tubes, and DNA was extracted from whole blood using a blood genotyping DNA extraction kit (Tiangen Biotech, Beijing, China). DNA samples were stored at –80°C until genotype analysis, which used the ligase detection reaction–PCR (LDR-PCR) method from Shanghai Biowing Applied Biotechnology Co., Ltd. (Shanghai, China) (www.biowing.com.cn).^{22,23} Genomic DNA extracted from the clinical samples was first subjected to multiplexed PCR to obtain a PCR product including rs7920721 and rs10164112. The DNA sequencer was then used to detect the LDR reaction products.

Statistical and bioinformatic analyses

PLINK v1.9 (<http://pngu.mgh.harvard.edu/purcell/plink/>) and SPSS 24.0 software (IBM Corporation, Armonk, NY, USA) were used to perform all statistical analyses, including association studies, Hardy–Weinberg equilibrium (HWE) tests and the calculation of genotype and allele frequencies between patients with AD and healthy controls.²⁴ *P*-values of allelic and genotypic tests were calibrated using Bonferroni correction and were considered statistically significant if they were less than 0.05. A power calculation of our

Table 1 Demographic characteristics of the study participants

Characteristics	AD (n=278)	Controls (n=509)	P-value	OR (95% CI)
Age, years (mean ± SD)	72.77±9.09	71.78±6.27	0.106	
Sex				
Men:women (%)	42.4:57.6	48.9:51.1	0.072	
MMSE score (mean ± SD)	10.93±7.18	28.12±3.83	<0.001	
Marital status (%)				
Married	69.8	91.6		
Widower	29.5	7.1		
Divorced	0.7	1.4	<0.001	
Education level (%)				
Primary	46.8	12		
Incomplete primary	1.4	0.2		
Upper secondary	18	31.2		
Lower secondary	27.3	46.2		
Bachelor or equivalent	6.5	10.4	<0.001	
APOE genotype (%)				
ε2/ε2	0.7	1.2		
ε2/ε3	9.4	11.8		
ε2/ε4	1.1	0.2		
ε3/ε3	57.6	70.5		
ε3/ε4	29.1	15.7		
ε4/ε4	2.2	0.6	<0.001	
APOE ε4 ⁺ vs ε4 ⁻ (%)	32.4 vs 67.6	16.5 vs 83.5	<0.001	2.422 (2.718–3.414)

Note: Bold figures indicate $P < 0.05$.

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination.

sample size was carried out using PS software (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>).^{25,26} ORs and 95% CI were calculated to assess the influence of any difference in heterogeneity.

Multivariate logistic regression was carried out to analyze the association between the SNP and susceptibility to AD after adjusting for age, gender and the *APOE* ε4 allele in the additive, dominant or recessive models. We defined various genetic models such as A2A2 vs (A1A1+ A1A2) for dominant, (A1A2+ A2A2) vs A1A1 for recessive and A1A1 vs A1A2 vs A2A2 for additive (A1: minor allele; A2: major allele).

Results

In this study, we analyzed the data from 278 patients with AD and 509 unrelated healthy controls. The demographic and clinical characteristics of the participants are summarized in Table 1. There were no significant differences in age ($P=0.106$) or gender ($P=0.106$) between the two groups. However, there were significant differences in MMSE scores, marital status, education level and *APOE* genotype between the AD and control groups ($P < 0.001$). One copy of the *APOE* ε4 allele was a significant risk factor for AD ($P < 0.001$, OR =2.422, 95% CI=2.718–3.414).

Genotype distributions were in HWE for rs7920721 and rs10164112 in both the AD and control groups ($P > 0.05$). The

total genotyping rate of all individuals was 100%. In addition, the power of this study for both SNPs were estimated to be ~70% using PS software (assumption condition: $\alpha=0.05$, $P_0=0.25$, $n=556$, $m=1.83$, $\Psi=1.339$).

The results of the association study suggested that SNP rs10164112 within *STARD6* was significantly associated with the risk of AD after Bonferroni correction ($P_{\text{allele}}=0.0254$, OR =1.339, 95% CI: 1.064–1.685; $P_{\text{genotype}}=0.0460$) (Table 2). Subsequently, according to *APOE* ε4 status, we stratified our data to investigate whether *APOE* ε4 influenced the relationship between SNPs and AD susceptibility risk. The allele and genotype frequencies of *STARD6* rs10164112 were significantly different between AD patients and healthy controls in the *APOE* ε4 carriers (ε4⁺: $P_{\text{allele}}=0.0016$, $P_{\text{genotype}}=0.0072$) (Table 2). However, there were no significant differences in the genotype and allele frequencies of the rs7920721 SNP closest to *ECHDC3* between the AD and control groups.

Multivariate logistic regression analyses were applied to re-evaluate the relation between *STARD6* rs10164112 and AD susceptibility risk in subjects with *APOE* ε4 status while adjusting for age and gender under different genetic models (Table 3). In *APOE* ε4 carriers, the minor T allele of *STARD6* rs10164112 strongly increased the risk of AD under the additive and dominant models (the additive model: $P=0.0078$, OR =1.988, 95% CI: 1.198–3.298;

Table 2 Distribution of alleles and genotypes in APOE ε4-stratified samples

SNP (A1; A2) ^a	Groups	N	Allele, n (%)		OR (95% CI)	Allelic P-value	Bonferroni P-value	Genotype, n (%)			Genotypic P-value	Bonferroni P-value
			A1	A2				A1A1	A1A2	A2A2		
rs7920721 (G; A)	AD	278	152 (27.3)	404 (72.7)	1.022 (0.810–1.289)	0.8569 ^b		20 (7.2)	112 (40.3)	146 (52.5)	0.5635 ^b	
	Control	509	274 (26.9)	744 (73.1)			28 (5.5)	218 (42.8)	263 (51.7)			
	AD	90	54 (30.0)	126 (70.0)	1.011 (0.639–1.601)	0.9613 ^b	8 (8.9)	38 (42.2)	44 (48.9)	0.2152 ^c		
	Control	84	50 (29.8)	118 (70.2)			3 (3.6)	44 (52.4)	37 (44.0)	0.9188 ^b		
rs10164112 (T; C)	AD	188	98 (26.1)	278 (73.9)	0.9852 (0.747–1.299)	0.9155 ^b	12 (6.4)	74 (39.4)	102 (54.3)			
	Control	425	224 (26.4)	626 (73.6)			25 (5.9)	174 (40.9)	226 (53.2)			
	AD	278	170 (30.6)	386 (69.4)	1.339 (1.064–1.685)	0.0127 ^b	24 (8.6)	122 (43.9)	132 (47.5)	0.0230 ^c	0.0460	
	Control	509	252 (24.8)	766 (75.2)			23 (4.5)	206 (40.5)	280 (55.0)	0.0036 ^c	0.0072	
APOE ε4 ⁺	AD	90	72 (40.0)	108 (60.0)	2.205 (1.384–3.514)	0.0008 ^b	14 (15.6)	44 (48.9)	32 (35.6)			
	Control	84	39 (23.2)	129 (76.8)			4 (4.8)	31 (36.9)	49 (58.3)			
	AD	188	98 (26.1)	278 (73.9)	1.054 (0.799–1.299)	0.7092 ^b	10 (5.3)	78 (41.5)	100 (53.2)	0.8681 ^b		
	Control	425	213 (25.1)	637 (74.9)			19 (4.5)	175 (41.2)	231 (54.4)			

Notes: P-values <0.05 are in bold after Bonferroni correction. ^aA1/A2 indicates minor allele/major allele; ^bPearson chi-squared test; and ^cFisher's exact test.
Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; SNP, single nucleotide polymorphism.

Table 3 Logistic regression analysis of rs10164112 in AD patients and controls

SNP	Groups	Model	P _{adj} -value	OR (95% CI)
rs10164112	Total ^a	ADD	0.0517	1.277 (0.998–1.634)
		DOM	0.1265	1.265 (0.936–1.711)
		REC	0.0826	1.716 (0.933–3.156)
	APOE ε4 ⁺ ^b	ADD	0.0078	1.988 (1.198–3.298)
		DOM	0.0172	2.169 (1.147–4.102)
		REC	0.0670	3.075 (0.924–10.23)
	APOE ε4 ⁻ ^b	ADD	0.6852	1.062 (0.793–1.424)
		DOM	0.7758	1.052 (0.743–1.488)
		REC	0.6519	1.198 (0.546–2.629)

Notes: ^aTotal sample; P-values in the logistic regression model, adjusted by gender, age and APOE ε4 status. ^bAPOE ε4⁺/APOE ε4⁻ subset; P-values in the logistic regression model, adjusted by gender and age. Bold figures indicate P<0.05.

Abbreviations: AD, Alzheimer's disease; ADD, the additive model; APOE, apolipoprotein E; DOM, the dominant model; REC, the recessive model; SNP, single nucleotide polymorphism.

the dominant model: P=0.0172, OR =2.169, 95% CI: 1.147–4.102).

Discussion

To our knowledge, this is the first study to associate the T allele of rs10164112 within *STARD6* with an increased risk for AD in the Han Chinese population. There were significant differences in the allele and genotype distributions of the *STARD6* rs10164112 polymorphism between the AD and control groups in subjects with the *APOE* ε4 allele. Thus, it is possible to suggest that the risk of AD increases with the combination of the T allele of rs10164112 and *APOE* ε4 alleles (OR_{ADD} =1.988, OR_{DOM} =2.169) in the Han Chinese population.

It was initially reported by Kim et al¹¹ that *STARD6* rs10164112 was significantly correlated with AD using multivariate logistic regression models (P≤0.0014, OR ≤0.037). Although the genotype and allele frequencies had a statistically significant correlation between *STARD6* rs10164112 and AD within the total sample of this study, the logistic regression models indicated no significant correlation in the total samples. In addition, inconsistent from the results reported by Kim et al,¹¹ the frequency of the rs10164112 “T” allele in the AD patients was significantly higher than that in the controls in this study. Moreover, when we compared the allele frequency of *STARD6* rs10164112 from different ethnic groups using dbSNP data from the 1,000 Genomes Project, the C allele frequency was 0.39, as shown in Figure 1, as it consists of different ethnic groups; however, it ranged from 0.06 to 0.70. The Han Chinese population (1,000 genomes) frequency is similar to what was described in the manuscript. Thus, our allele frequency analysis of these data for *STARD6* rs10164112 revealed substantial differences

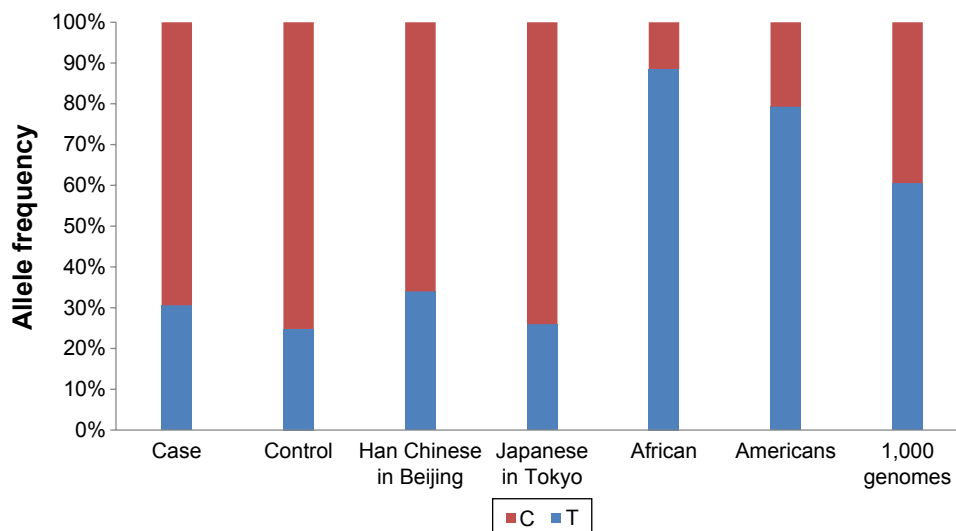


Figure 1 Allele frequency distribution of rs10164112 among different ethnic groups.

when compared to other ethnic groups (Figure 1). The differences in the rs10164112 polymorphism profiles suggested that populations from different geographies might exhibit genetic heterogeneity for AD. Therefore, in studies involving the association between the *STARD6* gene polymorphism and AD, racial and geographic aspects should be taken into account. Additional limitations of this study that should be considered are that our results may be influenced by the lack of statistical power (~70%) due to a limited sample size.

Conclusion

The rs10164112-T allele of the *STARD6* gene was not an independent risk factor for AD. However, this allele, combined with the *APOE* ϵ 4 allele, leads to an increased risk for AD in the studied Han Chinese population. When compared with the results of previous research, inconsistent results were obtained. Thus, in the future, the data need to be replicated and tested using large-scale genetic studies involving different ethnic groups.

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Author contributions

JJY and ZC conceived and designed the experiments. JJY, WF and JMY performed the experiments. JJY and WF analyzed the data. WF, HY, YW and XL contributed reagents/materials/analysis tools. JJY and CJ wrote the paper. All

authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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