

# Association of *OGGI* and *DLST* promoter methylation with Alzheimer's disease in Xinjiang population

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**Abstract.** Alzheimer's disease (AD) is a neurodegenerative disorder leading to progressive memory and cognitive impairment. Previous studies have identified multiple genes associated with AD. The aim of the present study was to validate the association of the five AD-associated variants, 8-oxoguanine DNA glycosylase 1 (*OGGI*) rs1052133, bridging integrator 1 rs744373, sortilin-related receptor 1, rs1133174, presenilin 2 rs8383, and nerve growth factor rs6330, in the Xinjiang Chinese population. In addition, the present study evaluated the contribution of the promoter methylation of two genes, *OGGI* and dihydrolipoamide succinyltransferase (*DLST*) to the risk of AD. A total of 17 AD cases and 34 controls were recruited from Xinjiang province in China. Genotyping was done by Sanger sequencing. DNA methylation assay was performed using quantitative methylation specific polymerase chain reaction. The study was unable to repeat the previous association of the five genetic polymorphisms with AD. However, *DLST* methylation levels were demonstrated to be significantly decreased in AD patients ( $P=0.027$ ), particularly in female AD patients ( $P=0.025$ ). Subgroup analysis by apolipoprotein E (*APOE*  $\epsilon 4$ ) genotype demonstrated that *OGGI* methylation levels were significantly

increased in *APOE* non- $\epsilon 4$  carriers compared with *APOE*  $\epsilon 4$  carriers ( $P=0.027$ ). In summary, the present study reported that *DLST* hypomethylation was significantly associated with AD in females, and that *OGGI* promoter methylation may interact with *APOE*  $\epsilon 4$  genotype.

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which has become a worldwide public health problem (1). The pathogenesis of AD is complex, and it may be contributed by genetic and environmental factors. The external environment can affect DNA methylation to change phenotype and gene expression (2). DNA methylation is an important epigenetic mechanism regulating the expression of aging genes in brain (3). The expression and closure of methylation regulatory genes are closely related to the human nervous system (4) and cognitive function (5).

The major challenge of AD is to identify new therapeutic targets and to develop new therapies for this disease (6). AD is closely related to tau hyperphosphorylation, oxidative stress, amyloid- $\beta$  ( $A\beta$ ) production, neuronal apoptosis, gene mutation, apolipoprotein E (*APOE*). Bridging integrator 1 (*BIN1*) is an important gene in the modulation of tau pathology, and *BIN1* knockdown was shown to significantly suppress tau-mediated neurotoxicity (7). Sortilin-related receptor 1 (*SORL1*) is a member of the low-density lipoprotein receptor family that reduces amyloid- $\beta$  ( $A\beta$ ) production by regulating the intracellular transport and processing of APP (8). Nerve growth factor (*NGF*) contributes to the survival, regeneration and death of neurons during aging and in neurodegenerative diseases (9). *PSEN2* is a transmembrane protein and AD-related presenilin mutations can alter intracellular calcium signaling, which leads to  $A\beta$  aggregation to form brain plaques and neuronal cell death (10). Genetic variation within these genes is associated with an increased risk of AD (9,11-14). The 8-oxoguanine DNA glycosylase 1 (*OGGI*) is a bifunctional enzyme with both glycosylase and AP lyase activities (15). Decreased *OGGI* activity occurs early in the progression of AD (16). *OGGI* was largely hypomethylated in LOAD and control blood DNA, and they do not support an increased promoter methylation of *OGGI* in blood DNA of AD

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patients (17). Dihydrolipoamide succinyltransferase (*DLST*) is a subunit enzyme of the  $\alpha$ -ketoglutarate dehydrogenase complex in the Krebs cycle. Polymorphisms of *DLST* were associated with AD in both Japanese and Caucasian populations (18-20).

In the present study, we aimed to validate the association of the five AD-associated variants (*OGGI* rs1052133, *BINI* rs744373, *SORLI* rs1133174, *PSEN2* rs8383, and *NGF* rs6330) with AD in Xinjiang population. We also tested the association of *OGGI* and *DLST* promoter methylation with AD.

## Materials and methods

Epidemiological investigation was carried out in Xinjiang province of China between 2014 and 2015. A total of 17 AD patients (75.65 $\pm$ 5.86 years) and 34 well-matched controls (77.59 $\pm$ 7.41 years) were selected for the present study (Table I). This study was approved by the First Affiliated Hospital of Xinjiang Medical University Ethics Committee. All the patients gave their written informed consent forms for the current study. The clinical diagnosis of AD was done according to the criteria of the Diagnostic and Statistical Manual-IV (DSM-IV). The details were the same as previously described (21). Whole blood was stored in EDTA tube at -80°C. Genomic DNA was extracted and dissolved in TE buffer, and then it was stored at -20°C. Polymerase chain reaction (PCR) was carried out in 40  $\mu$ l volume containing 2  $\mu$ l of each primer, 4  $\mu$ l genomic DNA, 12  $\mu$ l ddH<sub>2</sub>O and 20  $\mu$ l 2X HotTaq Master Mix. PCR was performed in a Veriti 96-well thermal cycler (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Genotyping was done using the Sanger sequencing. The primer sequences were TTACTTCTC CACGGACAAC and CAAGATTCTAACAGGACTCATC for the forward and the reverse primers of *PSEN2* rs8383 genotyping, GCCAGTCCATCTTCTTCT and ACCACA TCTTAGCCACAG for the forward and the reverse primers of *BINI* rs744373 genotyping, CATCCATACTGCCTGAGTC and CCTGTGAGTCCTGTTGAAG for the forward and the reverse primers of *NGF* rs6330 genotyping, GTGGATTCT CATTGCCTTC and AAAGTACTGCTTGATTG for the forward and the reverse primers of *OGGI* rs1052133 genotyping, and TGTGACTTGTGCTGTATGAT and ACG CTAGAAGAAGGCTTATC for the forward and the reverse primers of *SORLI* rs1133174 genotyping. PCR consisted of an initial melting step at 95°C for 10 min, 35 cycles (*NGF*, *BINI*, and *OGGI*) or 37 cycles (*PSEN2*) or 40 cycles (*SORLI*), and a final extension step at 72°C for 2 min. The cycling program was 95°C for 30 sec, 58°C (*NGF* and *BINI*) or 54°C (*OGGI*) or 57°C (*PSEN2*) or 53°C (*SORLI*) for 45 sec for annealing, and 72°C for 30 sec. DNA bisulphite conversion was done using the EZ DNA Methylation-Gold™ Kit (Zymo Research Corp., Irvine, CA, USA). The details of bisulphite conversion were the same as previously described (22). Promoter methylation status of *OGGI* and *DLST* were examined utilizing quantitative methylation-specific PCR (qMSP). The primer sequences were CGGTGGTTGAGTTTATTTTC and CTCCTTACGACT TATCTTCTC for the upstream and the downstream primers of *OGGI*, respectively. And the upstream and the downstream primer sequences of *DLST* were GTTGTAGTCGGGATA TTGG and CGAAACGAACCACTAACA, respectively.

**Statistical analysis.** SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. Comparison of demographical parameters between cases and controls was performed using the Student's t test for continuous variables and the  $\chi^2$  test for categorical data. Spearman rank correlation test was used to analyze the associations between gene methylation and metabolic characteristics.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

The characteristics of AD and control groups were presented in Table I. Our results showed the two groups were well paired according to the facts that there were no significant difference on gender, age, hypertension, diabetes, lipid levels, smoking and drinking status between the AD group and control group ( $P > 0.05$ ). As shown in Table II, there were no associations of the five genetic polymorphisms with AD. Further *APOE*  $\epsilon 4$  based subgroup analysis indicated there were no significant interaction of *APOE*  $\epsilon 4$  with the five genetic variants (Table III,  $P > 0.05$ ).

The promoter regions of *OGGI* and *DLST* were selected for the current methylation study (Fig. 1). In this study, we investigated the association of the methylation levels of *OGGI* and *DLST* genes with AD (Fig. 2). Although *OGGI* methylation was not associated with AD, our results showed that *OGGI* methylation was significantly lower in AD patients with *APOE*  $\epsilon 4$  allele than AD patients with *APOE* non- $\epsilon 4$  allele ( $P = 0.027$ ). Among AD patients older than 75 years old, the levels of *OGGI* methylation were significantly lower in AD patients carrying *APOE*  $\epsilon 4$  allele than AD patients who did not carry *APOE*  $\epsilon 4$  allele ( $P = 0.046$ ).

As shown in Fig. 2, *DLST* methylation levels were significantly lower in AD patients ( $P = 0.027$ ). Further subgroup analysis by gender showed that the association of *DLST* methylation with AD was specific in females ( $P = 0.025$ ). Further subgroup analysis by *APOE*  $\epsilon 4$  locus showed that *DLST* methylation was associated with AD in the *APOE* non- $\epsilon 4$  individuals ( $P = 0.029$ ). In the control group, the level of *DLST* methylation was positively correlated with TC ( $r = 0.401$ ,  $P = 0.019$ ; Table IV, Fig. 3). Further stratification by gender showed age and *OGGI* methylation levels were significantly correlated in AD group (male:  $r = 0.762$ ,  $P = 0.046$ ; female:  $r = -0.753$ ,  $P = 0.012$ ; Table V, Fig. 4). In control group, the level of *DLST* methylation was inversely correlated with age ( $r = -0.414$ ,  $P = 0.015$ ), and further stratified by gender showed that there was an inverse correlation between age and *DLST* methylation in males ( $r = -0.607$ ,  $P = 0.010$ ).

## Discussion

Previous studies have revealed the association of five variants with AD, including *OGGI* rs1052133, *BINI* rs744373, *SORLI* rs1133174, *PSEN2* rs8383, and *NGF* rs6330 (15,23-27). And *BINI* rs744373 was found to have no interaction with *APOE*  $\epsilon 4$  genotype (28). In the present study, we were unable to repeat the association of the above five variants with AD. And further *APOE*  $\epsilon 4$  based subgroup analysis indicated that *APOE*  $\epsilon 4$  did not have significant effects on five genetic polymorphisms. This might be explained by the moderate power and different ethnic background in the present pilot study. Future validation is needed in cohort with more samples.

Table I. Baseline clinical data of included subjects.

Characteristics	Cases (n=17)	Controls (n=34)	P-value
Age (years)	75.65±5.86	77.59±7.41	0.35
SBP (mmHg)	132.94±16.40	136.24±20.05	0.56
DBP (mmHg)	75.35±9.66	77.21±11.13	0.56
TG (mmol/l)	2.03±1.53	1.52±1.27	0.31
TC (mmol/l)	3.94±1.65	4.37±1.60	0.38
HDL (mmol/l)	1.41±0.30	1.29±0.45	0.33
LDL (mmol/l)	2.71±0.68	2.75±1.05	0.88
FBG (mmol/l)	4.85±0.80	5.15±1.10	0.33
Male/Female	7/10	17/17	0.55
Diabetes/Non-diabetes	1/16	7/27	0.34
Hypertension/Non-hypertension	9/8	20/14	0.69
Smoking/Non-smoking	2/15	4/30	1.00
Drinking/No drinking	1/16	2/32	1.00
APOE ε4/Not APOE ε4	8/9	2/31	0.002

SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; FBG, fasting plasma glucose.

Table II. Genotype and allele frequencies between cases and controls.

SNP	Case; control (MM/Mm/mm)	P-value	Case; control (M/m)	P-value
<i>PSEN2</i> (rs8383, C>T)	6/6/5; 7/22/5	0.12	18/16; 36/32	1.00
<i>NGF</i> (rs6330, C>T)	13/4/0; 23/10/1	0.83	30/4; 56/12	0.44
<i>SORL1</i> (rs1133174, A>G)	9/2/6; 19/7/8	0.57	20/14; 45/23	0.47
<i>OGG1</i> (rs1052133, G>C)	5/8/4; 6/20/8	0.60	18/16; 32/36	0.58
<i>BIN1</i> (rs744373, T>C)	5/7/5; 4/19/11	0.29	17/17; 27/41	0.32

NGF, nerve growth factor; SORL1, sortilin-related receptor 1; *OGG1*, 8-oxoguanine DNA glycosylase 1; BIN1, bridging integrator 1.

Table III. Analysis of the interaction between APOE ε4 and other variants.

SNP	Genotype	APOE ε4			Non-APOE ε4		
	Allele	Case	Control	P-value	Case	Control	P-value
<i>NGF</i>	CC/CT/TT	6/2/0	2/0/0	1.000	7/2/0	20/10/1	0.763
rs6330	C/T	14/2	4/0	1.000	16/2	50/12	0.647
<i>PSEN2</i>	CC/CT/TT	3/3/2	0/1/1	1.000	3/3/3	6/21/4	0.156
rs8383	C/T	9/7	1/3	0.582	9/9	33/29	0.809
<i>SORL1</i>	AA/AG/GG	3/4/1	0/1/1	0.667	6/2/1	20/6/5	1.000
rs1133174	A/G	10/6	1/3	0.285	14/4	46/16	1.000
<i>OGG1</i>	CC/ CG/GG	2/3/3	0/2/0	0.667	3/5/1	6/18/7	0.677
rs1052133	C/G	7/9	2/2	1.000	11/7	30/32	0.342
<i>BIN1</i>	CC/CT/TT	2/5/1	0/2/0	1.000	3/2/2	3/17/11	0.144
rs744373	C/T	9/7	2/2	1.000	8/6	23/39	0.168

NGF, nerve growth factor; SORL1, sortilin-related receptor 1; *OGG1*, 8-oxoguanine DNA glycosylase 1; BIN1, bridging integrator 1.

*DLST* is a core component of *KGDHC* which is essential in the citric acid cycle (29). Deficiency of *DLST* will increase production of free radicals thereby inducing mitochondrial damage (29), which leads to an increase in the generation of



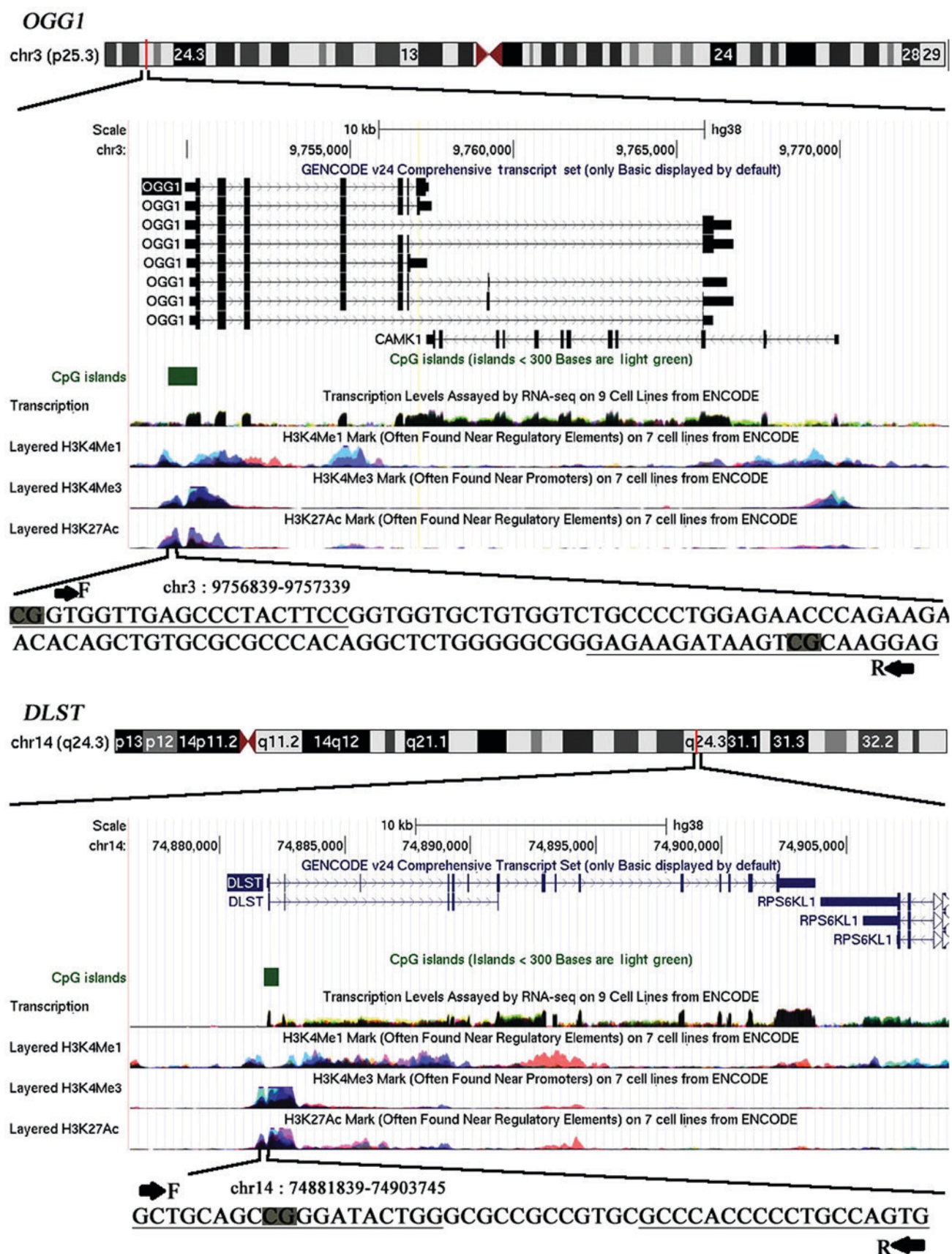


Figure 1. Locations of *OGG1* and *DLST* promoter CpG sites. The CpG island is represented by a green box. The qMSP primers are underlined and CpG site on primers is in gray. *OGG1*, 8-oxoguanine DNA glycosylase 1; *DLST*, dihydrolipoamide succinyltransferase; F, forwards primer; R, reverse primer.

reactive oxygen species (ROS). ROS damage various molecules, including DNA, protein and lipid, and induce apoptosis (30),

eventually leading to the occurrence of AD (31). The results of this study suggest that *DLST* hypomethylation may contribute

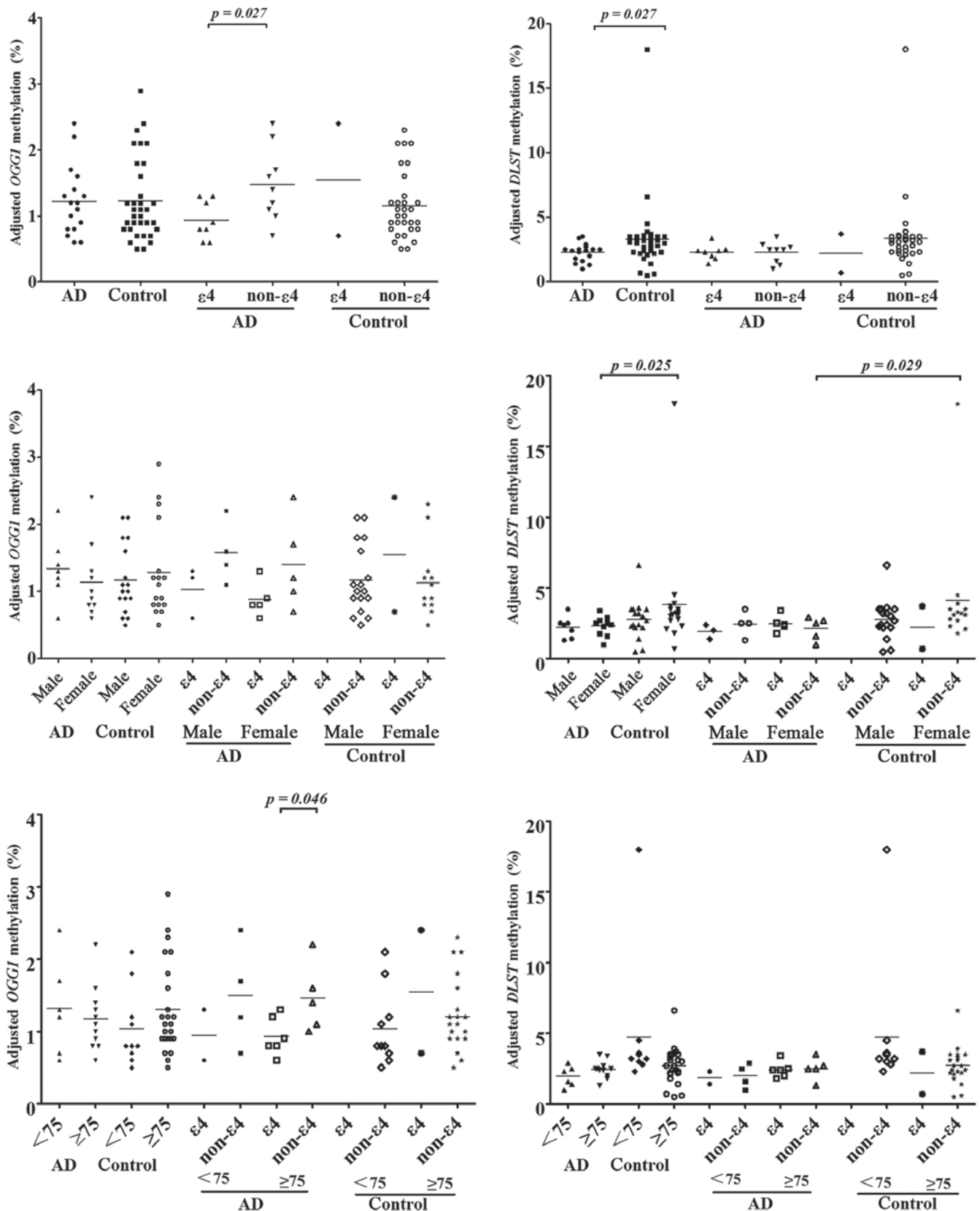


Figure 2. Comparisons of *OGG1* and *DLST* methylation levels between AD group and control group. The methylation levels in the case group and the control group were compared and stratified by gender, age, and whether or not they carried *APOE*  $\epsilon 4$  allele.  $P < 0.05$  was marked, indicating that the corresponding difference between the two groups was statistically significant. *OGG1*, 8-oxoguanine DNA glycosylase 1; *DLST*, dihydrolipoamide succinyltransferase; AD, Alzheimer's disease; *APOE*  $\epsilon 4$ , subjects with at least one *APOE*  $\epsilon 4$  allele; *APOE* non- $\epsilon 4$ , subjects with *APOE* non- $\epsilon 4$  allele.

to the pathogenesis of AD in females. Women are more likely to have AD than men because women tend live longer than

men (32-34). This finding might also help explain the sex differences in the risk of AD (35).

Table IV. Correlation tests between the DNA methylation and important parameters.

Variable	<i>OGGI</i>				<i>DLST</i>			
	Case		Control		Case		Control	
	r	P	r	P	r	P	r	P
Total								
FBG	0.309	0.228	-0.285	0.113	-0.336	0.187	-0.081	0.648
TG	-0.178	0.494	0.274	0.116	-0.020	0.939	0.009	0.962
TC	0.259	0.315	0.039	0.825	0.440	0.077	0.401	0.019
HDL	0.008	0.977	0.198	0.261	0.322	0.207	0.217	0.218
LDL	0.283	0.271	-0.019	0.914	0.322	0.207	0.217	0.218
Female								
FBG	0.347	0.326	-0.458	0.064	-0.623	0.055	0.156	0.550
TG	-0.197	0.586	0.198	0.447	0.197	0.586	-0.014	0.957
TC	0.282	0.430	-0.033	0.899	0.241	0.552	0.444	0.074
HDL	-0.357	0.312	0.247	0.338	0.463	0.178	0.163	0.533
LDL	0.464	0.177	0.051	0.845	0.111	0.760	0.145	0.579
Male								
FBG	0.635	0.125	0.006	0.983	0.208	0.654	-0.294	0.252
TG	-0.247	0.593	0.325	0.203	-0.194	0.676	-0.091	0.730
TC	0.382	0.398	0.279	0.278	0.675	0.096	0.396	0.116
HDL	0.110	0.814	0.093	0.721	0.662	0.105	0.252	0.328
LDL	0.255	0.628	-0.120	0.645	0.511	0.241	0.242	0.349

*OGGI*, 8-oxoguanine DNA glycosylase 1; *DLST*, dihydrolipoamide succinyltransferase; FBG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein.

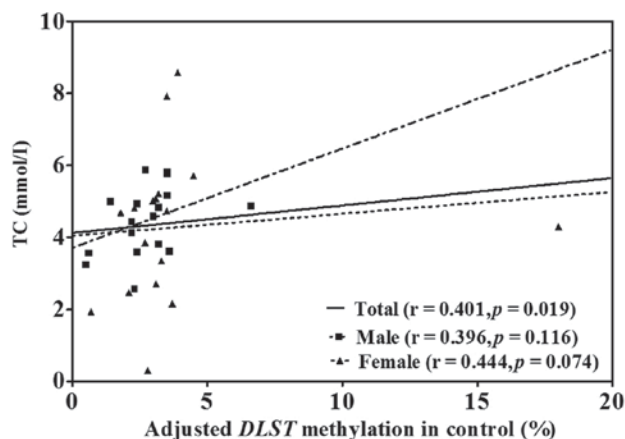


Figure 3. Pearson correlation between *DLST* methylation and TC. The upper panel shows the correlation between *DLST* methylation and TC in the control group. *DLST*, dihydrolipoamide succinyltransferase; TC, total cholesterol.

There were several limitations in the current study. Firstly, our pilot study only involved a moderate number of subjects (17 AD cases and 34 controls). This was due to the incidence rate of AD being low in Xinjiang. However, we chose a total of 51 well preserved samples, for which the transport process was reasonable and the basic informations were completed and matched. We were unable to validate the association of five gene polymorphisms (*OGGI* rs1052133,

*BIN1* rs744373, *SORL1* rs1133174, *PSEN2* rs8383, and *NGF* rs6330) with AD in the Xinjiang population. This might be due to the limited number of samples in this study. Secondly, we only selected a fragment in the promoter CpG rich region to represent the methylation of *OGGI* and *DLST*. The methylation of other regions of the two genes might be explored in the future. Thirdly, Xinjiang Uygur Autonomous Region is a multi-ethnic area. Future research with larger sample sets and more ethnic populations are required to confirm the present findings.

In summary, we found that the levels of *DLST* methylation were decreased in AD patients, especially in female AD patients. The results showed that the level of *OGGI* promoter methylation might be interacted with *APOE*  $\epsilon$ 4 genotype.

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Table V. Correlation tests between age and methylation levels of *OGGI* and *DLST*.

Age	<i>OGGI</i>				<i>DLST</i>			
	Case		Control		Case		Control	
	r	P	r	P	r	P	r	P
Total								
Methylation level	-0.079	0.763	-0.018	0.921	0.187	0.472	-0.414	<b>0.015</b>
Female								
Methylation level	-0.753	<b>0.012</b>	0.236	0.362	0.203	0.574	-0.076	0.771
Male								
Methylation level	0.762	<b>0.046</b>	-0.282	0.273	0.246	0.595	-0.607	<b>0.010</b>

Bold font represents positive results ( $P < 0.05$ ). *OGGI*, 8-oxoguanine DNA glycosylase 1; *DLST*, dihydrolipoamide succinyltransferase;

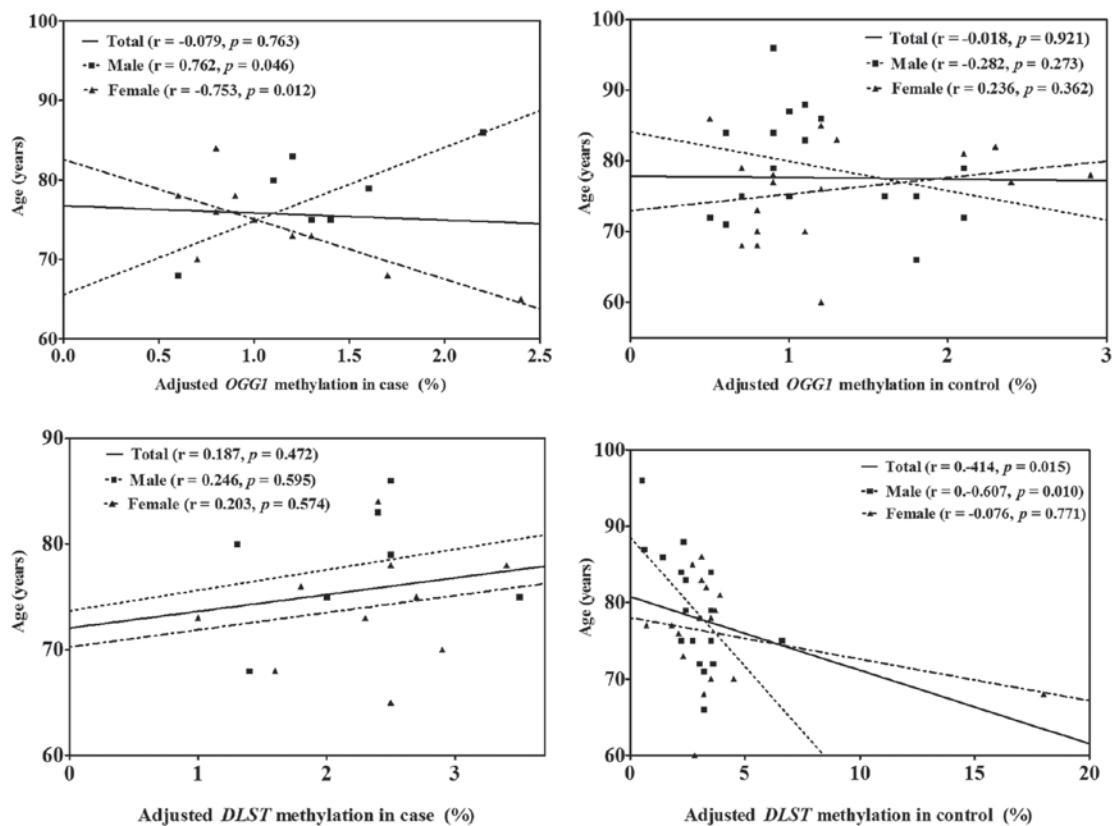


Figure 3. Correlation tests between age and DNA methylation in AD and control group. The upper panel shows the correlation between genes (*DLST* and *OGGI*) methylation and age in AD and control group. r represents correlation coefficient,  $P < 0.05$  represents statistical significance. AD, Alzheimer's disease; *DLST*, dihydrolipoamide succinyltransferase; *OGGI*, 8-oxoguanine DNA glycosylase 1.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

SD, XZ and QW conceived and designed the experiments. WC, TZ, YD, GL and XY performed the experiments.

WC and GL analyzed the data. GL and XY contributed reagents/materials/analysis tools. WC, TZ and YD wrote the manuscript.

### Ethics approval and consent to participate

The present study was approved by the First Affiliated Hospital of Xinjiang Medical University Ethics Committee. All the patients gave their written informed consent forms for the present study.



## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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