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Role of *ADH1B* rs1229984 and *ALDH2* rs671 gene polymorphisms in the development of Alzheimer's disease

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ABSTRACT. In the present study, we investigated the association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and the development of Alzheimer's disease in a Chinese population. Genotyping of the *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms was carried out by polymerase chain reaction-restriction fragment length polymorphism. Logistic regression analyses revealed that the AA genotype of *ADH1B* rs1229984 was associated with an increased risk of Alzheimer's disease (OR = 2.54, 95%CI = 1.19-5.41). In addition, *ADH1B* rs1229984 was also associated with elevated risk of Alzheimer's disease in both dominant (OR = 1.78, 95%CI = 1.09- 2.93) and recessive (OR = 2.33, 95%CI = 1.18-4.57) models. For *ALDH2* rs671, the AA genotype was correlated with an increased risk of Alzheimer's disease as compared to the GG genotype (OR = 4.57, 95%CI = 1.60-14.01). The *ALDH2* rs671 polymorphism was associated with Alzheimer's in both dominant (OR = 1.79, 95%CI = 1.08-2.97) and recessive (OR = 4.17, 95%CI = 1.49-12.67) models. In conclusion, we observed that

ADH1B rs1229984 and *ALDH2* rs671 polymorphisms increased the risk of Alzheimer's disease in all the genetic models.

Key words: *ADH1B*; *ALDH2*; Polymorphism; Alzheimer's disease

INTRODUCTION

Alzheimer's disease is a chronic neurodegenerative disease that usually starts slowly, but worsens over time. It is estimated that the prevalence of Alzheimer's disease is approximately 1-2% in people above 65 years of age (Campion et al., 1999), and 25-35% in people above 80 years of age (Hebert et al., 2003). The pathogenesis of Alzheimer's disease involves many environmental factors such as age, brain trauma or tumors, infection, and poisoning (Ting et al., 2016). A study conducted in 11,884 twins has shown that genetic predisposition accounts for 58-79% of Alzheimer's disease cases (Gatz et al., 2006). Previous studies have indicated that genetic polymorphisms in protein tyrosine kinase 2b, presenilin 2, apolipoprotein E, cytochrome 46A1, disrupted-in-schizophrenia-1, 3-hydroxy-3-methylglutaryl-CoA reductase, and sortilin receptor 1 all play essential roles in the development of this disease (Chang et al., 2016; Huang et al., 2016; Jia et al., 2016; Li et al., 2016; Suzuki et al., 2016; Zhang et al., 2016; Zheng et al., 2016). Previous studies have reported that alcohol consumption is associated with risk of Alzheimer's disease (Piazza-Gardner et al., 2013; Berntsen et al., 2015; Ilomaki et al., 2015). Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are two important enzymes for ethanol metabolism in the human body (Asakage et al., 2007; Dakeishi et al., 2008; Kang et al., 2009; Lee et al., 2015). ADH1B and *ALDH2* are two common ADH and ALDH proteins, and polymorphisms in *ADH1B* rs1229984 and *ALDH2* rs671 could cause alterations in enzymatic activities of these proteins, thus leading to the development of nervous system diseases including Alzheimer's disease (Song et al., 2014; Hu et al., 2015; Yoshimasu et al., 2015; Zhang et al., 2015). Therefore, we investigated the association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and the development of Alzheimer's disease in a Chinese population.

MATERIAL AND METHODS

Patients

Alzheimer's disease patients (N = 115) and control subjects (N = 236) were recruited from the Department of Neurology at the Remin Hospital of Wuhan University between October 2013 and April 2015. Alzheimer's disease was diagnosed based on NINCDS-ADRDA criteria proposed by the Department of Health and Human Services Task Force on Alzheimer's Disease (McKhann et al., 1984). Patients with a history of brain tumor, secondary Alzheimer's disease were excluded from this study Over the same period, control subjects were recruited from patients who visit the outpatient clinics in the Department of Pneumology, Department of Dermatology, and Department of Orthopedics at the Remin Hospital of Wuhan University. Control subjects were confirmed to be without

histories of brain tumor, Alzheimer's disease, neurological diseases, and end-stage liver or kidney diseases.

The general characteristics of Alzheimer's disease patients and control subjects were collected from a questionnaire, which was filled during face-to-face interviews by doctors or nurses. Information obtained from the study participants included gender, age, body mass index, family history of Alzheimer's disease, tobacco smoking, and alcohol drinking. A written informed consent was obtained from study subjects prior to their enrollment, and all study procedures were approved by the Ethics Committee of the Remin Hospital of Wuhan University. Of the investigated patients and controls, the mean ages were 68.54 ± 9.30 and 67.10 ± 9.59 years, respectively. There were 41 (35.65%) females and 74 (64.35%) males in the Alzheimer's disease group. In the control group, there were 87 (36.86%) females and 149 (63.14%) males.

DNA extraction and genotyping analysis

Peripheral blood (5 mL) from each subject was drawn and collected into vacuum tubes with 5% ethylenediaminetetraacetic acid (EDTA). DNA extraction was performed using the TIANamp Blood DNA Kit (Tiangen, Beijing, China), following the manufacturer protocol. Genotyping of *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms was carried out via polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis. The forward and reverse primer sequences for *ADH1B* rs1229984 were 5'-AATCTTTTGTGAATCTGAACAG-3' and 5'-GAAGGGGGGTCACCAGGTTG-3', respectively. The forward and reverse primers for *ALDH2* Glu487Lys were 5'-GTCAACTGCTATGATGTGTTTGG-3' and 5'-CCACCAGCAGACCCTCAAG-3', respectively. The restriction enzymes used for *ADH1B* rs1229984 and *ALDH2* rs671 digestion were MaeIII and EcoRI, respectively. The genotypes of *ADH1B* rs1229984 and *ALDH2* rs671 were determined using 3% agarose gel electrophoresis and EB staining.

Statistical analysis

Data are reported as percentages of total (categorical variables) or as means ± SD (continuous variables). The Student t-test was used to determine differences in means, and Pearson c2 or Fisher exact tests were used to assess inter-group differences. Allele frequencies were calculated by the gene-counting method, and each genotype was tested for departure from Hardy-Weinberg equilibrium (HWE) in the control population using c2 tests. Logistic regression analysis was performed in order to determine the odds ratios (OR) and 95% confidence intervals (95%CI) associated with risk to Alzheimer's disease, and the controls were used as the reference group. Statistical significance was set at $P < 0.05$.

RESULTS

As confirmed using the c2 test, patients with Alzheimer's disease were more likely to have a family history of Alzheimer's disease (c2 = 20.70, $P < 0.001$), and have no habit of alcohol consumption (c2 = 4.58, $P = 0.03$) (Table 1). However, no significant difference was observed between the Alzheimer's disease patients and controls with regards to age (c2

= 0.62, P = 0.43), gender (c2 = 0.05, P = 0.83), BMI (c2 = 0.23, P = 0.63), and tobacco smoking (c2 = 0.25, P = 0.62).

Table 1. Demographic variables of Alzheimer's disease patients and controls.

Variables	Patients (N = 115)	%	Controls (N = 236)	%	χ^2 test	P value
Age (years)						
<65	37	32.17	86	36.44		
≥65	78	67.83	150	63.56	0.62	0.43
Gender						
Females	41	35.65	87	36.86		
Males	74	64.35	149	63.14	0.05	0.83
BMI						
<24	77	66.96	164	69.49		
≥24	38	33.04	72	30.51	0.23	0.63
Family history of Alzheimer's disease						
No	93	80.87	226	95.76		
Yes	22	19.13	10	4.24	20.70	<0.001
Alcohol consumption						
No	88	76.52	154	65.25		
Yes	27	23.48	82	34.75	4.58	0.03
Tobacco smoking						
No	66	57.39	142	60.17		
Yes	49	42.61	94	39.83	0.25	0.62

The genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 in the two study groups are shown in Table 2. Statistical analysis using the c2 test revealed significant differences in the genotype distributions of *ADH1B* rs1229984 (c2 = 7.55, P = 0.02) and *ALDH2* rs671 (c2 = 11.65, P = 0.003) between Alzheimer's disease patients and controls (Table 2). We found that genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 were in agreement with HWE in controls. However, the genotype distribution of *ALDH2* rs671 was in HWE in the patient group.

Table 2. Genotype distributions of *ADH1B* rs1229984 and *ALDH2* rs671 in the two study groups.

Variables	Patients (N = 115)	%	Controls (N = 236)	%	χ^2 test	P value
Age (years)						
<65	37	32.17	86	36.44		
≥65	78	67.83	150	63.56	0.62	0.43
Gender						
Females	41	35.65	87	36.86		
Males	74	64.35	149	63.14	0.05	0.83
BMI						
<24	77	66.96	164	69.49		
≥24	38	33.04	72	30.51	0.23	0.63
Family history of Alzheimer's disease						
No	93	80.87	226	95.76		
Yes	22	19.13	10	4.24	20.70	<0.001
Alcohol consumption						
No	88	76.52	154	65.25		
Yes	27	23.48	82	34.75	4.58	0.03
Tobacco smoking						
No	66	57.39	142	60.17		
Yes	49	42.61	94	39.83	0.25	0.62

Logistic regression analysis revealed that the AA genotype of *ADH1B* rs1229984 was associated with an increased risk of Alzheimer's disease (OR = 2.54, 95%CI = 1.19-5.41), and that *ADH1B* rs1229984 was associated with elevated risk of Alzheimer's disease in both dominant (OR = 1.78, 95%CI = 1.09-2.93) and recessive (OR = 2.33, 95%CI = 1.18-4.57) models (Table 3). For *ALDH2* rs671, the AA genotype was correlated with

increased risk of Alzheimer's disease as compared with the GG genotype (OR = 4.57, 95%CI = 1.60-14.01). Finally, the *ALDH2* rs671 polymorphism was associated with development of Alzheimer's disease in both dominant (OR = 1.79, 95%CI = 1.08-2.97) and recessive (OR = 4.17, 95%CI = 1.49-12.67) models.

Table 3. Association between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and Alzheimer's disease risk.

Variables	Patients (N = 115)	%	Controls (N = 236)	%	OR (95%CI)[1]	P value
ADH1B rs1229984						
Codominant						
GG	35	30.43	89	37.71	1.0 (Ref.)	-
GA	57	49.57	125	52.97	1.16 (0.68-1.98)	0.56
AA	23	20.00	23	9.75	2.54 (1.19-5.41)	0.01
Dominant						
GG	35	30.43	89	37.71	1.0 (Ref.)	-
GA+AA	103	89.57	147	62.29	1.78 (1.09-2.93)	0.01
Recessive						
GG+GA	92	80.00	214	90.68	1.0 (Ref.)	-
AA	23	20.00	23	9.75	2.33 (1.18-4.57)	0.01
ALDH2 rs671						
Codominant model						
GG	72	62.61	177	75.00	1.0 (Ref.)	-
GA	30	26.09	52	22.03	1.42 (0.80-2.47)	0.19
AA	13	11.30	7	2.97	4.57 (1.60-14.01)	0.01
Dominant						
GG	72	62.61	177	75.00	1.0 (Ref.)	-
GA+AA	43	37.39	59	25.00	1.79 (1.08-2.97)	0.02
Recessive						
GG+GA	102	88.70	229	97.03	1.0 (Ref.)	-
AA	13	11.30	7	2.97	4.17 (1.49-12.67)	0.02

[1]Adjusted for gender, age, family history of Alzheimer's disease, and alcohol consumption.

The interactions between the two gene polymorphisms and alcohol consumption with respect to risk of Alzheimer's disease are illustrated in Table 4. We observed that *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms are significantly associated with family history of Alzheimer's disease and alcohol consumption in the risk of this disease.

Table 4. Interaction between *ADH1B* rs1229984 and *ALDH2* rs671 polymorphisms and drinking status in risk of Alzheimer's disease.

Variables	*ADH1B* rs1229984		*ALDH2* rs671	
	Spearman correlation coefficient	P value	Spearman correlation coefficient	P value
Age (years)	0.047	0.36	0.036	0.49
Gender	0.063	0.22	0.059	0.32
BMI	0.061	0.27	0.040	0.42
Family history of Alzheimer's disease	0.172	<0.001	0.265	<0.001
Alcohol consumption	0.131	0.02	0.160	0.04
Tobacco smoking	0.035	0.48	0.045	0.37

DISCUSSION

Polymorphisms in *ADH1B* rs1229984 and *ALDH2* rs671 may influence the expression and function of proteins in enzyme metabolism, because the single nucleotide polymorphism could change the expression and quantities of protein in individuals. In the present study, we observed that the AA genotype of *ADH1B* rs1229984 or *ALDH2* rs671

was associated with the risk to Alzheimer's disease in a Chinese population. Previous studies have reported on the relationship between alcohol consumption and Alzheimer's disease, and have indicated that low levels of alcohol consumption could protect against dementia and reduce the mortality rate of mild Alzheimer's disease (Berntsen et al., 2015; Ilomaki et al., 2015). However, one large-scale study has reported that frequent alcohol consumption is associated with elevated risk of dementia (Langballe et al., 2015). Ethanol is not toxic to the human body; however, the acetaldehyde oxidized from ethanol is toxic. ADH and ALDH oxidize ethanol to acetaldehyde, which is then converted to acetate in the liver. The enzymatic activities of ADH and ALDH could influence the level of acetaldehyde in the human body. Therefore, polymorphisms in *ADH1B* and *ALDH2* could lead to differences in ethanol metabolism between individuals, and affect the accumulation of acetaldehyde in the human body. Previous studies have reported that *ALDH2* polymorphism is associated with development of Alzheimer's disease; however, the results were inconsistent among studies (Kamino et al., 2000; Shin et al., 2005; Wang et al., 2008; Zhou et al., 2010; Hao et al., 2011; Komatsu et al., 2014). Kamino et al. (2000) carried out a case-control study with 447 patients and age- and gender-matched controls, and indicated that *ALDH2* deficiency is a risk for late-onset Alzheimer's disease in the Japanese population. However, some studies reported opposite results. Shin et al. (2005) reported that the AA genotype of *ALDH2* does not play an important role in the etiology of dementia in the Korean population. Similarly, Zhou et al. (2010) reported that *ALDH2* does not play a role in the development of Alzheimer's disease in the Mongolian population. Komatsu et al. (2014) also did not find any significant association between *ALDH2* polymorphism and risk of Alzheimer's disease in the Japanese population. In a recent meta-analysis with 821 Alzheimer's disease patients and 1380 healthy controls, it was suggested that the GA and AA genotypes of *ALDH2* increase the risk of Alzheimer's disease in East Asian men (Hao et al., 2011). This was in agreement with our results, which showed that the AA genotype of *ALDH2* rs671 increased the risk of Alzheimer's development. It is possible that the discrepancies between individual studies are due to differences in populations, sample sizes, as well as case selection. To date, no studies have reported on the association between *ADH1B* polymorphism and risk of Alzheimer's disease. Therefore, here we show for the first time the role of *ADH1B* rs1229984 in Alzheimer's disease. However, the exact molecular mechanisms underlying the pathogenesis of Alzheimer's disease remain to be elucidated in future studies. Two limitations should be noted in our study. First, the study subjects were all recruited from one hospital within China, which may not be representative of the global population. Second, the sample sizes of this study were relatively small, which may reduce the statistical power of our analyses. In conclusion, we observed that *ADH1B* and *ALDH2* polymorphisms increased the risk of Alzheimer's disease development. Therefore, *ADH1B* and *ALDH2* genetic polymorphisms may be risk factors for Alzheimer's disease.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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