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Original Article

Association of *ADH2* and *ALDH2* genetic polymorphisms with susceptibility to Parkinson's disease in a Chinese population

Jidong Liu[1*], Shaohua Sui[2*], Lanyong Xu[3], Kai Lin[4], Jin Zong[5], Yang Yang[1], Hui Wang[6]

[1]Department of Neurosurgery, Zhumadian Central Hospital, Zhumadian, China; [2]Department of Emergency, Liao Cheng People's Hospital, Liaocheng, China; [3]Department of Neurosurgery, Gaotang County People's Hospital, Gaotang, China; [4]Department of Neurosurgery, Liao Cheng People's Hospital, Liaocheng, China; [5]Department of Neurosurgery, Liao Cheng Traditional Chinese Medicine Hospital, Liaocheng, China; [6]Department of Neurology, Liao Cheng People's Hospital, Liaocheng, China. [*]Equal contributors.

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Abstract: Parkinson's disease is a common disorder of neurodegenerative diseases. The pathological process of this disease is involved in many environmental and genetic factors. In this study, we investigated the role of *ADH2* Arg47His and *ALDH2* Glu487Lys genetic variations in the risk of developing Parkinson's disease in a Chinese population. Between March 2013 and June 2015, 107 patients with Parkinson's disease and 192 healthy controls were recruited in our study. The *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms were genotyped by polymerase chain reaction (PCR)-restriction fragment length polymorphism. Results of chi-square tests indicated a significant difference in the genotype distributions of *ALDH2* Glu487Lys (χ^2 = 6.85, P = 0.03) between the patients with Parkinson's disease and the controls. We also performed unconditional logistic regression analyses, and observed that the GA genotype (OR = 1.71, 95% CI = 0.97-3.01; P = 0.05) and AA genotype (OR = 2.94, 95% CI = 0.85-10.67; P = 0.04) of *ALDH2* Glu487Lys significantly elevated the risk of Parkinson's disease in comparison with the GG genotype. In addition, the A allele of *ALDH2* Glu487Lys was significantly correlated with an increased risk of Parkinson's disease when compared to the G allele (OR = 1.79, 95% CI = 1.15-2.80; P = 0.01). However, the polymorphism in *ADH2* Arg47His was not correlated with the risk of Parkinson's disease. In summary, this study indicates that *ALDH2* Glu487Lys polymorphism influences the development of Parkinson's disease in the Chinese population studied here.

Keywords: Parkinson's disease, *ADH2*, *ALDH2*, polymorphism

Introduction

Parkinson's disease is a common nervous system degenerative disease, and its incidence is next to Alzheimer's Disease [1]. The clinical manifestations of Parkinson's disease include static tremor, muscle rigidity, bradykinesia and abnormal gait posture, and the pathological feature of this disease is absence of dopanminergic neuron degeneration in substantia nigra compact and formation of Louis corpuscle [2, 3]. The etiology of Parkinson's disease is complication and involves a long term process with many environmental factors, including old age, exposure to herbicides and insecticides, traumatic brain injury, consumption of coffee and tobacco smoking et al. [2, 4]. However, not all individuals exposed to the same risk factors of Parkinson's disease would development this disease, indicating that more factors, such as hereditary factors, contribute to the development of this disease. Many molecular studies have widely studies, and many genetic factors contribute to the pathogenesis of Parkinson's disease, such as aldehyde dehydrogenase 2, vascular endothelial growth factor, synuclein, monoamine oxidase B, leucine-rich repeat kinase 2, Vitamin D receptor and Leucine-rich repeat kinase 2 genes [5-13].

A recent meta-analysis study with 32 article indicates that alcohol intake might be inversely correlated with the risk of Parkinson's disease [14]. Pharmacokinetic genes are involved in the metabolism of alcohol in human body, including alcohol deydrogenase (ADH) and aldehyde

Table 1. Primer sequences, restriction enzymes and amplified products for the ADH2 Arg47His and ALDH2 Glu487Lys polymorphisms

IL-10 polymorphism	Primer (5'→3')	Restriction enzymes	Amplified products, bp
ADH2 Arg47His	ATTCTGTAGATGGTGGCTGT (forward) GAAGGGGGTCACCAGGTTG (reverse)	*MaeII*	63
ALDH2 Glu487Lys	CCCTTTGGTGGCTAGAAGATG (forward) CCACACTCACAGTTTTCTCTTT	*MboII*	96

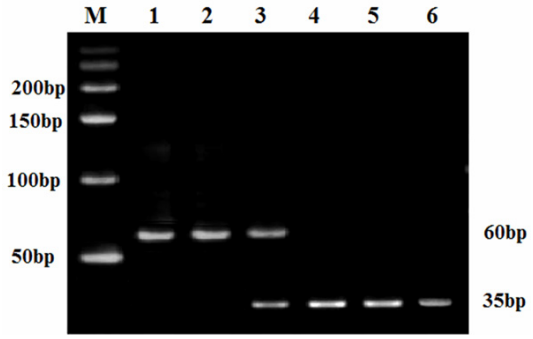

Figure 1. Amplified products of *ADH2* Arg47His. Lane 1 and 2: GG genotype; lane 3: GA genotype; lane 4, 5 and 6: AA genotype.

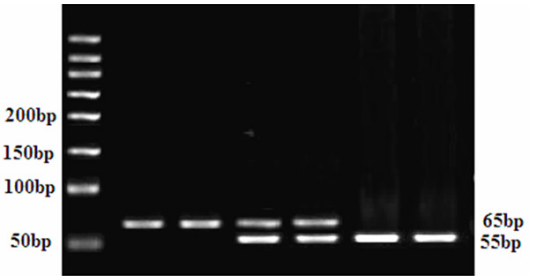

Figure 2. Amplified products of *ALDH2* Glu487Lys. Lane 1 and 2: GG genotype; lane 3 and 4: GA genotype; lane 5 and 6: AA genotype.

dehydrogenase (ALDH) [15-18]. When alcohol enter into human body, 90%-95% of them were metabolized by ADH and ALDH in liver. Ethanol is firstly catalyzed into acetaldehyde by ADH. Acetaldehyde is a high active and toxic substances, and it is catalyzed into harmless acetic acid by ALDH. Acetic acid then enters into Krebs cycle, and finally is metabolized into carbon dioxide and H_2O and excreted from human body [15-18]. Polymorphisms in *ADH2* and *ALDH2* could change the expression, activity and function of the wide type proteins, and thus affect the ethanol-metabolism activity [16, 19]. *ADH2* Arg47His and *ALDH2* Glu487Lys are two common genetic polymorphisms in the two proteins, and they could change the function of *ADH2* and *ALDH2* and affect the ethanol metabolism [16, 18]. However, few studies have reported the association between *ADH2* and *ALDH2* polymorphisms and risk of Parkinson's disease, but the results are conflicting [20, 21]. In this study, we investigated the role of *ADH2* Arg47His and *ALDH2* Glu487Lys genetic variations in the risk of developing Parkinson's disease in a Chinese population.

Material and methods

Subjects

Between March 2013 and June 2015, 107 patients with Parkinson's disease (n = 107) and 192 controls (n = 192) were recruited from the Department of Neurology of the Zhumadian Central Hospital, Gaotang County People's Hospital and Liao Cheng Traditional Chinese Medicine Hospital. The diagnosis of Parkinson's disease was according to the criteria specified by the UK Parkinson's disease Society Brain Bank Criteria [22].

The control subjects were selected from patients visiting the outpatient clinics in the Central Hospital of Zhumadian and Gaotang County People's Hospital. Subjects with a Parkinson's disease and other nervous system diseases were excluded from this study.

The demographic variables of all investigated subjects were obtained from a structure questionnaires. The drinking status was divided into two groups, including drinkers and non-drinkers. The clinical data of all investigated subjects were obtained from their medical records. All the investigated subjects signed an informed consent before enrollment. This study was approved by the ethics committee of the Central Hospital of Zhumadian, Gaotang County People's Hospital and Liao Cheng Traditional Chinese Medicine Hospital.

At the time of enrollment, the mean ages of the patients with Parkinson's disease and control

Table 2. Demographic and lifestyle variables of patients with Parkinson's disease and controls

Variables	Patients N = 107	%	Controls N = 192	%	χ^2 test	*P* value
Age, years						
<65	40	37.38	74	38.54		
≤65	67	62.62	118	61.46	0.04	0.84
Gender						
Females	43	40.19	87	45.31		
Males	64	59.81	105	54.69	0.73	0.39
Family history of Parkinson's disease						
No	101	94.39	192	100.00		
Yes	6	5.61	0	0.00	10.99	0.001
Alcohol consumption						
No	76	71.03	112	58.33		
Yes	31	28.97	80	41.67	4.74	0.02
Tobacco smoking						
No	73	68.22	127	66.15		
Yes	34	31.78	65	33.85	0.13	0.71

subjects were 68.40±8.45 and 67.25±8.30 years, respectively. There were 66 (57.39%) males in patients and 117 (54.67%) males in controls. A total of 37 (32.17%) patients and 60 (28.04%) controls had a history of alcohol consumption, and 43 (37.39%) patients and 72 (33.64%) controls had a history of tobacco smoking.

DNA extraction and genotyping of ADH2 Arg47His and ALDH2 Glu487Lys

DNA was extracted from the peripheral blood (5 mL) samples with the TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the manufacturer protocol. The *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms were genotyped by polymerase chain reaction (PCR)-restriction fragment length polymorphism. The primer sequences of *ADH2* Arg47His and *ALDH2* Glu487Lys were designed using Primer Premier 5.0. The primer sequences, restriction enzymes and amplified products were shown in **Table 1**. The cycling conditions for *ADH2* Arg47His and *ALDH2* Glu487Lys started with a denaturation at 97°C for 5 min; 35 cycles of denaturation at 94°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 30 s; final extension at 72°C for 10 min. The PCR products and digestive products were observed by electrophoresis on a 3%-agarose gel.

For the *ADH2* Arg47His gene, GG genotype had the restriction fragment length of 60 bp, AA genotype showed the 35 bp and 28 bp fragment lengthes, and the heterozygotes exhibited both fragments (**Figure 1**). For the *ALDH2* Glu487Lys polymorphism, the GG genotype presented the restriction fragment length of 65 bp, the AA genotype had 55 bp fragment length, and both fragments were present in the GA genotype (**Figure 2**).

Statistical analysis

Student's *t*-tests and chi-square tests were used to compare the demographic and clinical variables and genotype frequencies between patients and controls. Hardy-Weinberg equilibrium (HWE) of *ADH2* Arg47His and *ALDH2* Glu487Lys in the patients and controls was calculated using Pearson's Chi-square test. The association between the *ADH2* Arg47His and *ALDH2* Glu487Lys polymorphisms and Parkinson's disease was estimated using multiple logistic regression analyses, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The statistical calculations were performed by IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA). The *p*-value less than 0.05 was considered as statistically significant.

Results

In comparison with the controls, patients were more likely to have a family history of Parkinson's disease (χ^2 = 10.99, P = 0.001) and have no

Table 3. *ADH2* Arg47His and *ALDH2* Glu487Lys genotype distributions of the study groups

Variables	Patients N = 107	%	Controls N = 192	%	χ^2 test	*P*-value	χ^2 test HWE in patients	*P*-value	χ^2 test HWE in controls	*P*-value
ADH2 Arg47His										
GG	32	29.90	71	36.98						
GA	52	48.60	94	48.96						
AA	23	21.50	27	14.06	3.27	0.20	0.04	0.83	0.22	0.64
ALDH2 Glu487Lys										
GG	64	59.81	141	73.44						
GA	35	32.71	45	23.44						
AA	8	7.48	6	3.12	6.85	0.03	1.05	0.31	1.02	0.31

Table 4. Association of *ADH2* Arg47His and *ALDH2* Glu487Lys genetic mutations with the risk of Parkinson's disease

Variables	Patients N = 107	%	Controls N = 192	%	OR (95% CI)[1]	*P*-value
ADH2 Arg47His						
Co-dominant model						
GG	32	29.9	71	36.98	1.0 (Ref.)	-
GA	52	48.6	94	48.96	1.23 (0.69-2.18)	0.45
AA	23	21.5	27	14.06	1.89 (0.89-4.01)	0.07
Allele						
G	116	54.2	236	61.46	1.0 (Ref.)	-
A	98	45.8	148	38.54	1.35 (0.95-1.92)	0.08
ALDH2 Glu487Lys						
Co-dominant model						
GG	64	59.81	141	73.44	1.0 (Ref.)	-
GA	35	32.71	45	23.44	1.71 (0.97-3.01)	0.05
AA	8	7.48	6	3.12	2.94 (0.85-10.67)	0.04
Allele						
G	163	76.17	327	85.16	1.0 (Ref.)	-
A	51	23.83	57	14.84	1.79 (1.15-2.80)	0.01

[1]Adjusted for age, gender, and family history of Parkinson's disease. OR, Odds ratio; CI, confidence interval; Ref., reference value.

habit of alcohol drinking (χ^2 = 4.74, P = 0.02). However, no significant difference was observed between the two investigated groups with respect to age (χ^2 = 0.04, P = 0.84), gender (χ^2 = 0.73, P = 0.39), and tobacco smoking (χ^2 = 0.13, P = 0.71) (**Table 2**).

Results of chi-square tests indicated a significant difference in the genotype distributions of *ALDH2* Glu487Lys (χ^2 = 6.85, P = 0.03) between the patients with Parkinson's disease and the controls (**Table 3**), whereas the genotype frequencies of *ADH2* Arg47His were comparable between the two study groups (χ^2 = 3.27, P = 0.20), using chi-square test. Our results revealed that the genotype frequencies of *ADH2* Arg47His (HWE in patients: χ^2 = 0.04, P = 0.83; HWE in controls: χ^2 = 0.22, P = 0.64) and *ALDH2* Glu487Lys (HWE in patients: χ^2 = 1.05, P = 0.31; HWE in controls: χ^2 = 1.02, P = 0.31) were in line with the Hardy-Weinberg equilibrium in the patients and control subjects.

We also performed unconditional logistic regression analyses, and observed that the GA genotype (OR = 1.71, 95% CI = 0.97-3.01; P = 0.05) and AA genotype (OR = 2.94, 95% CI = 0.85-10.67; P = 0.04) of *ALDH2* Glu487Lys sig-

nificantly elevated the risk of Parkinson's disease in comparison with the GG genotype (**Table 4**). In addition, the A allele of *ALDH2* Glu487Lys was significantly correlated with an increased risk of Parkinson's disease when compared with the G allele (OR = 1.79, 95% CI = 1.15-2.80; P = 0.01). However, the polymorphism in *ADH2* Arg47His could not infleunce the susceptibility to Parkinson's disease in this population.

Discussion

Currently, genome-wide associated studies have shown several gene polymorphisms that are involved in the risk of Parkinson's disease [23]. In this study, we assessed the association between polymorphisms in *ADH2* Arg47His and *ALDH2* Glu487Lys and Parkinson's disease, and revealed that the GA and AA genotypes and A allele of *ALDH2* Glu487Lys were associated with the pathogenesis of Parkinson's disease in the Chinese population studied here.

ALDH2 is located at chromosome 12q24.2 with a length of 44kb, and is composed of 517 amino acid residues polymorphisms. In the process of detoxification, the enzyme encoded by the *ALDH2* can catalyze the transformation of toxic acetaldehyde and other aliphatic aldehyde products to acetic acid [24-26]. Up to now, a total of 84 single nucleotide polymorphisms are found in the *ALDH2*, but the rs671 (Glu487Lys) is the widely investigated. The *ALDH2* Glu487Lys GA genotype has only 6.25% of the catalytic activity of GG genotype, and the *ALDH2* Glu487Lys AA genotype is lack of catalytic activity. *ALDH2* also contributes to detoxifying adehydes in the brain, and previous experimental studies have reported that *ALDH2* is expressed in midbrain dopamine neuron [27, 28]. It is reported that a common loss of function genetic polymorphism, *ALDH2* Glu487Lys AA is common observed in northeast Asians and is associated with the risk of Alzheimer's disease [28-30]. A recent experimental study has indicated that the impaired detoxification of biogenic aldehydes by ALDH2 is associated with the pathophysiology of Parkinson's disease [31].

ALDH2 genetic mutations could induce genetic and molecular aberrations, which could result in risk of several types of central nervous system related diseases [29, 30, 32-34]. In a Japanese study by Kamino et al., it was observed that dosage of the *ALDH2* Glu487Lys A allele significantly affected age at onset of patients with homozygous for polymorphisms and development of late-onset Alzheier's disease [32]. In a study by Michel et al., it reported that *ALDH2* activity was associated with the putamen of patients with Parkinson's disease in comparison to controls [35]. In a meta-analysis conducted by Hao et al., which included 821 Alzheimer's disease and 1380 healthy controls, it was shown that the ALDH2 Glu487Lys GA/AA genotype elevated the development of Alzheimer's disease in east Asian men [29]. However, some studies reported contradicting results. For example, in a study by Zhou et al., involving 106 unrelated Mongolian Spradic Alzheimer disease patients and 100 controls, it found that *ALDH2* Glu487Lys did not influence the development of Alzheimer's disease [36]. Notably, in a Chinese study conducted by Yao et al., involving in 148 stroke patients, it stated that the A allele in *ALDH2* Glu487Lys is an independent protective variable for patients who have had stroke and have a history of heavy alcohol consumption [33]. Similarly, in a Japanese study by Komatsu et al., it was shown that *ALDH2* Glu487Lys polymorphism did not modify the risk of Alzheimer's disease [32].

Currently, only three studies have examined the role of *ALDH2* in the development of Parkinson's disease [20, 21, 37]. In a study conducted by Fitzmaurice et al., involving 6 tagSNPs, it was shown that *ALDH2* was associated with the pathogenesis of Parkinson's disease, but the *ALDH2* Glu487Lys did not influence the risk of this disease [20]. In another study conducted by Zhang et al., including 584 patients and 582 control subjects, it was reported that haplotype of rs4767944, rs441 and rs671 were associated with the risk of *ALDH2* genetic variations [21]. In a recent study done by Yu et al., including 139 patients with Parkinson's disease, it was shown that cognitive impairments was more frequent in individuals harboring inactive ALDH2 group [37]. The exact molecular mechanisms of *ADH2* and *ALDH2* for the pathogenesis of Parkinson's disease are needed to be elucidated in future studies.

This study has two limitations when interpreting the results. First, the other genes except for *ALDH2* Glu487Lys may influence the risk of

Parkinson's disease, and gene-gene interaction should be considered in further studies. Second, the small sample size could be responsible for the low statistical power of the differences found between study groups. Therefore, further studies with large-scale sample sizes are greatly required to confirm our results.

In summary, this study suggests that *ALDH2* Glu487Lys polymorphism influences the development of Parkinson's disease in the Chinese population studied here, whereas *ADH2* polymorphism does not. Further studies are greatly needed to confirm our results.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hui Wang, Department of Neurology, Liao Cheng People's Hospital, No. 67 West Dongchang Road, Liaocheng, China. Tel: +86-635-8513679; Fax: +86-635-8513679; E-mail: wanghuih77@163.com

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