

# The role of *ALDH2* and *ADH1B* polymorphism in alcohol consumption and stroke in Han Chinese

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## Abstract

The genes encoding the enzymes for metabolising alcohol dehydrogenase 1B (*ADH1B*) and aldehyde dehydrogenase 2 (*ALDH2*) — exhibit genetic polymorphism and ethnic variations. Although the *ALDH2*\*2 variant allele has been widely accepted as protecting against the development of alcoholism in Asians, the association of the *ADH1B*\*2 variant allele with drinking behaviour remains inconclusive. The goal of this study was to determine whether the polymorphic *ADH1B* and *ALDH2* genes are associated with stroke in male Han Chinese with high alcohol consumption. Sixty-five stroke patients with a history of heavy drinking (HDS) and 83 stroke patients without such a history (NHDS) were recruited for analysis of the *ADH1B* and *ALDH2* genotypes from the stroke registry in the Tri-Service General Hospital, Taipei, Taiwan, between January 2000 and December 2001. The allelotypes of *ADH1B* and *ALDH2* were determined using the polymerase chain reaction–restriction fragment length polymorphism method. The HDS patients (3 per cent) showed a significantly lower *ALDH2*\*2 allele frequency than NHDS patients (27 per cent) ( $p < 0.001$ ). After controlling for age, patients with HDS were associated with a significantly higher occurrence of cigarette smoking ( $p < 0.01$ ) and liver dysfunction ( $p < 0.01$ ). Multiple logistic regression analyses revealed that the *ALDH2*\*2 variant allele was an independent variable exhibiting strong protection (odds ratio 0.072; 95 per cent confidence interval 0.02–0.26) against HDS after adjustment for hypertension, diabetes mellitus, smoking status and liver dysfunction. By contrast, allelic variations in *ADH1B* exerted no significant effect on HDS. The present study indicated that, unlike *ALDH2*\*2, *ADH1B*\*2 appears not to be a significant negative risk factor for high alcohol consumption in male Han Chinese with stroke.

**Keywords:** alcohol dehydrogenase, aldehyde dehydrogenase, Han Chinese, stroke, high alcohol consumption, allelic variation

## Introduction

Stroke is the third leading cause of death and the major cause of disability requiring long-term institutionalisation in Taiwan.<sup>1</sup> Epidemiological evidence has shown that heavy drinking is a major risk factor for all stroke subtypes.<sup>2</sup>

Alcohol metabolism is one of the biological determinants that can significantly influence drinking behaviour and the development of alcoholism and alcohol-related organ damage.<sup>3,4</sup> Most ethanol elimination occurs via oxidation to acetaldehyde and acetate, catalysed principally by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase

(ALDH), respectively.<sup>5</sup> The genes encoding both enzymes exhibit polymorphism and ethnic variations.<sup>6,7</sup> The allelic variant *ALDH2\*2* is best known for its role in ethanol metabolism and has been shown to be protective against the development of alcohol dependence.<sup>8,9</sup> Although the *ADH1B\*2* variant has also been documented as a negative risk factor for developing alcoholism, studies of its effect on drinking behaviour in Asian populations have been inconclusive.<sup>10–12</sup> Among East Asians, including Han Chinese, Japanese and Koreans, 80–90 per cent of individuals carry the variant allele *ADH1B\*2*: this encodes the high-activity ADH1B allozyme which catalyses the oxidation of ethanol to acetaldehyde.<sup>4,13</sup> *ADH1B\*2* occurs with a much lower frequency in Caucasian and black populations.<sup>8</sup> The variant *ALDH2\*2* allele encodes the very-low-activity allozyme of ALDH2, impairing the conversion of acetaldehyde to acetate.<sup>4</sup> This inborn error of acetaldehyde metabolism occurs uniquely in about half of East Asians but is rarely seen in other ethnic groups.<sup>14</sup>

The *ALDH2\*2* variant has been reported to be involved in alcohol-related diseases, including oropharyngolaryngeal, oesophageal and stomach cancer,<sup>15</sup> colorectal cancer,<sup>16</sup> breast cancer,<sup>17</sup> asthma<sup>18</sup> and myocardial infarction.<sup>19,20</sup> Recently, the *ALDH2* polymorphism has been found to contribute to variations in the efficacy of nitroglycerin treatment for angina and heart failure.<sup>21,22</sup> Epidemiological studies indicate that heavy alcohol consumption may increase the risk of stroke;<sup>23–27</sup> however, the potential association of allelic variations of *ADH1B* and *ALDH2* with stroke in relation to high alcohol consumption has never been documented. The present study was undertaken to evaluate the influence of functional polymorphisms of *ADH1B* and *ALDH2* in stroke patients with a history of heavy drinking.

## Materials and Methods

### Demographic and clinical data

Study subjects were drawn from the patient data base for a previous case–control study conducted by one of the authors (G.-S.P.) between January

2000 and December 2001 at the Tri-Service General Hospital, Taipei, Taiwan.<sup>25</sup> A total of 524 male stroke patients with their first ever acute stroke had been recruited in the previous study and they all met the World Health Organization's stratified criteria for stroke. Patients with a history of previous stroke, head trauma, brain stroke precipitated during surgery or angiography, receiving therapeutic anticoagulation or antiplatelet therapy, with a bleeding diathesis, a history of illicit drug use, or concomitant serious medical illness such as malignancy, uraemia, cirrhosis of the liver, sepsis, meningoencephalitis, autoimmune disorders, vasculitides, evidence of cerebral vascular malformation or symptoms of a transient ischaemic attack were excluded. All of the recruited stroke patients received examinations including a head computed tomography (CT) scan, blood pressure measurement, an electrocardiogram (ECG), a chest X-ray, a complete blood cell count, prothrombin time (PT), partial thromboplastin time (PTT) and serum electrolyte determinations and a blood biochemistry analysis. The head CT scan was performed to differentiate haemorrhagic stroke (which has two subtypes: intracerebral haemorrhage [ICH] and subarachnoid haemorrhage [SAH]) from ischaemic stroke. Stroke outcome was measured using a modified Rankin scale at discharge. Potential risk factors for stroke were recorded by interviews, clinical examinations and laboratory tests. Diabetes mellitus (DM) was defined as patients having a fasting glucose level of 140 mg/dl or higher, or a non-fasting glucose level of 200 mg/dl or higher, or currently taking medication for DM. Hypertension was defined as patients having a systolic blood pressure greater than 140 mmHg, a diastolic blood pressure greater than 90 mmHg, or currently receiving treatment for hypertension. Hypercholesterolaemia was defined as patients having a fasting total serum cholesterol level greater than 200 mg/dl or currently receiving treatment for hypercholesterolaemia. Hypertriglyceridaemia was defined as patients having a fasting serum triglyceride level greater than 160 mg/dl or currently receiving treatment for hypertriglyceridaemia. Hyperuricaemia was defined as patients having a

serum uric acid level greater than 8.0 mg/dl or currently taking medication for hyperuricaemia. The smoking status was recorded as cigarettes currently smoked per day. Heart disease was diagnosed from a resting ECG, echocardiography or coronary catheterisation. Liver dysfunction was defined as patients having elevated blood levels of either glutamic oxaloacetic transaminase (GOT) or glutamic pyruvic transaminase (GPT) (each greater than 40 IU/L). Stroke patients with a history of heavy drinking (HDS) were defined as having a chronic alcohol consumption of over 45 g of ethanol per day<sup>26</sup> or a recent mean alcohol intake exceeding 300 g of ethanol per week.<sup>27</sup> Stroke patients without such a history (NHDS) were characterised as not having a history of regular alcohol consumption of over 45 g of ethanol per day or 300 g of ethanol per week. Of the 524 male stroke patients, sixty-eight were HDS and 456 were NHDS. From this sample, sixty-five HDS and 83 NHDS were randomly recruited for the genotyping study of *ADH1B* and *ALDH2*. The experimental procedures were approved by the Institutional Review Board for Human Studies at the Tri-Service General Hospital, and informed consent was obtained from each patient, after the nature and possible consequences of participation in the study had been explained.

### Genotyping

DNA was extracted from leukocytes, and the allelotypes of *ADH1B* and *ALDH2* were determined using polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) as described previously.<sup>28</sup>

### Statistical analysis

The categorical variables were compared using the Pearson chi-square test. Continuous variables, which are expressed as mean  $\pm$  standard deviation, were compared using Student's unpaired *t* test. The odds ratio (OR) and 95 per cent confidence interval (CI) after adjustment for confounding variables were evaluated by multiple logistic regression analysis. The statistical analyses were performed using

the SAS version 9.1 statistical programs (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 148 men with a history of stroke were recruited into the study. The study group consisted of 65 HDS men, aged 31 to 83 years, and the control group consisted of 83 NHDS men, aged 34 to 85 years. The daily alcohol consumption in the HDS group was estimated to be  $119 \pm 59$  g prior to the stroke. The average daily alcohol consumption in the NHDS group was negligible, since most of the men in this group drank rarely or only occasionally.

The clinical characteristics of patients are shown in Table 1. The mean age of stroke onset was significantly younger in the HDS group ( $58 \pm 14$  years) compared with the NHDS group ( $63 \pm 12$  years) ( $p < 0.05$ ). With further stratification of

**Table 1.** Clinical characteristics of patients with HDS and NHDS. Figures in parentheses are percentages. Statistical comparison was evaluated by the chi-square test. Values for age and blood pressure are expressed as mean  $\pm$  SD

Characteristic	NHDS (n = 83)	HDS (n = 65)	p value
Age, years	63 $\pm$ 12	58 $\pm$ 14	0.020
SBP, mmHg	154 $\pm$ 32	151 $\pm$ 30	0.477
DBP, mmHg	85 $\pm$ 20	88 $\pm$ 16	0.282
Stroke type			0.058
Infarction	61 (73.5)	38 (58.5)	
Haemorrhage	22 (26.5)	27 (41.5)	
MRS			0.230
1	7 (8.4)	14 (21.5)	
2	23 (27.7)	15 (23.1)	
3	24 (28.9)	16 (24.6)	
4	15 (18.1)	12 (18.5)	
5	9 (10.8)	3 (4.6)	
6	5 (6.1)	5 (7.7)	

Abbreviations: DBP, diastolic blood pressure; MRS, modified Rankin scale; SBP, systolic blood pressure.

genotypes *ADH1B* or *ALDH2*, the onset ages showed no significant difference between the HDS and NHDS groups (*ALDH2*\*2/\*2 homozygotes were excluded from the comparison, as no such genotype was found in the HDS group). Twenty-seven (41.5 per cent) of 65 HDS patients and 22 (26.5 per cent) of 83 NHDS patients were haemorrhagic. The occurrence of haemorrhagic stroke in HDS patients was marginally statistically higher than that in the NHDS patients ( $p = 0.058$ ). Since heavy drinking was found to be a common risk factor for stroke in the ICH and SAH subtypes,<sup>29–33</sup> both subtypes were included in the analysis. Only a very small number of SAH cases were found in the stroke patients (none in HDS and four in NHDS). No significant differences were

found in blood pressure or in the modified Rankin scale between the HDS and NHDS groups.

The relative numbers of patients with hypertension ( $p < 0.05$ ) and DM ( $p < 0.01$ ) were significantly lower in the HDS group than in the NHDS group, but the relative numbers of current smokers ( $p < 0.001$ ) and those with liver dysfunction ( $p < 0.001$ ) were significantly higher in the HDS group. After adjustment for age (Table 2), only the numbers of current smokers ( $p < 0.01$ ) and those with liver dysfunction ( $p < 0.01$ ) remained significantly higher in the HDS patients than in the NHDS patients. Laboratory blood test data revealed that only the serum GOT level in HDS patients was significantly higher than that in NHDS patients ( $p < 0.05$ ). There was no significant difference in

**Table 2.** Age-adjusted risk factors and laboratory data for HDS patients. Figures in parentheses are percentages. Statistical comparison was evaluated by the multiple logistic regression analysis. Values for laboratory data are expressed as mean  $\pm$  SD

Variables	NHDS (n = 83)	HDS (n = 65)	p value	OR	95% CI
<b>Risk factors</b>	<b>No. (%)</b>	<b>No. (%)</b>			
Hypertension	63 (75.9)	38 (58.5)	0.122	0.517	0.23–1.19
Diabetes mellitus	25 (30.1)	8 (12.3)	0.300	0.590	0.22–1.60
Smoking	37 (44.6)	47 (72.3)	0.004	3.269	1.45–7.36
Hypercholesterolaemia	24 (28.9)	14 (21.5)	0.330	0.617	0.23–1.63
Hypertriglyceridaemia	20 (24.1)	10 (15.4)	0.216	0.520	0.19–1.47
Heart disease	13 (15.7)	9 (13.8)	0.688	1.251	0.42–3.73
Hyperuricaemia	12 (14.4)	14 (21.5)	0.369	1.643	0.56–4.85
Liver dysfunction	3 (4.6)	17 (26.1)	0.003	7.552	1.95–29.2
<b>Laboratory data means <math>\pm</math> SD</b>					
TG, mmol/L	155.2 $\pm$ 84.5	160.5 $\pm$ 93.3	0.830	0.999	0.99–1.01
TC, mmol/L	187.9 $\pm$ 46.3	177.0 $\pm$ 45.7	0.577	0.997	0.99–1.09
GOT, U/L	23.7 $\pm$ 10.7	71.4 $\pm$ 174.7	0.039	1.044	1.00–1.09
GPT, U/L	22.0 $\pm$ 15.4	44.0 $\pm$ 75.0	0.096	0.961	0.92–1.01
PT, s	11.3 $\pm$ 0.57	11.8 $\pm$ 1.5	0.970	1.013	0.53–1.95
PTT, s	25.8 $\pm$ 3.9	28.0 $\pm$ 5.0	0.355	1.052	0.95–1.17
PLT, / $\mu$ l	220487 $\pm$ 69370	197721 $\pm$ 77945	0.148	1.000	1.00–1.00

Abbreviations: PLT, platelet; TC, total cholesterol; TG, triglyceride.

GPT, PT and platelet counts between the HDS and NHDS groups.

Both the genotype ( $p < 0.001$ ) and allele frequencies ( $p < 0.001$ ) of *ALDH2* in the HDS group were significantly different from those in NHDS group (Table 3). The frequencies of *ADH1B* genotypes and alleles were, however, similar in the two groups. Multiple logistic regression analyses showed that the *ALDH2*\*1/\*2 genotype was an independent variable with strong protection (OR 0.030; 95 per cent CI 0.002–0.396;  $p < 0.0078$ ) against high alcohol consumption in stroke patients (Table 4) after adjustment for hypertension, DM, smoking status, liver dysfunction and *ADH1B* genotype. By contrast, allelic variations of *ADH1B* exerted no significant effect

on the risk of heavy drinking in stroke patients by logistic regression analysis. *ADH1B* and *ALDH2* also showed no significant interaction in the risk for heavy drinking in stroke patients (Table 4).

## Discussion

The present study revealed a significant difference in *ALDH2* genotypes between the HDS and NHDS groups. The allele frequencies of *ALDH2*\*2 were significantly lower in the HDS group (3 per cent) than in the NHDS group (27 per cent). The variant allele frequency in the HDS group was not significantly different ( $p = 0.056$ ) from that found in the previous study of Han Chinese alcohol-dependent patients (8 per cent for *ALDH2*\*2).<sup>28</sup> Moreover, the

**Table 3.** Genotype and allele distribution of *ADH1B* and *ALDH2* in patients with HDS and NHDS. The statistical comparison was evaluated by the Pearson chi-square test

Gene	N	Genotype number (frequency)			p Value	Allele number (frequency)		
		*1/*1	*1/*2	*2/*2		*1	*2	p Value
<i>ADH1B</i>								
NHDS	83	10 (0.12)	38 (0.46)	35 (0.42)		58 (0.35)	108 (0.65)	
HDS	65	9 (0.14)	26 (0.40)	30 (0.46)	0.78	44 (0.34)	86 (0.66)	0.84
<i>ALDH2</i>								
NHDS	83	45 (0.54)	31 (0.37)	7 (0.08)		121 (0.73)	45 (0.27)	
HDS	65	61 (0.94)	4 (0.06)	0 (0.00)	< 0.001	126 (0.97)	4 (0.03)	< 0.001

**Table 4.** Risk of functional polymorphisms of *ADH1B* and *ALDH2* for HDS. HDS ( $n = 65$ ); NHDS ( $n = 83$ ). Statistical comparison was evaluated by multiple logistic regression after adjustment for hypertension, DM, smoking and liver dysfunction and the rest of the genotypes of *ADH1B* and *ALDH2*. The *ALDH2*\*2/\*2 genotype was not included for comparison, as no such genotype was found in the HDS group. Reference groups for *ADH1B* and *ALDH2* were *ADH1B*\*1/\*1 and *ALDH2*\*1/\*1, respectively

Variable	Regression coefficient	Standard error	p value	Odds ratio	95% confidence interval
<i>ADH1B</i> *1/*2	-0.4196	0.69	0.5428	0.66	0.170–2.539
<i>ADH1B</i> *2/*2	-0.2972	0.70	0.6725	0.74	0.187–2.947
<i>ALDH2</i> *1/*2	-3.5167	1.32	0.0078	0.030	0.002–0.396
<i>ADH1B</i> × <i>ALDH2</i>	0.7031	0.8658	0.4167		
Constant	1.2854	0.7012	0.0668		

frequency in the NHDS group was also similar ( $p = 0.421$ ) to that in their healthy control group (24 per cent for *ALDH2\*2*).<sup>28</sup> Unexpectedly, the allelic variations of *ADH1B* showed similar frequencies in the two study groups. The allele frequencies of *ADH1B\*2* in the HDS (66 per cent) and NHDS (65 per cent) groups appeared lower ( $p = 0.027$ ) than that in the non-alcoholic group of Han Chinese (73 per cent)<sup>28</sup> but significantly higher ( $p < 0.001$ ) than that in the alcoholic group (46 per cent).<sup>28</sup> This might be due, in part, to the HDS group in the present study being subject to alcohol abuse or alcohol dependence rather than to alcohol dependence alone, and in part due to the involvement of stroke with alcoholism. The results suggest that the additional disease factors associated with stroke may influence the association between *ADH1B* polymorphism and high alcohol consumption. Recently, it was reported that *ADH1B\*2* was not related to drinking behaviour in East Asians<sup>10–12</sup> and that the variant allele showed no protective effects against alcoholism in antisocial alcoholics among Han Chinese in Taiwan.<sup>34</sup> It is worth noting that, unlike the *ALDH2\*2* variant allele,<sup>9</sup> the physiological basis of protection by the *ADH1B\*2* variant allele against developing alcohol dependence has not been resolved.<sup>8,25</sup>

The identification of risk factors for stroke, awareness of the relative contribution of these factors and knowledge of the interactions between them are essential for stroke prevention. The present study revealed that, without adjustment for age, the frequencies of hypertension and DM were significantly lower in the HDS than the NHDS group, and those of current cigarette smoking and liver dysfunction were significantly higher in the HDS than in the NHDS group. After controlling for age, only smoking status and liver dysfunction remained significantly different between the two groups (Table 2). Heavy alcohol consumption has been reported to be associated with cigarette smoking and to be a positive risk factor for liver dysfunction and stroke.<sup>23–25,35</sup>

Alcoholism is a pharmacogenetic behavioural disorder involving complex gene–gene and gene–environment interactions.<sup>36</sup> Current evidence

indicates that metabolic gene alleles *ALDH2\*2* and *ADH1B\*2* may independently influence the risk of alcoholism in Han Chinese and Koreans.<sup>28,37</sup> To date, the *ALDH2\*2* variant allele has been shown to be the strongest genetic modifier of drinking behaviour and risk of alcoholism.<sup>28,37,38</sup> Previous genotype–phenotype correlation studies have demonstrated that non-alcoholic Asian individuals carrying the *ALDH2\*2* variant allele, regardless of their *ADH1B* genotype, responded to low-to-moderate doses of alcohol with markedly increased acetaldehyde levels, pronounced cardiovascular haemodynamic effects and unpleasant subjective feelings.<sup>25,39–41</sup> These adverse reactions to acetaldehyde may considerably reduce the frequency and quantity of alcohol consumption,<sup>41,42</sup> thereby providing protection against excessive drinking and the development of alcoholism.<sup>39,43</sup> More recent studies have indicated that physiological tolerance or an innate low response to the alcohol sensitivity reaction may contribute to the development of alcoholism in heterozygous *ALDH2\*1/\*2* alcohol-dependent patients.<sup>44</sup> Notably, homozygous *ADH1B\*2/\*2* individuals who carry the normal *ADLH2\*1/\*1* genotype did not exhibit blood acetaldehyde accumulation after ingestion of alcohol or show alcohol flush reactions or experience unpleasant subjective perceptions.<sup>40,43</sup> Logistic regression analyses of the combinatorial genotypes of *ADH1B* and *ALDH2* in Han Chinese<sup>8,28</sup> and Koreans<sup>37</sup> indicate that the allelic variations of these two genes may independently influence the risk of alcoholism. These observations imply that *ADH1B* and *ALDH2* might have different target substrates or distinct target organs in affecting drinking behaviour and alcoholism. Interestingly, the *ADH1B\*1* allele frequency in NHDS subjects in the present study was significantly higher ( $p < 0.05$ ) than that in non-alcoholic healthy controls in the previous study.<sup>28</sup> This is consistent with a prospective Japanese cohort study which found that the normal *ADH1B\*1* allele was associated with an increased risk of cerebral infarction and lacunae after adjustment for alcohol consumption.<sup>45</sup> Thus, it seems that the *ADH1B* genotype may be involved not only in ethanol

metabolism, but also in some unknown biological function which influences the occurrence of stroke. Further studies, with larger samples of both HDS and NHDS subjects, are required to confirm the observations of the current study.

## Conclusion

The heterozygous *ALDH2*\*1/\*2 genotype is a negative risk factor for high alcohol consumption with stroke, while smoking and liver dysfunction are positive risk factors. By contrast, *ADH1B* genotypes appear to have no influence on heavy drinking with stroke.

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