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Aldehyde Dehydrogenase 2 (*ALDH2*) Glu504Lys Polymorphism Affects Collateral Circulation and Short-Term Prognosis of Acute Cerebral Infarction Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E 1,2 Yun Qu
C 2 Huilong Zhang
A 2 Haiyong Li
C 2 Limei Yu
G 2 Ying Sun
F 1 Yuguo Chen

1 Department of Emergency, Qilu Hospital, Shandong University, Jinan, Shandong, P.R. China
2 Department of Emergency, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, Shandong, P.R. China

Corresponding Author: Yuguo Chen, e-mail: gfengxxss@163.com
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Background: Acute cerebral infarction is a major clinical subtype of ischemic stroke that has become a leading cause of death and disability worldwide. Aldehyde dehydrogenase 2 (*ALDH2*) is an important oxidative enzyme in alcohol metabolism. The polymorphism of *ALDH2* Glu504Lys polymorphism modifies the activity of this enzyme. However, the potential association between the allelic variation of *ALDH2* Glu504Lys with collateral circulation and short-term prognosis of acute cerebral infarction remains unclear.

Material/Methods: A total of 394 patients with acute cerebral infarction were recruited for *ALDH2* genotyping using direct sequencing. Cerebrovascular stenosis and collateral circulation were evaluated by digital subtraction angiography (DSA). Short-term prognosis was assessed in accordance with the modified Ranking Scale (mRS).

Results: We identified 297 as EAS and 394 as IAS. There were more patients with occluded blood vessel in the opened group and far fewer in the unopened group. *ALDH2* polymorphism was significantly different among the primary, secondary, and tertiary opened groups. ALDH2 gene Glu504Lys was significantly associated with short-term prognosis. The genotype GA+AA of ALDH2 gene Glu504Lys locus was an independent risk factor of poor 90-day prognosis.

Conclusions: *ALDH2* Glu504Lys could be a risk factor for collateral circulation and a negative predictor for short-term prognosis in acute cerebral infarction in Han Chinese. *ALDH2* Glu504Lys could be a new therapeutic target for patients with acute cerebral infarction.

MeSH Keywords: Atherosclerosis • Prognosis • Stroke

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Background

Stroke is the second most deadly disease worldwide, particularly in developing countries like China [1]. Each year, 75% of stroke survivors suffer from physical or mental disabilities in varying degrees, which reduce the quality of life and put great burden and stress on individuals, families, and society [2,3]. Ischemic stroke is the most common type of stroke worldwide [4], and acute cerebral infarction is the main clinical subtype [5–8]. Cerebral infarction can block the intracranial large artery and instantly cause necrocytosis, which manifests as central nervous system dysfunction. In our previous research, we found no significant correlation between the clinical National Institutes of Health Stroke Scale (NIHSS) score of acute cerebral infarction and intracranial arterial stenosis [9]. In addition to hemadostenosis concerns, the formation of arterial stenosis and the condition of collateral circulation also affect the severity of clinical symptoms and signs of stroke [10,11]. The collateral circulation of cerebral vessels to some extent determines the severity of stoke and the ultimate paralyzed areas [12,13]. Thus, further study of factors influencing formation of collateral vessels in acute cerebral infarction patients is meaningful.

In humans, ethyl alcohol is translated into acetaldehyde with the help of ethanol dehydrogenase, and acetaldehyde is catalyzed by acetaldehyde dehydrogenase (ALDH) to eventually generate acetic acid. In this process, ALDH is the key enzyme that possesses many isozymes. Among these isozymes, ALDH2, mainly distributed in mitochondria, plays a very important role in the oxidation of acetaldehyde to acetic acid. However, the mutation of *ALDH2* allele makes the amino acid at 504 site in its encoded enzyme change from glutamate (Glu) to lysine (Lys), expressed as Glu504Lys, which could have an impact on the activity of ALDH2. Initial studies on the Glu504Lys polymorphism of *ALDH2* gene found it is involved in hepatitis, liver cirrhosis, alcoholic myocardiopathy, and many other alcohol-related diseases, as well as malignant tumors [14]. Further research also focused on its complex influence on coronary atherosclerotic heart disease (CAD) [14–18] and some neurologic disorders, like Parkinson disease and Alzheimer disease [19–22].

Our preliminary studies found a complicated relation between *ALDH2* Glu504Lys and intracranial or extracranial artery stenosis [9,23]. Cranial arterial collateral circulation is closely related to arterial stenosis disease and prognosis, whose clinical significance should be evaluated. Nevertheless, the role of *ALDH2* Glu504Lys polymorphism in cranial arterial collateral circulation and short-term prognosis in patients with acute cerebral infarction has been unclear. The aim of the present study was to investigate the potential association of allelic variation of *ALDH2* Glu504Lys with collateral circulation and short-term prognosis patients with acute cerebral infarction, and to perform an in-depth exploration of the possible mechanism.

Material and Methods

Clinical Specimens

A total of 394 acute cerebral infarction patients were selected from Qilu Hospital of Shandong University and the Affiliated Yantai Yuhuangding Hospital of Qingdao University between January 2014 and September 2015. All of them were diagnosed based on clinical data and cranial MRI examination. The protocol of this trial was in accordance with the relevant stipulations established by the Ethics Committee of Qilu Hospital of Shandong University and the Affiliated Yantai Yuhuangding Hospital of Qingdao University. Informed consent was obtained from patients and control subjects, signed by themselves or their relatives. The inclusion criteria were: 1) all the cases in the patient group satisfied the World Health Organization (WHO) diagnostic standard of acute stroke; 2) the formation of new thrombus was confirmed by magnetic resonance diffusion weighted imaging (DWI) technique; 3) participants must be over age 18 years; 4) the participants must be first-onset acute ischemic stroke patients; 5) participants are willing to provide medical record data and consent to participate in this clinical research; 6) acute cerebral infarction subtype was confirmed according to the cerebral infarction classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [24]. Exclusion criteria were: 1) patients were non-Han Chinese in Shandong Province; 2) patients had possibility of cardiogenic brain embolism; 3) patients suffered from intracranial hemorrhage, transient cerebral ischemia, or other nervous system lesions not caused by acute cerebral infarction; 4) patients once showed a hemorrhage tendency after taking an anticoagulant drug, or had a history of drug abuse, or were diagnosed with other serious diseases such as malignant tumor, abnormal liver function, severe infection, or autoimmune disorder; 5) heavy drinkers consuming more than 210 g alcohol per week [25]; 6) patients who rejected intracranial vascular DSA examination.

Clinical data collection

The clinical data contained patients' basic information like age, sex, and their medical history, including hypertension history (records of high blood pressure in the past, regular antihypertensive therapy receiver, systolic pressure ≥140 mmHg or a diastolic pressure ≥90 mmHg measured at least 3 times during hospitalization), diabetes mellitus history (past record, regular hypoglycemic therapy, a random plasma glucose ≥11.1 mmol/l or a fasting plasma glucose ≥7.0 mmol/l detected twice in hospital), and family history of cerebrovascular disease.

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Detailed information on clinical data collection is presented in Supplementary Table 1.

Biochemical and regular examination

The blood sample was collected from fasting patients' peripheral cubital vein on the second morning after entering the hospital, and the clinical biochemical and regular examination were performed to obtain the value of total cholesterol, triglyceride, uric acid, and homocysteine.

Cerebral vascular DSA examination in patient group

Two weeks after onset, a digital subtraction angiography (DSA) for the whole brain vessel was performed by 2 experienced doctors, and the entire process was double-blinded. The result of imaging was judged by 2 doctors, and disagreements were resolved by a third doctor. According to the imaging characteristics, 3 groups were classified:

In determining the existence of angiostenosis, the degree of extracranial and intracranial arterial stenosis was estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) standard [26] and the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) standard [27], given as:

$$\text{Degree of extracranial arterial stenosis (\%)} = \frac{\text{artery diameter at stenotic terminal} - \text{artery diameter at most stenotic site}}{\text{artery diameter at stenotic terminal}} \times 100\%$$

$$\text{Degree of intracranial arterial stenosis (\%)} = \frac{1 - \text{artery diameter at most stenotic site}}{\text{artery diameter of identical artery}} \times 100\%$$

Referring to the NASCET standard, stenotic degree ≥50% indicated the existence of stenosis or occlusion.

In the stenotic site of the vessel, the concrete zones of extracranial vessels where a narrow might occur are the common carotid artery, the internal carotid artery (C1 segment), and the vertebral arteries (V1–V3 segments). The internal carotid artery (C2–C7 segments), vertebral artery (V4 segment), middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and basilar artery constitute the intracranial vessels. Based on the result of DSA examination, all the patients with symptomatic intracranial or extracranial acute cerebral infarction stenosis were split into 3 groups: 1) simple intracranial atherosclerotic stenosis (IAS), with only IAS but no extracranial stenosis; 2) simple extracranial atherosclerotic stenosis (EAS), just EAS and no sign of intracranial stenosis; and 3) intracranial and extracranial joint atherosclerotic stenosis (IC-EC), with both intracranial and extracranial arteries with atherosclerotic stenosis.

In the collateral circulation, in general, the compensatory collateral circulation of the cerebral vessel consists of 3 levels of pathways. The primary collateral circulation is the circle of Willis, which is the most crucial pathway through which the blood in the front and back of the brain rapidly communicates. The secondary compensatory circulation is achieved via the combination of ophthalmic artery, leptomeningeal anastomosis, and other small collateral vessels with their anastomoses. The tertiary circulation involves neovascularization, and it usually takes some time to form after ischemic attack [28]. Based on the DSA evaluation method, the ASITN/SIR grade of blood flow was applied in this trial. Patients with grades 0–2 were assigned to the incomplete collateral circulation establishment group, the unopened group, and subjects with grades 3–4 were assigned to the good establishment group [28].

ALDH2 genotype detection

The peripheral venous blood was collected to detect patient genotype. The method of gene polymorphism detection had been stated in detail in previous studies [9,23]. In brief, the target DNA fragment extracted from venous blood was identified by specific primer and amplified through PCR technique. Electrophoresis was conducted to confirm PCR products. The purification and sequencing were completed by a biotechnology company.

Short-term prognosis

In this clinical trial, patients' short-term prognosis was assessed in accordance with the modified Ranking Scale (mRS) [29], after excluding the acute cerebral infarction stroke cases found by DSA examination, thrombolytic therapy receivers, and systematic rehabilitation trainees. According to the prognosis at 90-day follow-up, a score of 2 was set as the boundary. Patients with scores <2 were included in the good group, which suggested that there was no or slight disability, without influence on daily life. Scores ≥2 indicated a poor prognosis, with obvious disability.

Statistical analysis

All statistical analyses were performed using SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA). Numerical variables are expressed as mean ± standard deviation (SD). After testing for Gaussian distribution, Student's *t*-test or Mann-Whitney test was applied for two-group comparisons. Enumeration data are presented as frequency or percentage, using the chi-square test. To avoid the influence of confounding factors, multiple logistic regression analysis was used to analyze the connection between *ALDH2* Glu504Lys and clinical index. *P* value <0.05 suggested that the result had statistical significance.

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Table 1. The distribution of vascular stenosis type in acute cerebral infarction patient group.

	Group	Stenosis (cases, %)	
EAS		297	(42.98%)
	CCA	5	(0.72%)
	EC-ICA	124	(17.95%)
	EC-VA	168	(24.31%)
IAS		394	(57.02%)
	IC-ICA	79	(11.43%)
	MCA	136	(19.68%)
	ACA	56	(8.11%)
	IC-VA	80	(11.58%)
	BA	22	(3.18%)
	PCA	21	(3.04%)

CCA – common carotid artery; EC-ICA – extracranial internal carotid artery; EC-VA – extracranial vertebral artery; IC-ICA – intracranial internal carotid artery; MCA – middle cerebral artery; ACA – anterior cerebral artery; IC-VA – intracranial vertebral artery; BA – basilar artery; PCA – posterior cerebral artery.

Results

The distribution of intracranial and extracranial vascular stenosis

EAS and IAS were detected by DSA, 297 (42.73%) were identified as EAS and 394 (57.27%) were identified as IAS. As shown in Table 1, among the EAS patients, the most frequent type of EAS was extracranial vertebral artery (EC-VA, 24.31%), and the least frequent type of EAS was common carotid artery (CCA, 0.72%).

Among the IAS patients, the middle cerebral artery (MCA, 19.68%) was the most frequent type of IAS, whereas intracranial vertebral artery (IC-VA) and intracranial internal carotid artery (IC-ICA) were over 11% of the IAS patients. Besides, BA and PCA occupied over 3% of the IAS patients.

The establishment of intracranial and extracranial collateral circulation

According to the result of DSA examination, the 394 subjects were divided into the opened group (178, 45.18%) and the unopened group (216, 54.82%). There were more patients with occluded blood vessel in the opened group (136 cases, 77.27%), and far fewer in the unopened group (40 cases, 22.73%, Table 2). However, the number of patients with stenosis less than 100% was far less in the opened group (42, 10.66%) than in the unopened group. In addition, among the opened group, 117 cases (65.73%) were primary opening, 33 (18.54%) were secondary opening, and 28 (15.73%) were tertiary opening.

The correlation between the *ALDH2* polymorphism and the opened class of collateral circulation

According to the genotype detection results, patients were separated into the wild-type group (GG) and the mutation group (GA+AA). As shown in Table 3, *ALDH2* polymorphism was significantly different among the primary, secondary, and tertiary opened groups (χ^2=16.97, *P*=0.0002).

The correlation between the 90-day prognosis and the genotype of patients

The 394 patients were grouped into a good (217 cases) and a poor (177 cases) prognosis group based on their mRS scores. The statistical analysis showed that *ALDH2* gene Glu504Lys was significantly associated with 90-day mRS scores (OR=1.672, 95%CI=0.501–0.600, *P*=0.013, Table 4).

Logistics regression analysis between multiple 90-day prognostic factors and the genotype of patient group

In Table 5, through the logistic regression analysis, in addition to the history of diabetes (*P*=0.031), NIHSS (*P*=0.000), and poor collateral circulation opening (*P*=0.001), the genotype GA+AA of

Table 2. The relationship between the opened and unopened condition of collateral circulation and the intracranial or extracranial arterial stenosis degree.

Stenosis degree	Opened group (cases, %)			Unopened group (cases, %)
	Primary	Secondary	Tertiary	
Stenosis <50%	2	0	0	37
50≤ Stenosis <100%	38	0	2	139
Occlusion	77	33	26	40
Total	**117**	**33**	**28**	**216**

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Table 3. The relationship between the opened class of collateral circulation and the *ALDH2* gene polymorphism.

	Primary opened, n (%)	Secondary opened, n (%)	Tertiary opened, n (%)	Total, n
GG	104 (26.40%)	39 (9.90%)	93 (23.60%)	236
GA+AA	42 (10.66%)	21 (5.33%)	95 (24.11%)	158
Total, n	146	60	188	394
Chi-square	16.97			
P	0.0002*			

Chi-square test was applied for statistical analysis, * with statistical significance.

Table 4. The correlation between the 90-day prognosis and the genotype of patient group.

		mRS		OR (95% CI)	*P*
		Good (mRS ≤1)	Poor (mRS >1)		
GG	Count	142	94	1.672 (0.501-0.600)	0.013*
	%	62.24	37.76		
GA+AA	Count	75	83		
	%	46.61	53.39		

* With significant difference; mRS – modified Ranking Scale.

Table 5. Logistics regression analysis between multiple 90-day prognostic factors and the genotype of patient group.

	OR (95% CI)	*P*
Age	0.996 (0.970–1.023)	0.769
Gender	0.819 (0.458–1.464)	0.5
Diabetes history	1.835 (1.057–3.186)	0.031*
Hypertension history	0.934 (0.525–1.662)	0.817
Cerebrovascular disease family history	0.849 (0.475–1.517)	0.58
Uric acid level	0.999 (0.996–1.002)	0.674
Cholesterol level	0.914 (0.697–1.198)	0.515
Triglyceride level	1.198 (0.858–1.672)	0.289
HCY value	1.031 (0.959–1.108)	0.407
NIHSS	4.354 (2.601–7.286)	0.000*
Collateral vessels condition	2.540 (1.486–4.341)	0.001*
ALDH2 genotype	0.570 (0.326–0.998)	0.049*

* With significant difference. HCY value – Homocysteine value; NIHSS – National Institutes of Health Stroke Scale.

ALDH2 gene Glu504Lys locus was also an independent risk factor of poor 90-day prognosis (adjusted OR=0.570, 95%CI=0.326-0.998, *P*=0.049), with a reduced relevance.

Discussion

Stroke is widely recognized as a major health problem which endangers life worldwide. The extensive research on stroke has used many different methods. The association of genetic polymorphisms with prognosis of patients with acute cerebral infarction remains controversial. Our findings suggest that *ALDH2* Glu504Lys is a risk factor for collateral circulation and a negative predictor for short-term prognosis in acute cerebral infarction in Han Chinese. The rate of good collateral vessels was significantly lower in the mutation group (GA+AA) than in the GG group. In addition, *ALDH2* GA and AA genotypes were negatively correlated with 90-day good prognosis of patients.

The inseparable connection of cerebral collateral vessel establishment with the acute stage of cerebral infarction, the ultimate infarct area, and the disease progression have already been illustrated in previous studies [12,13]. The brain collateral circulation can make a perfusion compensation via collateral vessels when a serious stenosis or occlusion occurs in the primary cerebral artery [28]. In the past, thrombolysis with rtPA was the only accepted drug therapy for acute ischemic stroke, which also has defects. Yao et al. found that high serum homocysteine level is reversed in acute ischemic stroke patients after tPA treatment [30]. Fu et al. found that solitaire stent embolectomy is a safe and effective alternative to simple venous thrombolytic therapy, and it can significantly improve short-term neurological function and long-term prognosis in acute cardiogenic cerebral embolism [31]. The collateral

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circulation is a vital indicator in assessing the prognosis of acute ischemic stroke [11], and in patients with cerebral stenosis or occlusion, the infarction area depends to some extent on whether fast and effective collateral circulation exists [32], and multiple studies had proved that brain tissue is protected by abundant collateral vessels [33]. We statistically analyzed the opening status of collateral circulation in acute stroke patients, showing the severe stenosis is usually accompanied with a higher proportion compensation opening. Kang reported that for acute ischemic stroke, the mechanism of cerebral collateral circulation establishment might be the pressure difference between the 2 sides of adjacent ramus communicans; this is caused by the acute stenosis and occlusion of the intracranial artery, which redistributes blood flow [34]. This is why high opening rate is always observed in severe cases. In general, the grade of collateral circulation was 3, and among them, the primary compensation, also known as the circle of Willis [35,36], was the main force, regardless of whether stenosis occurred in the anterior or posterior circulation. The compensatory potential of the circle of Willis is associated with its variation and the caliber of the communicating artery, which was also found in the present study. Regardless of stenotic degree, the primary compensation was always the dominate pathway. When local blood pressure was relatively low, as in remote vessels, the secondary collateral circulation, consisting of ophthalmic arterial countercurrent and leptomeningeal collateral channels, opened [37,38]. If secondary circulation is still insufficient to supply blood to distal sections of the artery, third-class compensation increases, which involves angiogenesis [38]. We also investigated aggravation of arterial narrowing, in which the secondary and tertiary collateral circulation plays a larger role, in accordance previous reports. The establishment of collateral circulation and the degree of vessel stenosis were positively correlated, and the degree increased with concomitant enhancement of the opening scale [37,39].

Studies have assessed effect of the cranial collateral circulation opening situation on the prognosis of acute ischemic stroke [11], showing the association between the recurrence rate of ischemic cerebrovascular disease and the establishment of collateral vessel. Wei et al., [40] reported that the development of arterial collateral vessel and angiogenesis after ischemia contributed to recover of blood-supply of ischemic tissues and accelerated their functional rehabilitation. The aim of the present study was to determine if, in patients with acute cerebral infarction, the mutation of Glu504Lys in ALDH2 gene is an independent risk factor for the establishment of collateral circulation, as well as opening of the tertiary collateral vessel. As demonstrated by Reinhard et al., the formation of tertiary compensatory circulation mainly relies on the generation of new vessels [38]. In the ischemic and hypoxic microenvironment, the expression level of angiogenesis-related incentives such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), angiogenin (ANG) [41], and many other growth factors, induced new vascular generation and collateral circulation. Therefore, it was speculated that ALDH2 might impact the process of angiogenesis through regulating the expression of relevant growth factors. However, due to dramatic variance in the level of these growth factors before and after a stroke, correlational studies are still at the stage of animal testing [42]. In research on collateral circulation, especially in terms of angiogenesis [43], gene therapy [44,45] still is important. Therefore, in future studies, we plan to explore the mechanism by which the ALDH2 gene acts in the establishment of cerebrovascular collateral circulation. Polymorphism is also an important research field; polymorphism (rs12976445) interferes with the expression of miR-125a, which in turn increases expression of ET-1 in human endothelial cells [46].

Regarding the peak plerosis of neurons injured by stroke, which lasts for 3 months, the mRS score given in the 90-day follow-up after onset served as the index to appraise the short-term prognosis of cerebral infarction in this trial. Based on the analysis of experimental data, such as diabetes history, poor compensation opening, and high NIHSS score at admission, ALDH2 genotype was also an independent risk and the mutation type could increase the risk. However, when confounding factors like diabetes were excluded, the correlation remained with an apparent reduction, which also indicated that cerebral stroke has multiple causes. Numerous complicated causes accumulated and overlapped, or both counteracted and waned, and all these possibilities could exert different degrees of influence on the incidence of stroke and its prognosis.

This study has some limitations. Firstly, to explain this clinical phenomenon, the sample size should be expanded further. The main contribution of this study was establishing the relevance of the ALDH2 gene polymorphism to the cerebral acute cerebral infarction-induced stenosis and the collateral circulation opening clinically. Further research is needed to elucidate the underlying mechanism. Moreover, we did not perform long-term patient follow-up, so no conclusion about the long-term prognosis could be reached.

Conclusions

In the opened collateral circulation group, the primary circulation was most frequent, and with the increase of stenosis degree, the class of collateral vessel gradually increased. In the mutation group, a higher ratio of patients with incomplete intracranial vascular collateral circulation was observed, and the activity of ALDH2 had a major impact on opening of tertiary vessels. Furthermore, patients in the ALDH2 gene mutation

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group had a relatively higher risk of poor prognosis than those in the wild-type gene group.

Conflicts of interest

None.

Supplementary Table 1. The clinical data of abuse acute cerebral infarction patients.

Clinical characteristics	Acute cerebral infarction patients
Male/female	233/161
Mean age (years)	61.8±7.9
History of hypertension	308/76
History of T2DM	96/298
History of CAD	99/297

T2DM – type 2 diabetes mellitus; CAD – coronary artery disease.

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