Association between aldehyde dehydrogenase 2 gene rs671 G>A polymorphism and alcoholic liver cirrhosis in southern Chinese Hakka population

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Abstract

Background: Alcoholic liver cirrhosis (ALC) endangering people's health. The association between aldehyde dehydrogenase 2 (ALDH2) gene polymorphisms and ALC is not clear. To analyze the relationship between ALDH2 and ALC among Hakka population in southern China.

Methods: A total of 292 ALC patients and 278 controls were included in the study. The ALDH2 gene rs671 polymorphism was analyzed by polymerase chain reaction (PCR)-gene chip. Relevant information and medical records of these participants were collected.

Results: The ALC patients had higher percentage of smoking, lower prevalence of hypertension, higher level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bile acid (TBA), total bilirubin (Tbil), and direct bilirubin (Dbil), lower level of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) than controls. The proportions of the G/A genotype (p = 0.017), G/A plus A/A genotype (p = 0.023) and A allele (p = 0.031) were significantly higher in ALC patients than that of controls. ALC patients with G/A genotype had higher TC, HDL-C, and Apo-A1 than those with G/G genotype, while with A allele had higher HDL-C, and Apo-A1 than those with G allele. Logistic regression analysis indicated that ALDH2 SNP rs671 G/A plus A/A genotypes (A allele carriers) (OR 2.030, 95% CI 1.109–3.715, p = 0.022) in the dominant model was the risk factor for ALC.

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1 INTRODUCTION

Alcoholic liver disease (ALD) is one of the most common liver diseases. It is a liver disease caused by extensive liver cell necrosis induced by long-term heavy drinking. It usually presents as fatty liver in the initial stage and can progress to alcoholic hepatitis, liver fibrosis, and cirrhosis, seriously endangering people’s health and life safety. In 2017, about more than 129,000 people died of alcoholic liver cancer worldwide. There was an unflattering prevalence of ALD (4.5%) in China, estimated to affect at least 62 million people. The mild liver injury caused by alcohol can be reversed by long-term withdrawal from alcohol, but when the disease progresses to the terminal stage of ALD, the only effective treatment is liver transplantation. But liver transplantation has some disadvantages such as the probability of immune rejection of the donor and the high cost of the operation, so ALD has become one of the major health problems.

Alcoholic liver cirrhosis (ALC) is one of ALD without timely controlled and effective treatment, and then progress to the stage of liver cirrhosis. With the development of molecular biology and genetics, it is generally believed that liver cirrhosis and liver cancer are the result of multiple factors. They are closely related to environmental factors, genetic factors, and living habits. Alcohol consumption is a significant risk factor for ALC.

Acetaldehyde dehydrogenase 2 (ALDH2), as one of the important rate-limiting enzymes involved in alcohol metabolism, determines the accumulation of ethanol and acetaldehyde in the body, and its activity level is closely related to the occurrence of alcoholic liver disease. The level of ALDH2 activity in vivo is closely related to the ALDH2 gene polymorphisms. The human ALDH2 gene is located on chromosome 12q24.2 and composed of 13 exons. At present, some single nucleotide polymorphisms (SNPs) have been found in ALDH2 gene, and the most important is Glu504Lys polymorphism (SNP rs671, G>A, GAA>AAA, with the G corresponding to 1 allele, and A corresponding to 2 allele). Glu504Lys polymorphism can lead to the decreased activity of ALDH2.

Some studies reported that the ALDH2 polymorphism might association with susceptibility of ALC. Whereas, some studies have showed that there was no relationship between the ALDH2 polymorphism and ALC risk. As for the studies on the relationship between ALDH2 gene polymorphisms and ALC, different sample sizes, inclusion criteria, regions, and ethnicities, as well as different standards of alcohol consumption, lead to different or even opposite results in such studies.

Meizhou is a city located in the northeast of Guangdong Province, where the majority of residents are Hakka people. Up to now, there has been no report on the relationship between ALDH2 gene polymorphisms and ALC in this population. In the present study, ALDH2 rs671 G>A allele/genotype frequencies and the association between SNP rs671 of ALDH2 and ALC were analyzed among Hakka people in southern China.

2 MATERIALS AND METHODS

2.1 Population samples

A total of 570 individuals were recruited from the inpatients of Meizhou People’s Hospital (Huangtang Hospital), Guangdong province, China, from January 2016 to August 2020; the subjects consisted of 292 ALC patients and 278 individuals with non-ALC as controls. ALC was diagnosed by the clinician considering the etiology, history, clinical manifestations, complications, examinations, imaging, and histology. Patients with severe liver and kidney insufficiency, cardiovascular and cerebrovascular diseases, and malignant tumors were excluded. Information was recorded including age, sex, smoking history, alcohol abuse history, and risk factors for ALC. All control subjects were randomly selected from the Physical Examination Center of the Meizhou People’s Hospital during the same period. This case control study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and approved by the Human Ethics Committees of Meizhou People’s Hospital (Clearance No.: 2015-A-17).

2.2 Serum lipid measurements

Approximately 3 ml of venous blood from each subject was taken into tube containing no anticoagulant, and serum was isolated and tested promptly. Serum samples were evaluated using the Olympus AU5400 system (Olympus Corporation, Tokyo, Japan) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bile acid (TBA), total bilirubin (Tbil), direct bilirubin (Dbil), total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apolipoprotein B (Apo-B), and apolipoprotein A1 (Apo-A1). ALT, AST, ALP, and GGT analyses were carried out with the kinetic method. TBA with circulating enzymatic method, Tbil and Dbil with chemical oxidation method, respectively. TC, TG, LDL-C, HDL-C, and Apo-A1/
Apo-B analyses were carried out using cholesterol esterase/peroxidase (CHOD/PAP) enzymatic method, 25 Glycerophosphate oxidase/peroxidase (GPO-PAP) enzymatic method, 26 direct surfactant removal method, 27 direct immunoinhibition method, 28 and immunoturbidimetry method, 29 respectively.

2.3 | DNA extraction and genotyping assay

About 2 ml of venous blood from each subject was stored into tube containing ethylenediaminetetraacetic acid (EDTA), genomic DNA was extracted from whole blood using a QIAamp DNA Blood Mini Kit (Qiagen GmbH). The DNA concentration was measured using a Nanodrop 2000™ Spectrophotometer (ThermoFisher Scientific). The DNA was extracted from whole blood using a QIAamp DNA Blood Mini Kit (Qiagen GmbH). The DNA concentration was measured using a Nanodrop 2000™ Spectrophotometer (ThermoFisher Scientific). Polymerase chain reaction (PCR)-gene chip method was used for ALDH2 genotyping. PCR was performed with 25 μl reaction containing 50 ng of genomic DNA, 0.5 mM of each primer, 0.25 mM dNTPs, and 2 U Taq polymerase with denaturation step: 94°C for 5 min; amplification of 35 cycles: 94°C for 25 sec, 56°C for 25 sec, and 72°C for 25 sec; final elongation: 72°C for 5 min. The specific hybridization reaction was carried out between the amplification product and the detection probe fixed on the chip, and the color of the specific hybridization signal was made by enzymatic chromogenic reaction. The ALDH2 genotypes were analyzed using the BaiO Array Doctor Version 2.0 genotype analysis software (BaiO Technology Co., Ltd), according to the manufacturer’s instructions. Positive control, negative control, and blank control were used for quality control. When the positive control, negative control, and blank control were controlled, the test results of this batch of samples are reliable.

2.4 | Statistical analysis

Data analysis was performed using SPSS statistical software version 21.0 (IBM Inc). Student’s t test or the Mann-Whitney U test was used for continuous data analysis. The Hardy-Weinberg equilibrium (HWE) of ALDH2 genotypes in both ALC patients and controls were assessed using the chi-square test. Genotype composition ratios and allele frequencies between groups were analyzed by the chi-square test. Logistic regression analysis was applied to assess the interactions between ALDH2 polymorphisms and various factors in ALC, p < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Population characteristics

The study included 570 participants, including 292 patients with ALC (283 males and 9 females) and 278 individuals with non-ALC (207 males and 71 females) as controls. The ALC patients’ average age was 54.57 ± 10.14 years, with 53.44 ± 18.45 years for controls. The ALC patients had higher percentage of smoking (43.2% vs. 14.0%, p < 0.001), and lower proportion of hypertension (4.8% vs. 20.5%, p < 0.001), higher level of ALT (62.03 ± 78.16 vs. 33.82 ± 26.26 U/L, p < 0.001), AST (131.74 ± 157.63 vs. 39.18 ± 28.37 U/L, p < 0.001), ALP (167.50 ± 115.88 vs. 78.87 ± 28.11 U/L, p < 0.001), GGT (359.44 ± 419.52 vs. 40.70 ± 71.16 U/L, p < 0.001), TBA (62.09 ± 63.78 vs. 4.31 ± 7.80 μmol/L, p < 0.001), Tbil (79.16 ± 90.17 vs. 16.00 ± 10.80 μmol/L, p < 0.001), and Apo-B (44.83 ± 59.42 vs. 5.26 ± 4.94 μmol/L, p < 0.001). The ALC patients had lower level of TC (3.93 ± 1.95 vs. 4.40 ± 1.43 mmol/L, p = 0.001), HDL-C (0.95 ± 0.55 vs. 1.22 ± 0.38 mmol/L, p < 0.001), LDL-C (2.20 ± 1.19 vs. 2.44 ± 0.97 mmol/L, p = 0.008), and Apo-A1 (0.73 ± 0.40 vs. 1.04 ± 0.30 g/L, p < 0.001). There were no statistically significant differences in the percentage of diabetes (p = 0.529), the level of TG (p = 0.455), and the level of Apo-B (p = 0.061) (Table 1).

3.2 | Genotype and allele frequencies of ALDH2 gene

The genotype distributions in both the ALC patients and controls were consistent with Hardy-Weinberg equilibrium ($\chi^2 = 0.347$, p = 0.841 and $\chi^2 = 0.657$, p = 0.805, respectively). The proportion of the G/G homozygous of the SNP rs671 was significantly lower in patients with ALC (87.0%) than that of controls (92.8%) (p = 0.023, OR 0.518, 95% CI 0.293–0.915), while the proportion of the G/A heterozygous was significantly higher in patients with ALC (12.3%) than that of controls (6.5%) (p = 0.017, OR 2.031, 95% CI 1.124–3.670). The proportion of the G/A plus A/A genotypes was significantly higher in patients with ALC (13.0%) than that of controls (7.2%) (p = 0.023, OR 1.930, 95% CI 1.093–3.407). There were no statistically significant differences when compared the proportion of A/A homozygous genotype between ALC patients and control participants (0.7% vs. 0.7%, p = 0.961). The allele frequencies of G and A allele in patients with ALC were 93.2% and 6.8%; compared to 96.0% and 4.0% in controls, respectively, there was statistically significant differences (p = 0.031) (Table 2).

3.3 | Clinical characteristics of ALC patients stratified by ALDH2 variants

The laboratory test results of ALC patients stratified by ALDH2 variants were compared (A/A genotype was not included in this analysis because there were only two patients with A/A genotype). ALC patients with G/A heterozygous genotype had higher TC (4.54 ± 2.72 vs. 3.83 ± 1.89 mmol/L, p = 0.043), higher HDL-C (1.13 ± 0.57 vs. 0.92 ± 0.54 mmol/L, p = 0.026), and higher Apo-A1 (0.90 ± 0.48 vs. 0.70 ± 0.37 g/L, p = 0.004) than those with G/G genotype. The clinical characteristics between ALC patients with G and A allele were compared, ALC patients with A allele had lower percentage of alcoholism (86.8% vs. 96.9%, p = 0.015).
higher HDL-C (1.14 ± 0.56 vs. 0.95 ± 0.55 mmol/L, p = 0.045), and higher Apo-A1 (0.92 ± 0.49 vs. 0.73 ± 0.39 g/L, p = 0.007) than those with G allele. There were no statistically significant differences in the percentage of smokers, hypertension, and diabetes, the level of ALT, AST, ALP, GGT, TBA, Tbil, Dbil, TG, LDL-C, and Apo-B between ALC patients with G/G genotype and G/A genotype, between ALC patients with G and A allele, respectively (Table 3).
3.4 Logistic regression analysis of risk factors associated with ALC

Logistic regression analysis was performed to determine independent predictors for ALC. Univariate regression analysis and multiple logistic regression analysis indicated that there was significantly high risk of ALC in the presence of smoker (p < 0.001), and low risk of ALC in the presence of hypertension (p < 0.001).

The possible association of the ALDH2 genotypes with potential risk factors for ALC was based on three genetic modes of inheritance, such as the co-dominant mode (ALDH2 G/A vs. ALDH2 G/G, ALDH2 A/A vs. ALDH2 G/G), dominant mode (ALDH2 G/A plus ALDH2 A/A vs. ALDH2 G/G), and recessive mode (ALDH2 A/A vs. ALDH2 G/G plus ALDH2 G/A). The ALDH2 G/A plus A/A genotypes in the dominant model (ALDH2 G/A plus ALDH2 A/A vs. ALDH2 G/G) (smoking- and drinking-adjusted OR 2.030, 95% CI 1.109–3.715, p = 0.022) was significant risk factor for the presence of ALC (Table 4).

4 DISCUSSION

Liver cirrhosis is a pathological stage characterized by diffuse fibrous pseudolobules forming intrahepatic and extrahepatic vascular proliferation. In recent years, the proportion of ALC in the etiological composition of cirrhosis has shown a significant increase.30 ALC is the final stage of ALD caused by long-term heavy drinking.31,32

This study suggests that ALDH2 SNP rs671 G>A polymorphism is a susceptibility site for ALC in Hakka people in southern China. The proportions of the G/A, and G/A plus A/A genotypes and A allele were significantly higher in patients with ALC than that of controls. In patients with ALC, the allele of ALDH2 SNP rs671 A allele was not significantly associated with hematologic indicators of liver function impairment. Logistic regression analysis of risk factors for ALC was performed after adjusting for several potential confounding factors. Smoking, hypertension, and ALDH2 SNP rs671 G/A plus A/A genotypes (A allele carriers) in the dominant model were the risk factors for ALC.

Some studies reported that the ALDH2 polymorphism might association with susceptibility of ALC.9,13-15 Moreover, the study reported that ALDH2 SNP rs671 A allele was the risk factor for ALC.13 Our study is consistent with this study. Another study showed that the ALDH2 SNP rs671 A allele was significantly less frequent in the ALC group than in the control groups.14 The frequency of the ALDH2 G/G genotype was higher than the ALDH2 G/A genotype in ALC patients.15 Whereas, some studies have showed that there was no statistically significant relationship between the ALDH2 SNP rs671 polymorphism and ALC risk.16-19 According to the above studies, the results on the relationship between ALDH2 gene polymorphism and ALC are inconsistent. Different sample sizes, regions, and ethnicities,
as well as different alcohol consumption, may lead to different or even opposite conclusions in such studies.

There were researches showed that, the ALDH2 gene with SNP rs671 G allele encodes a protein with highly active in acetaldehyde conversion. Therefore, this population is more prone to consume more alcohol and progress to alcohol dependence, which leads to liver damage. Therefore, this allele is considered as a risk factor for ALC. However, the ALDH2 gene with SNP rs671 A allele encodes a low activity protein with weak ability to clear acetaldehyde. Therefore, people with A allele will actively reduce ethanol intake and have a lower incidence of alcohol dependence and are less likely to suffer from ALC. Therefore, A allele is considered to be a protective factor of ALC. Another view is that the individuals with G/G homozygous have higher ALDH2 activity and faster processing rate of ethanol and acetaldehyde, so the acetaldehyde level in vivo remains low even though they consume more alcohol. However, the ALDH2 enzyme activity in individuals with A/A homozygous is too low, and various adverse reactions may occur quickly after a small amount of drinking, so the alcohol intake is significantly reduced and low incidence of ALC. However, the alcohol intake and ALDH2 enzyme activity of individuals with G/A heterozygotes are in the middle level, which leads to the accumulation of acetaldehyde in the body and makes them more susceptible to alcoholic diseases.

In the present study, there were only 2 ALC patients with A/A homozygous, and they had no history of alcohol abuse, only occasionally drink in small amount. The ALDH2 enzyme activity is too low in vivo, after a small amount of alcohol can quickly appear a variety of adverse reactions. Simultaneously, such population has a weak ability to clear acetaldehyde, so the persons carry this allele will actively reduce ethanol intake, so the proportion of A/A homozygous in the ALC patients is may lower than that in the other people.

In addition, ALC patients with G/A genotype had higher TC, HDL-C, and Apo-A1 than those with G/G genotype, while with A allele had higher HDL-C, and Apo-A1 than those with G allele in this study. One study showed that drinkers with ALDH2 rs671 G/A genotype and A allele have lower TG level and higher HDL-C level. It is consistent with the results of this study. However, Wada et al studied the association between ALDH2 gene polymorphisms and HDL-C, and the results showed that only ALDH2 SNP rs671 (G/A) has relationship between HDL-C. It showed that the serum HDL-C level of individuals with A allele was significantly lower than that of wild-type homozygous individuals. Another study showed that the ALDH2 G/A group had lower average levels of TC and HDL-C. In general, ALDH2 may regulate serum lipid levels through the process of oxidative stress in vivo, and gene variation may lead to dyslipidemia.

There are some shortcomings in this study. First of all, this study is a retrospective study, there may be selection bias because patients were selected from one medical institution. Secondly, the patients’ drinking status was recorded according to the description of patients and their family members and medical documents. The patients’ drinking status may deviate from the real situation, and the real drinking status may be higher than the recorded situation. Thirdly, the relationship between clinical indicators, drinking status, and ALDH2 gene polymorphism in patients with ALC was analyzed in this study. For this special patient group, it is not clear whether there is a relationship between ALC and related complications. The last, the number of subjects in this research is relatively small, so there

| Variables | Genotypes | Unadjusted values | Adjusted values | | |
|---|---|---|---|---|---|
| | | OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
| Smoking | G/G | 1.000(reference) | | | |
| | G/A | 2.000(0.260–15.381) | .505 | 1.922(0.240–15.407) | .538 |
| | A/A | 0.984(0.138–7.043) | .988 | 0.942(0.109–8.143) | .957 |
| Hypertension | G/G | 1.000(reference) | | | |
| | G/A + A/A | 1.930(1.093–3.407) | .023 | 2.030(1.109–3.715) | .022 |
| Diabetes | G/G + G/A | 1.000(reference) | | | |
| | A/A | 0.952(0.133–6.803) | .961 | 1.795(0.223–14.459) | .583 |

Note: p < 0.05 was considered statistically significant.
Abbreviations: CI, confidence interval; OR, odds ratio.
may be some deviations in the results. It is necessary to increase the sample size for the research, which is the focus of our next work.

5 | CONCLUSION

In the present study, ALDH2 A allele (G/A + A/A genotypes) increased the risk of developing alcoholic liver cirrhosis among Hakka people in southern China. Our results need to be confirmed by further studies with large samples. The results should enrich the relevant data and provide valuable information for the future related research.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Dehui Zeng and Heming Wu designed the study. Heming Wu, Qingyan Huang and Zhikang Yu collected clinical data. Dehui Zeng and Qingyan Huang analyzed the data. Heming Wu prepared the manuscript. All authors were responsible for critical revisions, and all authors read and approved the final version of this work.

ETHICS APPROVAL

The study was approved by the Ethics Committee of Medicine, Meizhou People’s Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou Hospital Affiliated to Sun Yat-sen University.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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