Association Between ALDH2 Polymorphisms and the Risk of Diabetes Mellitus in Hypertensive Patients

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Background: Aldehyde dehydrogenase 2 (ALDH2) polymorphisms have been extensively studied in patients with hypertension (HTN) and diabetes mellitus (DM) in recent years. However, it is unclear whether ALDH2 polymorphisms are correlated with the risk of developing DM in patients with HTN. This study was designed to examine the association between ALDH2 single nucleotide polymorphism (SNP) rs671 and the risks of DM in patients with HTN.

Methods: This study retrospectively analyzed the patients with HTN who were treated in Meizhou People’s Hospital from August 2016 to December 2020, 788 HTN patients with DM as case patients, and 1632 HTN patients without DM history as controls. ALDH2 polymorphisms were analyzed using a polymerase chain reaction (PCR)-gene chip. Differences in ALDH2 genotypes between subjects and controls were compared. To analyze the relationship between ALDH2 genotype and DM risk, multiple logistic regression analysis was performed after adjusting for gender, age, smoking history, and drinking history.

Results: The proportion of the G/A plus A/A genotype was significantly higher in patients with DM than in controls (52.8% vs 48.2%, P=0.033). DM patients with G/A genotype had lower LDL-C (P=0.017) than those with G/G genotype. The results of logistic regression analysis indicated that the G/A genotype increased the risk of DM in HTN patients, with an adjusted odds ratio (OR) of 1.209 (95% confidence interval (CI) 1.010–1.446) (P=0.038), whereas the G/A plus A/A genotype in the dominant model increased the risk of DM significantly, with an adjusted OR of 1.203 (95% CI 1.013–1.428) (P=0.035).

Conclusion: ALDH2 A allele (G/A + A/A genotype) increased the risk of DM in patients with HTN.

Keywords: aldehyde dehydrogenase 2, gene polymorphism, hypertension, diabetes mellitus

Introduction

Hypertension (HTN) is a critical cardiovascular risk factor that may lead to stroke, coronary heart disease, and other diseases worldwide, and is the leading cause of death in China.1,2 A study has shown that approximately 23.2% of Chinese people aged 18 years or older had HTN, of which only 15.3% achieved blood pressure control.3 However, the annual incidence of HTN continues to increase, and it has become a significant global disease burden.4 Diabetes mellitus (DM) is a chronic medical condition that frequently co-exists with HTN.5 Tatsumi et al and Wei et al showed that DM is almost 1.5 to 2.5 times as likely to develop in patients with HTN than in normotensive patients.6,7 Meanwhile, a study in China indicated that the prevalence of DM was approximately 20% among HTN patients and suggested that HTN may be a provoking factor for the development of diabetes.8 When combined with DM, HTN has been shown to predict and promote an increased risk of cardiovascular disease events and all-cause mortality over and above each risk factor alone, thereby increasing morbidity and mortality.9 Therefore, predicting whether HTN patients would have a DM risk is very important for both prevention and treatment. With the development of molecular biology and genetics, there has been considerable overlap between DM and HTN in etiology and...
disease mechanisms, suggesting either shared genetic or environmental factors in the etiology.\textsuperscript{7,10} Thus, it is of great importance to investigate the risk factors of DM in patients with HTN.

Aldehyde dehydrogenase 2 (ALDH2) is a mitochondrial enzyme responsible for detoxification of alcohol-derived acetaldehyde and endogenous aldehydes.\textsuperscript{11} ALDH2 is widely distributed in human liver, kidney, heart, lung, brain, and other tissues.\textsuperscript{12,13} The ALDH2 gene is located on chromosome 12 (12q24) and contains 13 exons.\textsuperscript{14} ALDH2 activity in vivo is closely related to the ALDH2 gene polymorphisms.\textsuperscript{15} Currently, some single nucleotide polymorphisms (SNPs) have been identified in ALDH2 gene. Exon 12 of the human ALDH2 gene has a G to A mutation (SNP rs671), resulting in a mutation of the glutamate residue at position 504 to lysine, which reduces the activity or even complete loss of the ALDH2 enzyme. According to this genetic mutation, ALDH2 can be classified into 3 different genotypes: wild-type (Glu504Glu), mutant heterozygote (Glu504Lys), and mutant homozygote (Lys504Lys). The Glu504Lys polymorphism can lead to a 30–50% enzyme activity of ALDH2.\textsuperscript{16,17}

Studies have reported that the ALDH2 polymorphism may be associated with susceptibility to HTN and DM.\textsuperscript{12,18–20} However, in patients with HTN, the association between ALDH2 polymorphisms and DM risk remains unclear. Meizhou is a city located in the northeast of Guangdong Province, where the majority of residents are Hakka people.\textsuperscript{21} To date, there have been no reports on the relationship between ALDH2 polymorphisms and the risk of DM in HTN patients in this population. In the present study, ALDH2 rs671 G>A allele/genotype frequencies and the association between ALDH2 SNP rs671 and the risk of DM in HTN patients were analyzed among Hakka people in southern China.

Materials and Methods

Subjects

A total of 2420 individuals with HTN were recruited from the inpatients of Meizhou People’s Hospital, Guangdong, China, from August 2016 to December 2020, and consisted of 788 patients with DM and 1632 individuals without DM as controls. HTN and DM were diagnosed by a clinician based on the etiology, history, lifestyle characteristics, clinical manifestations, complications, and examinations.\textsuperscript{22–24} Individuals with pre-existing chronic illnesses such as cancer or diseases of the heart, liver, or kidney were excluded. Information about the factors that influence HTN was recorded, including age, sex, smoking history, and alcohol abuse history. All control subjects were randomly selected from the Meizhou People’s Hospital during the same period. Information on age, sex, history of smoking, and history of alcohol consumption was collected from the Hospital Information System (HIS) of Meizhou People’s Hospital. This case-control study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Human Ethics Committees of Meizhou People’s Hospital.

Biochemical Analysis

Approximately 3 mL of venous blood from each subject was placed in a tube without an anticoagulant, and the serum was isolated and tested promptly. Serum samples were evaluated using the Olympus AU5400 system (Olympus Corporation, Tokyo, Japan) for homocysteine (HCY), total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apolipoprotein B (Apo-B) and apolipoprotein A1 (Apo-A1). TC, TG, LDL-C, HDL-C, Apo-A1/Apo-B analyses were performed using the cholesterol esterase/peroxidase (CHOD/PAP) enzymatic method,\textsuperscript{25} glycerophosphate oxidase/peroxidase (GPO-PAP) enzymatic method, direct surfactant removal method,\textsuperscript{26} direct immunoinhibition method,\textsuperscript{27} and immunoturbidimetry method,\textsuperscript{28} respectively.

DNA Isolation and ALDH2 Genotyping

Approximately 2 mL of venous blood from each subject was stored in a tube containing ethylenediaminetetraacetic acid (EDTA), and genomic DNA was extracted from the whole blood using a QIAamp DNA Blood Mini Kit (Qiagen GmbH, North Rhine-Westphalia, Germany). DNA concentration was measured using a Nanodrop 2000\textsuperscript{TM} Spectrophotometer (ThermoFisher Scientific, Massachusetts, USA). Polymerase chain reaction (PCR)-gene chip method was used for ALDH2 genotyping. PCR was performed with 25 μL volume reaction containing 50 ng of genomic DNA, 0.5 pM 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 25s, 56°C for 25s, and 72°C for 25s; final elongation:72°C for 5 min. A specific hybridization reaction
was performed between the amplification product and the detection probe fixed on the chip, and the color of the specific hybridization signal was determined by an enzymatic chromogenic reaction. The ALDH2 genotypes were analyzed using the BaiO Array Doctor Version 2.0 gene chip image analysis software, and BaiO® BE-2.0 genotype analysis software (BaiO Technology Co, Ltd., Shanghai, China).

Statistical Analysis
Data analysis was performed using SPSS statistical software (version 21.0; IBM Inc., USA). Quantitative data are expressed as mean value ± standard deviation (SD). Normally distributed data were analyzed using the Student’s t-test. The significance of differences in the proportion of patients with a history of DM between the two groups was tested using the chi-square test ($\chi^2$). Differences in the distribution frequencies of genotypes and alleles between the two groups were analyzed using the $\chi^2$ test. Univariate logistic regression analysis was used to test the association between DM and ALDH2 polymorphisms, and the results are presented as unadjusted odds ratios (OR) with confidence intervals (95% CI). Multivariate logistic regression was used to determine the risk factors for developing DM in HTN patients with adjustment for potential covariates: age, sex, smoking, and alcoholism, and the results were presented as adjusted ORs. $P< 0.05$ was considered to be statistically significant.

Results
General Characteristics
This study included 2420 participants, including 788 patients with DM (522 males and 266 females) and 1632 individuals without DM (1088 males and 544 females) as controls. Table 1 presents the general characteristics and biochemical variables of the patients in the DM and control groups. No statistically significant differences were observed between the groups in age ($67.72\pm10.73$ vs $67.83\pm12.08$, $P=0.814$), different gender ($P=0.836$), smoking history ($8.5\%$ vs $18.0\%$, $P=0.789$), history of alcoholism ($1.6\%$ vs $3.5\%$, $P=0.836$), HCY ($17.26\pm8.14$ vs $17.24\pm8.39$, $P=0.852$), TC ($5.00\pm1.42$ vs $4.92\pm1.26$, $P=0.182$), and LDL-C level ($2.78\pm1.00$ vs $2.77\pm0.91$, $P=0.736$). However, the differences between the two groups of TG ($2.20\pm2.05$ vs $1.66\pm1.35$, $P<0.001$), HDL-C ($1.22\pm0.37$ vs $1.29\pm0.38$, $P=0.001$), Apo-A1 ($1.09\pm0.30$ vs $1.14\pm0.32$, $P=0.001$) and Apo-B ($0.89\pm0.30$ vs $0.85\pm0.26$, $P=0.010$) were statistically significant.

ALDH2 Genotype and Allele Distribution
The observed ALDH2 genotype distributions in both the DM patients and controls were in Hardy-Weinberg equilibrium ($\chi^2 = 1.992$, $P = 0.158$ and $\chi^2 = 0.030$, $P = 0.862$, respectively). The proportion of the G/A + A/A genotypes was

<table>
<thead>
<tr>
<th>Table 1 Clinical Characteristics of the DM and the Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (n=2420)</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male, n(%)</td>
</tr>
<tr>
<td>Female, n(%)</td>
</tr>
<tr>
<td>Smokers, n(%)</td>
</tr>
<tr>
<td>Alcoholism, n(%)</td>
</tr>
<tr>
<td>HCY, mmol/L</td>
</tr>
<tr>
<td>TG, mmol/L</td>
</tr>
<tr>
<td>TC, mmol/L</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
</tr>
<tr>
<td>Apo-A1, g/L</td>
</tr>
<tr>
<td>Apo-B, g/L</td>
</tr>
</tbody>
</table>

Notes: Values for age expressed as mean±SD.
Abbreviations: HCY, homocysteine; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.
significantly higher in patients with DM (52.8%) than in controls (48.2%) \((P=0.033, \text{ OR } 1.204, 95\% \text{ CI } 1.015–1.427)\). There were no statistically significant differences in the G/A, and A/A genotypes between the DM patients and controls. Moreover, no statistically significant difference was observed in the proportion of G/G plus G/A genotypes between patients with DM and control participants (91.8% vs 92.3%, \(P=0.652\)). The frequencies of the G and A alleles in patients with DM were 69.5% and 30.5%, respectively, compared to 72.1% and 27.9% in controls, respectively, which was not statistically significant difference \((P=0.063)\) (Table 2).

**Clinical Characteristics of DM Patients Stratified by ALDH2 Genotypes and Alleles**

The laboratory test results of patients with DM were analyzed according to ALDH2 variants, DM patients with ALDH2 G/G genotype had a higher percentage of male than those with the G/A and A/A genotypes \((P<0.001)\). Furthermore, compared with G/G and G/A individuals, A/A individuals had lower frequencies of smoking \((P=0.020)\) and alcohol consumption \((P=0.044)\). DM patients with the G/A genotype had lower LDL-C \((P<0.017)\) and Apo-B \((P<0.006)\) levels than those in patients with the G/G and A/A genotypes. The clinical characteristics of DM patients with G and A allele were also compared. DM patients with the A allele had a lower percentage of female \((P=0.003)\) than those with the G allele. There were no statistically significant differences in the percentage of smokers and alcohol consumption, age, HCY, TG, TC, HDL-C and Apo-A1 in patients with DM among G/G, G/A and A/A genotypes, as well as G and A alleles, respectively (Table 3).

**Table 2** The Prevalence of ALDH2 Glu504Lys (rs671) Variants in DM Patients Group and Controls Group

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Total (n, %)</th>
<th>DM Patients group (n, %)</th>
<th>Controls Group (n, %)</th>
<th>(P) value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G/G (1218)</td>
<td>372 (47.2)</td>
<td>846 (51.8)</td>
<td>0.033</td>
<td>0.831</td>
<td>0.701–0.985</td>
</tr>
<tr>
<td></td>
<td>G/A (1011)</td>
<td>351 (44.5)</td>
<td>660 (40.4)</td>
<td>0.055</td>
<td>1.183</td>
<td>1.066–1.324</td>
</tr>
<tr>
<td></td>
<td>A/A (191)</td>
<td>65 (8.2)</td>
<td>126 (7.7)</td>
<td>0.652</td>
<td>1.062</td>
<td>0.807–1.416</td>
</tr>
<tr>
<td>G/G + G/A</td>
<td>2229 (92.1)</td>
<td>723 (91.8)</td>
<td>1506 (92.3)</td>
<td>0.652</td>
<td>0.931</td>
<td>0.681–1.272</td>
</tr>
<tr>
<td>A/A + A/A</td>
<td>1202 (50.0)</td>
<td>416 (52.8)</td>
<td>786 (48.2)</td>
<td>0.033</td>
<td>1.204</td>
<td>1.015–1.427</td>
</tr>
<tr>
<td>Allele</td>
<td>G/G (3447)</td>
<td>1095 (69.5)</td>
<td>2352 (72.1)</td>
<td>0.063</td>
<td>0.883</td>
<td>0.774–1.007</td>
</tr>
<tr>
<td></td>
<td>A/A (1393)</td>
<td>481 (30.5)</td>
<td>912 (27.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HWE \((\chi^2, P)\): \(\chi^2=0.880, P=0.348\); \(\chi^2=1.992, P=0.158\); \(\chi^2=0.030, P=0.862\)

**Table 3** Clinical Characteristics of DM Patients Stratified by ALDH2 Variants

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>G/G (\text{ (n}=372))</th>
<th>G/A (\text{ (n}=351))</th>
<th>A/A (\text{ (n}=65))</th>
<th>(P) values</th>
<th>G allele (\text{ (G/G + G/A)}) (\text{ (n}=723))</th>
<th>A allele (\text{ (G/A + A/A)}) (\text{ (n}=416))</th>
<th>(P) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.99±10.86</td>
<td>68.34±10.41</td>
<td>68.48±11.56</td>
<td>0.201</td>
<td>67.65±10.66</td>
<td>68.37±10.58</td>
<td>0.274</td>
</tr>
<tr>
<td>Gender</td>
<td>Male, n(%)</td>
<td>280 (35.5)</td>
<td>204 (25.9)</td>
<td>(&lt;0.001)</td>
<td>484 (42.5)</td>
<td>242 (21.1)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Female, n(%)</td>
<td>92 (11.7)</td>
<td>147 (18.7)</td>
<td></td>
<td>239 (21.0)</td>
<td>174 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Smokers, n(%)</td>
<td>112 (14.2)</td>
<td>84 (10.7)</td>
<td>10 (1.3)</td>
<td>0.020</td>
<td>196 (17.2)</td>
<td>94 (8.3)</td>
<td>0.092</td>
</tr>
<tr>
<td>Alcohol, n(%)</td>
<td>26 (3.3)</td>
<td>11 (1.4)</td>
<td>2 (0.3)</td>
<td>0.044</td>
<td>37 (3.2)</td>
<td>13 (1.1)</td>
<td>0.114</td>
</tr>
<tr>
<td>HCY, μmol/L</td>
<td>17.58±7.02</td>
<td>16.88±7.29</td>
<td>18.04±11.51</td>
<td>0.332</td>
<td>17.24±7.15</td>
<td>17.06±8.09</td>
<td>0.698</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>2.21±2.26</td>
<td>2.16±1.81</td>
<td>2.33±2.01</td>
<td>0.827</td>
<td>2.19±2.05</td>
<td>2.19±1.84</td>
<td>1.000</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.05±1.45</td>
<td>4.91±1.36</td>
<td>5.24±1.54</td>
<td>0.150</td>
<td>4.98±1.41</td>
<td>4.96±1.40</td>
<td>0.808</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.22±0.36</td>
<td>1.23±0.39</td>
<td>1.17±0.31</td>
<td>0.451</td>
<td>1.23±0.37</td>
<td>1.22±0.38</td>
<td>0.885</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.84±1.02</td>
<td>2.68±0.95</td>
<td>2.99±1.10</td>
<td>0.017</td>
<td>2.76±0.99</td>
<td>2.72±0.98</td>
<td>0.555</td>
</tr>
<tr>
<td>Apo-A1, g/L</td>
<td>1.10±0.31</td>
<td>1.09±0.28</td>
<td>1.06±0.30</td>
<td>0.006</td>
<td>1.09±0.30</td>
<td>1.08±0.28</td>
<td>0.652</td>
</tr>
<tr>
<td>Apo-B, g/L</td>
<td>0.90±0.30</td>
<td>0.86±0.29</td>
<td>0.98±0.30</td>
<td></td>
<td>0.88±0.30</td>
<td>0.87±0.30</td>
<td>0.909</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium. Table 3 Clinical characteristics of DM patients stratified by ALDH2 variants.
Logistic regression analysis was used to evaluate independent predictors of DM. Univariate regression analysis was performed to obtain the unadjusted odds ratio (OR), and multiple logistic regression analysis was performed to obtain the adjusted OR. Relative analysis was used to evaluate the association between the genotypes frequencies of the ALDH2 gene polymorphisms and potential risk factors for DM. Three ALDH2 genetic modes of inheritance were identified: co-dominant mode (G/A vs G/G, A/A vs G/G, and A/A vs G/A), dominant mode (G/A + A/A vs G/G), and recessive mode (A/A vs G/G + G/A). Univariate logistic regression showed that ALDH2 rs671 G/A genotype (G/A vs G/G: OR 1.209, 95% CI: 1.012–1.445, \( P = 0.036 \)), and the G/A + A/A genotypes in the dominant model (G/A + A/A vs G/G: OR 1.204, 95% CI: 1.015–1.427, \( P = 0.033 \)) may increase the risk of DM in people with HTN.

The results of the multivariate logistic regression (adjusted for gender, age, smoking history, and drinking history) indicated that the G/A genotype increased the risk of DM in patients with HTN, with an adjusted OR of 1.209 (95% CI 1.010–1.446, \( P = 0.038 \)). Furthermore, the G/A + A/A genotype in the dominant model significantly increased the risk of DM, with an adjusted OR of 1.203 (95% CI 1.013–1.428, \( P = 0.035 \)). However, the A/A genotype was not an independent risk factor for DM in patients with HTN.

### Discussion

HTN is a common chronic disease and the most common preventable risk factor for all-cause death and disability worldwide.\(^{29}\) HTN commonly coexists with DM, leading to risk amplification.\(^{30}\) Some researchers have implied that focusing on the risk of developing DM may be beneficial for the treatment and control of HTN.\(^{31}\) ALDH2 polymorphisms are associated with HTN and DM, respectively.\(^{32,33}\)

We found that TG and Apo-B levels were higher, and HDL-C and Apo-AI levels were lower in the DM group than in the control group. Consistent with our results, a previous study showed that patients with abnormal lipid metabolism in HTN tend to have a higher risk of DM.\(^ {34} \) In a rural Chinese population, high serum TG level and TG/HDL-C ratio increase the risk of T2DM.\(^ {35} \) Low HDL-C level and high TG level increase the risk of T2DM in Chinese people.\(^ {36}\) Ji et al found a gender difference between lipid ratio and T2DM prevalence.\(^ {37}\) Therefore, regulating plasma lipid levels is a core issue for mitigating the risk of DM in patients with HTN. In addition, in present study, the proportion of alcohol in the DM patients with G/G genotype was significantly higher than that in the patients with G/A and A/A genotypes. People who carried the ALDH2 G/A and A/A genotypes have relatively low ALDH2 enzyme activity in the body, and various

### Table 4 Logistic Regression Analysis of Risk Factors Associated with DM in HTN Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Genotypes</th>
<th>Unadjusted Values</th>
<th>Adjusted Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>( P ) value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td></td>
<td>0.981 (0.820–1.175)</td>
<td>0.836</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.030 (0.844–1.259)</td>
<td>0.769</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.974 (0.803–1.181)</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.960 (0.650–1.417)</td>
<td>0.836</td>
</tr>
<tr>
<td>Age (≥60/&lt;60)</td>
<td>G/G</td>
<td>1.000 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>1.209 (1.012–1.445)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>1.173 (0.849–1.621)</td>
<td>0.333</td>
</tr>
<tr>
<td>Smokers (Yes/No)</td>
<td>G/G</td>
<td>1.000 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G/A + A/A</td>
<td>1.204 (1.015–1.427)</td>
<td>0.033</td>
</tr>
<tr>
<td>Alcoholism (Yes/No)</td>
<td>G/G + G/A</td>
<td>1.000 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A/A</td>
<td>1.075 (0.786–1.468)</td>
<td>0.652</td>
</tr>
</tbody>
</table>

**Notes:** \( P < 0.05 \) was considered statistically significant.

**Abbreviations:** OR, odds ratio; CI, confidence interval.

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adverse reactions can occur quickly after a small amount of alcohol. This group of people is less able to clear acetaldehyde, so people with ALDH2 G/A and A/A genotypes will actively reduce their intake of ethanol.\textsuperscript{38,39}

A study found that the prevalence of DM in HTN patients was about 20\%, suggesting that HTN may be a predisposition factor for DM development.\textsuperscript{8} It is consistent with our findings. A meta-analysis based on genome-wide association studies (GWAS) showed that the ALDH2 gene was associated with T2DM.\textsuperscript{40} Zhang et al reported that ALDH2 is one of the co-pathogenic genes of T2DM and mild cognitive impairment (MCI).\textsuperscript{41} Another study reported that the ALDH2 polymorphism might association with susceptibility to DM and showed a significantly lower risk of T2DM for ALDH2 G/G and G/A genotypes in China.\textsuperscript{42} Xu et al found that ALDH2 polymorphism is associated with an increased risk of T2DM in women with coronary artery disease (CAD).\textsuperscript{43} In terms of mechanism, Janus kinase-signal transducer and activator of transcription (JAK-STAT) is an important pathway of cytokine transduction, mainly involved in immune cell recognition and metabolic regulation.\textsuperscript{44,45} Studies have shown that Janus kinase 2 (JAK2) is related to insulin resistance, the destruction of JAK2 can promote insulin resistance and fat deposition, and the activation of JAK2 can cause STAT activation.\textsuperscript{46,47} STAT can activate insulin gene transcription and cell proliferation mediated by growth hormone or prolactin.\textsuperscript{48} Animal experiments have shown that STAT activation in islets can prevent lipid accumulation in islets and protect beta cells from the adverse effects of lipids, thus preventing the occurrence of diabetes.\textsuperscript{49} And the ALDH2 gene is associated with the JAK-STAT signaling pathway.\textsuperscript{50} According to the above studies, the results on the relationship between the risk of DM and HTN and the ALDH2 rs671 polymorphisms used as a predictor for the risk of T2DM still need more evidence with different sample sizes, regions, and ethnicities. Moreover, little is known about the link between ALDH2 gene polymorphisms and the risk of DM in HTN patients, and identification of susceptibility ALDH2 genes and other risk factors would be helpful for the prevention and treatment of DM in HTN patients.

In this study, no statistically significant differences were observed between the groups in terms of age, sex, smoking history, and alcohol consumption history. Studies have shown that the incidence of diabetes is related to age.\textsuperscript{51,52} Xue et al found that age is associated with an increased risk of DM.\textsuperscript{53} However, study has reported inconsistent results.\textsuperscript{54} This study showed that the incidence of DM in different age groups was not statistically significant. This may be related to the insufficient sample size of the study and age division. In addition, this study showed that gender is not a risk factor for DM in patients with HTN. DM is a major cardiovascular risk factor, and women with DM have a higher relative risk of cardiovascular events than men with DM.\textsuperscript{55} However, there are some differences in the results of some studies on the effect of gender on DM.\textsuperscript{56–58} Therefore, further research is needed to determine the effect of gender on DM risk. The relationship between smoking, alcohol consumption, and DM occurrence has been debated. Studies have shown that nicotine in tobacco affects the body composition, islet beta cells and insulin sensitivity.\textsuperscript{59} Holst et al showed that average weekly alcohol intake was associated with the risk of DM.\textsuperscript{60} Xue et al found that alcohol consumption is associated with an increased risk of DM.\textsuperscript{53} This study showed no clear correlation between the incidence of DM and smoking or alcohol consumption in HTN patients.\textsuperscript{60} In this study, there was no significant relationship between smoking and alcohol consumption and the risk of DM in HTN patients, which may be related to the differences in research methods, study sample size, and indicators included in the analysis of different studies, which need to be confirmed by further research.

The present study showed that patients who carried the G/A genotype had a 1.21-fold increased risk of developing DM. After adjusting for other established risk factors, the ALDH2 rs671 G/A genotype was an independent risk factor for DM in patients with HTN. However, this study had some limitations. First, this was a retrospective study, and there may have been selection bias because the patients were selected from one medical institution. Second, we analyzed the relationship between clinical indicators, smoking and drinking status, and ALDH2 gene polymorphisms in patients with HTN, without paying much attention to other complications. Third, all the participants in the present study had HTN, which made it more useful for specific patients. Finally, the region of the subjects in this study was relatively limited; therefore, there may be some deviations in the results. It is necessary to increase the sample size for this study, which will be the focus of our future work.

**Conclusion**

In the present study, among patients with HTN, the ALDH2 G/A + A/A genotype increased the risk of DM. Our results need to be confirmed in future studies with larger sample sizes. The results should enrich relevant data and provide valuable information for future research.
Abbreviations
ALDH2, Aldehyde dehydrogenase 2; HTN, hypertension; DM, diabetes mellitus; HCY, homocysteine; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.

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

Ethics Approval
As this study was a retrospective study, it was not possible for all participants to return to the hospital to sign informed consent. All participants were informed on the study procedures and goals and the informed consent from all the participants was obtained in verbal form through the telephone communication, which approved by the Ethics Committee of the Meizhou People’s Hospital. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People’s Hospital (Clearance No.: 2021-A-60).

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Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure
The authors declare that they have no competing interests in this work.

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