Introduction

Coronary heart disease (CHD) is a major health threat and the most common cause of death worldwide. Urbanization is estimated to further raise CHD incidence in China. The etiology of CHD includes both genetic and environmental factors. Lifestyle...

Original Article

Association of the AGXT2 V140I Polymorphism with Risk for Coronary Heart Disease in a Chinese Population

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Aim: Asymmetric dimethylarginine (ADMA) is a nitric oxide synthase (NOS) inhibitor that decreases NO production and promotes the development of cardiovascular diseases. Alanine-glyoxylate aminotransferase 2 (AGXT2) plays an important role in ADMA metabolism. This study was designed to explore the association of the AGXT2 V140I (rs37369 G>A) polymorphism with risk for coronary heart disease (CHD) in a Chinese population.

Methods: A case-control study including 1103 controls and 942 CHD patients was performed. The patients were genotyped for rs37369 using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Plasma ADMA concentration in healthy controls was measured by an enzyme-linked immunosorbent assay (ELISA).

Results: The rs37369 GG genotype was significantly overrepresented in CHD patients compared to the controls (18.5% versus 14.8%, \( p = 0.025 \)), and it was significantly associated with increased risk for CHD in smokers (OR = 2.21, 95% CI: 1.24-3.92, \( p = 0.007 \)) and marginally increased CHD risk for individuals with diabetes mellitus (OR = 1.92; 95% CI: 0.94-3.91, \( p = 0.074 \)). The association between rs37369 and CHD risk was further increased in smokers with diabetes mellitus (OR = 3.32, 95% CI: 1.14-9.67, \( p = 0.028 \)). Patients who smoked and were rs37369 GG homozygous showed significantly higher plasma ADMA levels than carriers of the rs37369 A allele (\( p = 0.004 \)). However, in non-smokers, patients homozygous for rs37369 GG showed significantly lower plasma ADMA concentrations than carriers of the rs37369 A allele (\( p = 0.003 \)). Furthermore, smokers homozygous for rs37369 GG showed significantly higher plasma ADMA concentrations than non-smokers with the same genotype (\( p = 0.012 \)).

Conclusion: The AGXT2 rs37369 polymorphism is associated with increased risk for CHD in smokers and in diabetes mellitus patients. This increased risk may be due to increased plasma ADMA levels.


Key words: Alanine-glyoxylate aminotransferase 2, Coronary heart disease, Diabetes mellitus, Asymmetric dimethylarginine, rs37369 polymorphism
Atherosclerosis is the fundamental pathogenesis for CHD, while endothelial dysfunction is the initial step for the development of atherosclerosis. Asymmetric dimethylarginine (ADMA) is an endogenous NO synthase (NOS) inhibitor and has been suggested to be a link between inflammation and endothelial dysfunction in humans. ADMA can accelerate atherosclerosis through decreasing NO bioavailability and stimulating inflammation. In addition, the contribution of the known variants in CHD heritability is limited. Therefore, additional efforts are necessary to pinpoint the causal genetic variants for CHD, provide pathophysiological insights for CHD, and identify novel therapeutic targets for the disease.

Methods

Study Subjects

A total of 942 patients with angiographically-proven CHD hospitalized at the Xiangya Hospital in Hunan province, China were recruited between November 2009 and December 2012. CHD was defined as luminal stenosis ≥50% in at least one major coronary artery branch or myocardial infarction. The controls included 1103 gender- and age-matched subjects who attended routine health screenings in the outpatient clinics of the same hospital. Diabetic mellitus (DM) was diagnosed as a fasting plasma glucose (FPG) ≥7.0 mmol/L or history of DM therapy. Inclusion and exclusion criteria for the cases and controls were as previously described. The controls were subjects without histories of hypertension, diabetes mellitus, ischemic heart disease, and chronic heart failure. None of the controls had ever shown symptoms of ischemic heart disease, such as angina, before sampling. The case report form (CRF) was used to collect information including age, gender, duration of CHD, cigarette smoking, and alcohol drinking. A similar questionnaire was also obtained from the controls. Venous blood samples were drawn from all participants and used for the preparation of hemocytes and plasma samples by centrifuging (3,000 rpm) for 10 minutes at 4°C. Hemocytes and plasma samples were stored at −80°C for DNA extraction and ADMA detection, respectively. All subjects underwent routine blood and biochemistry tests, which included serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), creatinine, and FPG. All participants were Han Chinese from Changsha or the surrounding counties, and signed informed consents.
were obtained. The study protocol was approved by the Ethics Committee of the School of Pharmaceutical Sciences, Central South University, Changsha and registered on http://www.chictr.org/ (registration number: ChiCTR-RCC-12002817).

**AGXT2 V140I Genotyping**

Genomic DNA was extracted from peripheral blood leukocytes using the standard phenol/chloroform method. Genotyping of the AGXT2 V140I polymorphism was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primers used for PCR amplification were as follows: 5’- TAGGGACGCTCCCCCTAGAAT -3’ (forward), and 5’-TCTAAGCCCAAACCTTCTCTCT -3’ (reverse). PCR products (2 μL) were digested with 3 U BbsI (Thermo Fisher Scientific, Waltham, MA, USA) overnight at 37°C. The digested PCR products were then analyzed by electrophoresis on a 2.5% agarose gel and visualized under UV light after ethidium bromide staining.

**Determination of ADMA Concentration**

The concentration of plasma ADMA in healthy subjects was measured by ELISA according to the manufacturer’s instructions (CUSABIO BIOTECH Co., Ltd, Wuhan, China). Briefly, 100 μL of plasma samples or standard solutions were added to the wells of the 96-well ELISA plate and incubated for 2 hours at 37°C. OD values were detected with a microplate reader (Beckman Coulter, Pasadena, CA, USA) at a wavelength of 450 nm. Data was presented as μmol/L.

**Results**

**Clinical and Laboratory Characteristics**

The general characteristics of the cases and con-
AGXT2 Polymorphism and CHD Risk

CHD, an association analysis stratified by smoking status was performed. All smokers in the study were heavy smokers with cigarette smoking ≥27 packages per year. No significant differences in genotype distribution of the rs37369 genotypes were observed between cases and controls in either smokers (p = 0.074) or non-smokers (p = 0.133). However, when the logistic regression analysis was performed, rs37369 GG homozygotes showed an increased risk of CHD compared to carriers of the rs37369 A allele in smokers (OR = 2.21, 95% CI: 1.24-3.92, p = 0.007, Table 2).

Case-Case Analysis of AGXT2 rs37369 G > A Genotype Distribution in Cases with and without DM

DM is an established risk factor for atherosclerosis and CHD. To clarify whether the association of rs37369 with CHD risk is modified by DM status, further analysis of AGXT2 rs37369 genotype distribution in patients with or without DM was carried out. As shown in Table 3, the rs37369 GG genotype was significantly overrepresented in CHD cases with DM as compared with CHD cases without DM (24.6% versus 16.7%, p = 0.010, Table 3) or the controls (24.6% versus 14.8%, p = 0.0004, Table 3). Logistic regression analysis showed that the rs37369 GG genotype was associated with a marginally increased CHD risk as compared with carriers of the rs37369 A allele (OR = 1.92, 95% CI: 0.94-3.91, p = 0.074).

### Table 2. Association between the AGXT2 rs37369 polymorphism and risk for CHD in a Chinese population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CHD cases n (%)</th>
<th>Controls n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>293 (31.1)</td>
<td>385 (34.9)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td>475 (50.4)</td>
<td>555 (50.3)</td>
<td>1.31 (1.03-1.65)b</td>
<td>1.33 (0.95-1.87)</td>
</tr>
<tr>
<td>GG</td>
<td>174 (18.5)</td>
<td>163 (14.8)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td><strong>Non-smokers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>160 (29.6)</td>
<td>274 (33.9)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td>282 (52.1)</td>
<td>412 (50.9)</td>
<td>1.25 (0.93-1.67)</td>
<td>1.17 (0.75-1.85)</td>
</tr>
<tr>
<td>GG</td>
<td>99 (18.3)</td>
<td>123 (15.2)</td>
<td>1.31 (1.03-1.65)b</td>
<td>1.33 (0.95-1.87)</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>133 (33.2)</td>
<td>111 (37.8)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td>193 (48.1)</td>
<td>143 (48.6)</td>
<td>1.46 (0.96-2.22)</td>
<td>2.21 (1.24-3.92)c</td>
</tr>
<tr>
<td>GG</td>
<td>75 (18.7)</td>
<td>40 (13.6)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

a Adjusted for sex, age, smoking status (yes/no), history of alcohol drinking (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), hyperlipidemia (yes/no), and CHD in first-degree relatives (yes/no). OR, odds ratio; CI, confidence interval.
b p = 0.025, c p = 0.007.

trols are summarized in Table 1. Patients with CHD showed significantly higher systolic blood pressure (SBP), diastolic blood pressure (DBP), serum low-density lipoprotein (LDL) levels, fasting plasma glucose (FPG) and lower serum high-density lipoprotein (p < 0.001) compared to the controls. CHD patients also showed a higher prevalence of smoking, hypertension and DM (p < 0.001) and family history of CHD in first-degree relatives (p = 0.016). No significant differences in gender, age, serum total cholesterol and triglyceride, history of alcohol consumption and hyperlipidemia were observed between patients and controls (p > 0.05).

### Association between the AGXT2 rs37369 G > A Polymorphism and Risk for CHD

As shown in Table 2, genotype distribution of the AGXT2 rs37369 polymorphism in both the cases and the controls were in agreement with the Hardy-Weinberg equilibrium ($\chi^2_1 = 0.58$, p = 0.45 and $\chi^2_1 = 2.63$, p = 0.10, respectively). The AGXT2 rs37369 GG (V140V) genotype was overrepresented in CHD patients compared to controls (18.5% versus 14.8%, p = 0.025, Table 2). When adjusted for cardiovascular risk factors, including sex, age, smoking status, history of alcohol drinking, hypertension, DM, hyperlipidemia, and family history of CHD in first-degree relatives, no significant association between the AGXT2 rs37369 polymorphism and risk of CHD was observed (OR = 1.33, 95% CI: 0.95-1.87, p = 0.098, Table 2).

Considering that smoking is a risk factor for CHD, an association analysis stratified by smoking status was performed. All smokers in the study were heavy smokers with cigarette smoking ≥27 packages per year. No significant differences in genotype distribution of the rs37369 genotypes were observed between cases and controls in either smokers (p = 0.074) or non-smokers (p = 0.133). However, when the logistic regression analysis was performed, rs37369 GG homozygotes showed an increased risk of CHD compared to carriers of the rs37369 A allele in smokers (OR = 2.21, 95% CI: 1.24-3.92, p = 0.007, Table 2).
sampling. No significant difference in plasma ADMA levels was observed among the rs37369 genotypes in the entire cohort. In non-smokers, plasma ADMA concentrations in subjects heterozygous for the rs37369 AG genotype (0.68 ± 0.06 μmol/L, n = 126) and carriers of the major rs37369 A allele (AA + AG, 0.65 ± 0.04 μmol/L, n = 184) were significantly higher than those in subjects homozygous for the rs37369 GG genotype (0.45 ± 0.05 μmol/L, n = 43; AA versus GG, p = 0.011 and 0.003, respectively, Fig. 1). However, in smokers, both the rs37369 AA genotype (0.55 ± 0.08 μmol/L, n = 32) and the rs37369 AG genotype (0.47 ± 0.08 μmol/L, n = 38) showed significantly lower plasma ADMA levels compared to subjects homozygous for the rs37369 GG genotype (0.92 ± 0.16 μmol/L, n = 14, AA versus GG, p = 0.019; AG versus GG, p = 0.004; AA + AG versus GG: p = 0.004, Fig. 1). Smokers with the rs37369 GG genotype showed significantly increased plasma ADMA levels compared to non-smokers with the same genotype (0.92 ± 0.16 μmol/L, n = 14 versus 0.45 ± 0.05 μmol/L, n = 43; p = 0.012, Fig. 1).

### Combined Interaction of Smoking and DM with rs37369 and CHD Risk

As rs37369 was found to be associated with CHD risk in both smokers and patients with DM, we further subgrouped the cases and controls with concomitant consideration of smoking and DM status. As shown in Table 4, the rs37369 GG genotype was significantly overrepresented in smoking cases with type 2 diabetes mellitus (T2DM) (28.5%) compared to smoking controls (13.6%, p = 0.002) or smokers without T2DM (16.4%, p = 0.013). In non-smokers, the rs37369 GG genotype frequency was also significantly higher in cases with DM (24.6%) than in controls (22.3%), as compared with corresponding controls, p = 0.013, compared with patients who smoke do not have DM.

### Influence of AGXT2 rs37369 G>A Polymorphism on Plasma ADMA Levels in Healthy Subjects

Plasma ADMA concentration was determined in 311 randomly selected healthy controls who were not given drug treatment at least 2 weeks before blood

### Table 3. Association between the AGXT2 rs37369 polymorphism with CHD risk stratified by diabetes mellitus status

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls</th>
<th>Cases with DM</th>
<th>Cases without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>385 (34.9)</td>
<td>69 (33.3)</td>
<td>224 (30.5)</td>
</tr>
<tr>
<td>AG</td>
<td>555 (50.3)</td>
<td>87 (42.1)</td>
<td>388 (52.8)</td>
</tr>
<tr>
<td>GG</td>
<td>163 (14.8)</td>
<td>51 (24.6)</td>
<td>123 (16.7)</td>
</tr>
</tbody>
</table>

Adjusted for sex, age, smoking status (yes/no), history of alcohol drinking (yes/no), hypertension (yes/no), hyperlipidemia (yes/no), and CHD in first-degree relatives (yes/no). DM, diabetes mellitus.

### Table 4. Genotype distribution of the AGXT2 rs37369 polymorphism in CHD patients and controls stratified by both smoking status and type 2 diabetic mellitus

<table>
<thead>
<tr>
<th>Cases subgroup</th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>274 (33.9)</td>
<td>412 (50.9)</td>
<td>123 (15.2)</td>
</tr>
<tr>
<td>Cases without DM, n (%)</td>
<td>117 (28.5)</td>
<td>224 (54.5)</td>
<td>70 (17.0)</td>
</tr>
<tr>
<td>Cases with DM, n (%)</td>
<td>43 (33.1)</td>
<td>58 (44.6)</td>
<td>29 (22.3)</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls, n (%)</td>
<td>111 (37.8)</td>
<td>143 (48.6)</td>
<td>40 (13.6)</td>
</tr>
<tr>
<td>Cases without DM, n (%)</td>
<td>107 (33.0)</td>
<td>164 (50.6)</td>
<td>53 (16.4)</td>
</tr>
<tr>
<td>Cases with DM, n (%)</td>
<td>26 (33.8)</td>
<td>29 (37.7)</td>
<td>22 (28.5)</td>
</tr>
</tbody>
</table>

a p = 0.041, b p = 0.002, as compared with corresponding controls, c p = 0.013, compared with patients who smoke do not have DM.
AGXT2 Polymorphism and CHD Risk

showed the highest urinary 3-aminoisobutyrate levels\(^\text{17}\). A recent metabolomics GWAS by Rhee et al. confirmed the association between the AGXT2 polymorphism and plasma BAIB acid levels, and determined that the AGXT2 rs37370 polymorphism accounts for approximately 36% estimated heritability in plasma BAIB acid levels\(^\text{21}\). The rs37370 polymorphism is also observed to be associated with plasma triglycerides (TAGs) and cholesteryl esters (CEs) in opposite directions\(^\text{21}\). Another GWAS has also demonstrated a suggestive association between the rs37369 A allele and a modest increase in DBP\(^\text{14}\). Collectively, these studies support the loss-of-function variant at the AGXT2 locus. In our study, we observed that rs37369 was associated with increased risk for CHD in smokers and in DM patients, which further confirmed the functionality of rs37369. In contrast to the previous study\(^\text{17}\), the rs37369 A (140I) allele is the major allele in our Chinese population. We speculate that the remarkable inter-ethnic difference in allele frequency of the polymorphism may explain the high prevalence of hyper-BAIB aciduria in Asians.

The role of AGXT2 in ADMA metabolism and human traits has attracted increasing interest in recent years\(^\text{14, 15, 17, 19}\). Genetic associations of AGXT2 polymorphisms with the human metabolome, such as hyper-BAIB aciduria and lipid homeostasis, have been observed\(^\text{17, 21}\). Hyper-BAIB aciduria is an autosomal recessive trait commonly found in Asians with a prevalence of approximately 40%\(^\text{15, 22}\). A previous GWAS has shown that the rs37369 polymorphism is strongly associated with hyper-BAIB aciduria and is a likely causative SNP of hyper-BAIB aciduria\(^\text{17}\). Subjects homozygous for the minor-allele rs37369 AA (I140I) showed the highest urinary 3-aminoisobutyrate levels\(^\text{17}\). A recent metabolomics GWAS by Rhee et al. confirmed the association between the AGXT2 polymorphism and plasma BAIB acid levels, and determined that the AGXT2 rs37370 polymorphism accounts for approximately 36% estimated heritability in plasma BAIB acid levels\(^\text{21}\). The rs37370 polymorphism is also observed to be associated with plasma triglycerides (TAGs) and cholesteryl esters (CEs) in opposite directions\(^\text{21}\). Another GWAS has also demonstrated a suggestive association between the rs37369 A allele and a modest increase in DBP\(^\text{14}\). Collectively, these studies support the loss-of-function variant at the AGXT2 locus. In our study, we observed that rs37369 was associated with increased risk for CHD in smokers and in DM patients, which further confirmed the functionality of rs37369. In contrast to the previous study\(^\text{17}\), the rs37369 A (140I) allele is the major allele in our Chinese population. We speculate that the remarkable inter-ethnic difference in allele frequency of the polymorphism may explain the high prevalence of hyper-BAIB aciduria in Asians.

**Discussion**

To our knowledge, the results presented here represent the first report to demonstrate that the AGXT2 rs37369 polymorphism is associated with risk for CHD. Our data showed that the rs37369 GG (V140V) genotype was overrepresented in CHD patients, and the genotype was associated with increased risk for CHD in smokers with an OR of 2.21 (95% CI: 1.24-3.92) after adjustment for conventional cardiovascular risk factors. Further analyses also indicated that the rs37369 GG genotype was associated with increased risk for CHD in patients with DM, thus suggesting a gene-disease interaction on CHD risk. In smokers with DM, carriers of the rs37369 GG genotype had increased CHD risk (OR=3.32, 95% CI: 1.14-9.67). Moreover, we observed that the rs37369 polymorphism affected plasma ADMA levels in healthy subjects, with subjects homozygous for rs37369 GG genotype showing significantly higher plasma ADMA levels than smokers with the rs37369 A allele.

Fig. 1. Influence of AGXT2 rs37369 polymorphism on plasma ADMA level in healthy subjects.

Data are expressed as the mean ± SEM. The plasma ADMA concentration was determined by ELISA. *p<0.05, **p<0.01, as compared with GG genotype in interclass, *p<0.05, as compared with rs37369 GG genotype in non-smokers.
CHD risk via affecting plasma ADMA levels.

The mechanism to explain how cigarette smoking changes the influence of rs37369 on plasma ADMA levels remains unknown. DDAH1 is reported to be the major enzyme involved in ADMA degradation in the body\textsuperscript{[13]}. The transcription factor sterol response element binding protein 1c (SREBP1c) is a DDAH1 repressor\textsuperscript{[23]}. Interestingly, Agxt2 knockdown has been shown to increased SREBP-1 expression in zebrafish\textsuperscript{[21]}. These reports suggest positive regulation of AGXT2 on DDAH1 expression through SREBP-1. Furthermore, DDAH1 is inhibited by cigarette smoking extracts\textsuperscript{[24]}. As the rs37369 polymorphism also decreases AGXT2 activity\textsuperscript{[17]}, we hypothesize a synergistic effect of cigarette smoking and the rs37369 polymorphism on DDAH1 inhibition, and subsequent ADMA metabolism, in subjects with the rs37369 GG genotype.

We also observed that the association between rs37369 and CHD risk was more apparent in smokers with DM, and no obvious association between rs37369 and CHD was observed in non-smokers or subjects without DM. Similar gene-diabetes interaction on CHD risk is also reported elsewhere\textsuperscript{[25]}. Both diabetes and cigarette smoke extract are reported to decrease DDAH activity\textsuperscript{[23, 26]}. We hypothesize that the contribution of AGXT2 in ADMA metabolism may be increased in smokers and T2DM patients when DDAH is inhibited; thus, the effect of rs37369 is increased under smoking or diabetic disease status. However, because we were unable to enroll DM patients (especially T2DM patients) without CHD complications, we cannot exclude any direct association between rs37369 and DM risk.

In addition to the ADMA metabolism, the observed association between rs37369 and CHD risk may also be explained by other mechanisms. Dyslipidemia and homoarginine are also risk factors for CHD\textsuperscript{[27, 28]}. Recent GWAS have shown that rs37369 is associated with serum homoarginine\textsuperscript{[29]}, while the AGXT2 rs37370 polymorphism can affect plasma levels of triglycerides and CEs\textsuperscript{[21]}. Therefore, rs37369 may increase CHD risk by additional mechanisms in addition to affecting the ADMA metabolism.

We must acknowledge some limitations in our study. First, we obtained results from only one population with a limited sample size. Therefore, our findings would need to be replicated with a larger sample size. Second, the exact function of the rs37369 polymorphism was not studied. Further studies are needed to confirm the influence of this polymorphism on the AGXT2 activity.

Conclusion

In summary, this is the first study to demonstrate that the AGXT2 rs37369 polymorphism is associated with an increased risk for CHD in a Chinese population, specifically in smokers and individuals with T2DM. We speculate that the rs37369 polymorphism is responsible for increasing the plasma ADMA levels. Our study is the first to show evidence that AGXT2 is important in cardiovascular diseases (CVDs) and suggests an alternative target for therapeutic strategies of CVDs. However, additional studies in different populations are needed to confirm these findings, and further investigations to determine the functional role of the rs37369 polymorphism are necessary.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

References


20) Guo YJ, Chen L, Bai YP, Li L, Sun J, Zhang GG, Yang TL, Xia J, Li YJ, Chen XP: The ALDH2 Glu504Lys polymorphism is associated with coronary artery disease in Han Chinese: Relation with endothelial ADMA levels. Atherosclerosis, 2010; 211: 545-550


