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Original Article

Association between Angiopoietin-2 Gene Polymorphisms and Susceptibility to Coronary Artery Disease

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Abstract

Background: Angiopoietin-2 (Angpt2) is associated with the progression of coronary artery disease (CAD). This research aimed to investigate the possible association between single nucleotide polymorphisms (SNPs) of *ANGPT2* and CAD.

Methods: This research was performed in a hospital from the eastern region of China. From February 2019 to June 2019, 222 patients with CAD were newly diagnosed and 403 healthy controls were confirmed by physical examinations. The distribution frequency of five SNPs of the *ANGPT2* (rs11137037, rs2442598, rs12674822, rs1823375, and rs734701) in all participants was analyzed by real-time polymerase chain reaction (PCR) with SNP locus-specific probes.

Results: Our data showed that the participants with the TT genotype of rs2442598 were at reduced risk of CAD compared with wild-types (adjusted odds ratio [AOR] = 0.511, 95% CI: 0.283–0.923). The participants with the AC and AC+CC genotypes of rs11137037 were at greater risk of CAD compared to wild-types (AOR = 1.754, 95% CI: 1.140-2.699; AOR = 1.731, 95% CI: 1.165–2.573, respectively). In addition, carriers of the GG+TT genotypes of rs12674822, showed more significant high-density lipoprotein than those of GG genotype, in addition, carriers of the GG+TT genotypes of rs12674822, showed more significant high-density lipoprotein than those of GG genotype (P=0.037).

Conclusion: These findings, as well as analysis of the haplotype, clearly indicate that *ANGPT2* SNPs were highly correlated with susceptibility to CAD among the Han Chinese population.

Keywords: Angiopoietin-2, Coronary artery disease, Single nucleotide polymorphism

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Introduction

Coronary artery disease (CAD) is a common disorder in which coronary atherosclerosis leads to narrowing or occlusion of the coronary vascular lumen, resulting in myocardial ischemia, hypoxia, and even necrosis.[1,2] With the improvement of living standards, the high mortality and morbidity resulting from CAD has attracted increased attention in China.[3] Although CAD is related to blood lipids, hypertension, diabetes, lifestyle, obesity, and dietary habits, the genetic background is also a strong independent risk factor.[4,5] The association between genetic variation and CAD has been demonstrated by numerous studies.[6] Thus, identifying genetic factors is crucial for CAD, which can help us predict the occurrence and development of the disease earlier.

In clinical practice, in order to ensure adequate blood supply to the myocardium and prevent myocardial infarction, vascular recanalization has become the principal treatment regimen.[7,8] As a self-compensating mechanism, angiogenesis can provide oxygen to the severely ischemic myocardium that is sufficient to improve prognosis.[9,10] Compensatory angiogenesis has been found in various diseases of ischemia and hypoxia; therefore, angiogenesis may be helpful in the diagnosis and treatment of CAD. Angiopoietin-2 (Angpt2) is an important factor in angiogenesis.[11] It functions by reducing vascular stability, promoting the activation of endothelial cells, and promoting the formation and remodeling of new blood vessels.[12] Previous studies focused on Angpt2 to identify the relationship between Angpt2 protein and CAD. Serum levels of Angpt2 were significantly increased among patients with CAD, which were significantly decreased after percutaneous coronary intervention, thereby showing the close correlation between serum levels of Angpt2 and the severity of coronary artery stenosis.[13] In another study, it was shown that the expression level of Angpt2 in serum of patients with CAD combined with heart failure was relatively high.[14] Therefore, Angpt2

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is considered a biomarker of myocardial ischemia and vascular remodeling. We hypothesize that the Angpt2 genes are different in populations with CAD, and that they might help us predict susceptibility to CAD in the CAD population.

Single nucleotide polymorphisms (SNPs) indicate the variation of a single nucleotide in the genome.[15] *ANGPT2* SNPs predict the prognosis of disease and the degree of risk for conditions, such as type 2 diabetes, neovascular age-related macular degeneration, polypoidal choroidal vasculopathies, acute lung injury and lung tumors, etc.[16-19] However, studies on the correlation between SNPs of *ANGPT2* and CAD are limited in China. Therefore, in this study, we aimed to explore whether *ANGPT2* SNPs are associated with the risk of CAD.

Materials and Methods

Participants

Participants were recruited from a tertiary hospital located in the central region of Zhejiang province, China. After excluding patients with tumors, kidney failure, autoimmune diseases, sepsis, and other diseases,[20-23] 222 patients diagnosed with CAD for the first time were recruited consecutively from February 2019 to June 2019. The criteria for the diagnosis of CAD were defined as coronary angiography with more than 50% stenosis. The control group consisted of 403 healthy volunteers who underwent physical examination in the same hospital. Healthy status was confirmed as no symptoms or abnormality in examinations indicating CAD or other diseases of the exclusion criteria mentioned above.

From all participants, clinical data were collected, including age, gender, tobacco, alcohol consumption, previous medical history, blood lipids related index, electrocardiogram (ECG), and cardiac function as proposed by the New York Heart Association.[24]

Blood Sample Collection and DNA Extraction

Prior to percutaneous coronary intervention, 3-5 mL venous blood was collected from each subject in a vacuum collector containing EDTA, then centrifuged to obtain blood cells. The DNA was harvested from the blood cells using a DNA extraction kit (Qiagen, Germany) and stored in TE buffer.[19]

Angpt2 Polymorphisms

Five *ANGPT2* (OMIM accession number: 601922) SNPs (rs11137037, rs2442598, rs12674822, rs1823375, and rs734701) were selected and appropriate probes were designed as described previously.[18,25,26]

Genotyping

The polymerase chain reaction (PCR) reaction mix consisted of a volume of 10 μL, including genomic DNA, TaqMan Genotyping Master Mix (Applied Biosystems, USA), and probes. Details of amplification conditions, genotypes determination and data analysis are described in our previous study.[19]

Statistical Analysis

To analyze the data, the IBM SPSS Statistics v24.0 statistical software (Armonk, New York, USA) was used, and all measurement data were assumed to be normally distributed. Genotype distribution was tested using the Hardy-Weinberg Equilibrium law. Independent samples *t* test (for quantitative data) and Fisher's exact test (for count data) were used to compare the data of controls with CAD patients. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated using multiple logistic regression models. Haplotype frequencies were analyzed by the Haploview software as described previously.[27] $P < 0.05$ was considered statistically significant.

Results

We found the patients' mean age in the CAD group at 66.44 ± 9.61 years, and that of patients in the control group at 57.61 ± 12.71 years ($P < 0.001$, Table 1). The clinical data of the two groups were compared statistically. The frequencies of smoking history, drinking history, and the apolipoprotein A1/B ratio were significantly different ($P < 0.01$) between the two groups. Regarding ECG and heart failure status of patients in the CAD group, patients with changes in the ST segment of their ECG accounted for 36% of the patients in this group, and patients with the cardiac function of class III and IV accounted for 16.2%.

A comparison of *ANGPT2* genotypes in 403 healthy individuals and 222 CAD patients is presented in Table 2. In both the CAD and the healthy control groups, the most common genotypes in rs2442598, rs734701, rs1823375, rs11137037, and rs12674822 were AT, TC, CC, AA, and GT, respectively. In rs2442598, individuals bearing the TT genotype were less likely to have CAD compared to patients with the AA genotype (adjusted odds ratio [AOR] = 0.551; 95% CI, 0.283–0.923; $P < 0.05$). In rs11137037, patients bearing the AC genotype were by 1.754-folds more likely to suffer from CAD compared to patients bearing the AA genotype (AOR = 1.754; 95% CI 1.140–2.699; $P < 0.05$) and patients bearing AC+CC were by 1.731-folds more likely compared to patients bearing AA (AOR = 1.731; 95% CI 1.165-2.573; $P < 0.05$). These data indicated that AC and AC+CC genotypes were more likely to be associated with CAD. No significant differences were observed in rs734701, rs1823375, rs12674822, and other genotypes when comparing CAD patients and healthy controls.

An independent samples t-test was employed to compare *ANGPT2* SNPs with clinical data (Table 3), the GT+TT genotype of rs12674822 having a significance in high-density lipoprotein compared to the GG genotype in CAD patients ($P = 0.037$).

Table 4 shows that in rs734701, rs11137037, and rs12674822, patients with the T/C/G haplotype had a higher risk of CAD than patients bearing the T/A/T haplotype (AOR = 1.574; 95% CI 1.034–2.396; $P < 0.05$),

Table 1. Subjects' Characteristics

Variable	Controls n = 403 (%)	Patients n = 222 (%)	*P* Value
Gender			
Female	192 (47.6)	70 (31.5)	<0.001
Male	211 (52.4)	152 (68.5)	
Smoking			
No	356 (88.3)	111 (50.0)	<0.001
Yes	47 (11.7)	111 (50.0)	
Alcohol			
No	339 (84.1)	119 (53.6)	<0.001
Yes	64 (15.9)	103 (46.4)	
NYHA classification			
I + II		186 (83.8)	-
III + IV		36 (16.2)	
ECG			
Negative		142 (64.0)	-
Positive		80 (36.0)	
	Mean ± SD	**Mean ± SD**	
Age (y)	57.61 ± 12.71	66.44 ± 9.61	<0.001
Triglyceride (mmol/L)	1.573 ± 1.032	1.7254 ± 1.123	0.088
Total cholesterol (mmol/L)	4.807 ± 0.911	3.957 ± 1.100	<0.001
High-density lipoprotein (mmol/L)	1.269 ± 0.313	1.077 ± 0.274	<0.001
Low-density lipoprotein (mmol/L)	2.762 ± 0.825	2.198 ± 0.912	<0.001
Apolipoprotein A1/B	1.594 ± 0.599	1.727 ± 0.728	0.023

Statistical significance was analyzed by independent samples *t* test or chi-square test. NYHA, New York heart association; ECG, Electrocardiogram; SD, Standard deviation.

while patients bearing the T/A/G haplotype were less likely to have CAD compared to patients with the T/A/T haplotype, suggesting it has a protective effect against the disease (AOR = 0.187; 95% CI 0.072–0.489; $P < 0.05$).

Discussion

CAD has a complex pathology and no theory can fully explain the underlying mechanisms involved in its occurrence and development. Current clinical approaches, such as percutaneous transluminal coronary intervention, and thrombolytic and anticoagulant drugs are relatively mature and can effectively alleviate the patients' condition and reduce the risk of disease.[28-30] Furthermore, angiogenesis may be a therapeutic approach for CAD when recanalization is not tolerated.[31]

Angpt2 is a member of a family of cytokines that can promote angiogenesis and includes Angpt1, Angpt2, Angpt3, Angpt4, and tyrosine kinase receptors 1 and 2 (tie-1, tie-2).[20] In a previous study, it was shown that the expression of serum Angpt2 is higher in individuals with CAD, suggesting that Angpt2 can be used as a potential clinical indicator for predicting CAD.[32] In addition, Angpt2 appears to be related to myocardial blood flow reperfusion, indicating that it may play a role in the prognosis of CAD.[33,34] In a number of studies, it was shown that Angpt2 indirectly participates in the regulation of inflammation by inducing sensitivity to TNF-alpha, thereby promoting the adhesion of endothelial cells.[35] It is well known that inflammation is a cause of CAD.[11] In addition, Qin et al[36] found a key role for Angpt1 and Angpt2 in the development and maintenance of collateral coronary vessels in patients with severe CAD. Considering that CAD is a disease which is closely related to angiogenesis, it is feasible to predict the relationship between ANGPT2 polymorphisms and the risk of CAD.

In this study, we explored the relationship between *ANGPT2* SNPs and CAD. Our candidate SNPs were found to be significantly correlated with diseases related to angiogenesis.[18,25] So far, few studies have been performed to determine whether the five SNPs are associated with CAD in the Han Chinese population. In patients, the TT genotype in rs2442598 is protective against CAD. In previous studies, rs2442598 has demonstrated a significant correlation with psoriasis,[37] and a correlation between psoriasis and myocardial ischemia was also observed.[38] In this study, we found that rs2442598 was correlated with CAD. In rs11137037, compared with subjects bearing the wild-type (AA), the AC and AC+CC genotypes were positively correlated with CAD. Interestingly, statistical differences were observed between different genotypes of rs12674822 in the high-density lipoprotein. Moreover, in previous studies, it was shown that the ApoA1/ApoB ratio

Table 2. *Angpt2* Genotype Frequencies in CAD Patients and Controls

Variable	Controls n = 403 (%)	Patients n = 222 (%)	OR (95% CI)	AOR (95% CI)
rs2442598				
AA	96 (23.8)	59 (26.6)	1.00 (reference)	1.00 (reference)
AT	214 (53.1)	123 (55.4)	0.935 (0.631–1.385)	0.837 (0.529–1.324)
TT	93 (23.1)	40 (18.0)	0.700 (0.428–1.145)	0.511 (0.283–0.923)*
AT+TT	307 (76.2)	163 (73.4)	0.864 (0.593–1.258)	0.731 (0.471–1.135)
rs734701				
TT	142 (35.2)	78 (35.1)	1.00 (reference)	1.00 (reference)
TC	183 (45.4)	89 (40.1)	0.885 (0.609–1.288)	1.004 (0.646–1.563)
CC	78 (19.4)	55 (24.8)	1.284 (0.825–1.997)	1.229 (0.720–2.098)
TC+CC	261 (64.8)	144 (64.9)	1.004 (0.713–1.415)	1.078 (0.716–1.621)
rs1823375				
CC	205 (50.9)	107 (48.2)	1.00 (reference)	1.00 (reference)
CG	161 (40.0)	95 (42.8)	1.130 (0.801–1.596)	0.977 (0.644–1.483)
GG	37 (9.1)	20 (9.0)	1.036 (0.573–1.872)	1.248 (0.650–2.399)
CG+GG	198 (49.1)	115 (51.8)	1.113 (0.802–1.544)	1.039 (0.705–1.531)
rs11137037				
AA	201 (49.4)	91 (41.0)	1.00 (reference)	1.00 (reference)
AC	143 (35.5)	89 (40.1)	1.375 (0.957–1.975)	1.754 (1.140–2.699)*
CC	59 (14.6)	42 (18.9)	1.572 (0.986–2.508)	1.719 (0.956–3.093)
AC+CC	202 (50.1)	131 (59.0)	1.432 (1.029–1.995)*	1.731 (1.165–2.573)*
rs12674822				
GG	117 (29.0)	65 (29.3)	1.00 (reference)	1.00 (reference)
GT	177 (43.9)	105 (47.3)	1.068 (0.725–1.573)	1.366 (0.862–2.166)
TT	109 (27.1)	52 (23.4)	0.859 (0.548–1.345)	0.843 (0.489–1.454)
GT+TT	286 (71.0)	157 (70.7)	0.988 (0.689–1.417)	1.167 (0.755–1.803)

The odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated by multiple logistic regression models, and adjusted for age.
* $P < 0.05$.

Table 3. Clinical Parameters of CAD Patients with Different Genotypes at rs12674822

Parameter	GG (n = 65)	GT+TT (n = 157)	*P* Value
	Mean ± SEM	Mean ± SEM	
Triglyceride (mmol/L)	1.71 ± 1.01	1.73 ± 1.17	0.865
Total cholesterol (mmol/L)	3.88 ± 1.07	3.99 ± 1.11	0.480
High-density lipoprotein (mmol/L)	1.02 ± 0.24	1.10 ± 0.28	0.037*
Low-density lipoprotein (mmol/L)	2.18 ± 0.91	2.21 ± 0.91	0.798
Apolipoprotein A1/ B	1.61 ±0.60	1.78 ± 0.77	0.097

Statistical significance was analyzed by independent samples t-test between clinical parameters and the *ANGPT2* rs12674822 polymorphisms.

negatively correlated with CAD, while ApoB positively correlated with CAD.[39] In clinical studies, ApoA1, ApoB, and ApoA1/ApoB have been shown to be closely correlated with ST-segment elevation in the myocardium, thereby providing a basis for diagnosis of disease through which we believe that rs12674822 may be correlated with the risk of CAD.[40] In addition, based on haplotype analysis, we found that individuals bearing the T/C/G haplotype in rs734701, rs11137037, and rs12674822 had a higher risk of CAD, while carriers of the T/A/G haplotype had a lower risk. Thus, haplotype analysis has helped us improve our ability to predict the risk of the disease.[41]

Angpt2 has been analyzed in a number of diseases. Some studies have shown that the 1233A/G locus of *ANGPT2* was associated with type 2 diabetes.[16] There are four SNPs in *ANGPT2* that may be related to neovascularization in retinal diseases.[17] Studies on various *ANGPT2* SNPs demonstrated that Angpt2 significantly correlated with the risk of diseases related to angiogenesis. In a previous report, it was shown that increased levels of Angpt2 were associated with hypertension and diabetes.[42] Moreover, in obese individuals, serum levels of Angpt2 are higher

Table 4. Distribution Frequency of *ANGPT2* Haplotypes in Patients with CAD and Controls

Haplotype Block			Control n = 806 (%)	Patients n = 444 (%)	OR (95% CI)	AOR (95% CI)
rs734701 T/C	rs11137037 A/C	rs12674822 G/T				
T	A	T	273 (33.9)	148 (33.3)	Reference	Reference
C	A	G	187 (23.2)	108 (24.3)	1.065 (0.781-1.453)	1.116 (0.803-1.551)
C	C	G	95 (11.7)	62 (14.0)	1.204 (0.825-1.756)	1.364 (0.911-2.041)
T	C	G	77 (9.5)	60 (13.5)	1.437 (0.971-2.128)	1.574 (1.034-2.396)*
T	C	T	65 (8.1)	32 (7.2)	0.908 (0.569-1.450)	0.946 (0.578-1.549)
T	A	G	52 (6.5)	5 (1.1)	0.177 (0.069-0.454)	0.187 (0.072-0.489)*
C	C	T	24 (3.0)	19 (4.3)	1.460 (0.774-2.754)	1.703 (0.863-3.362)
C	A	T	33 (4.1)	10 (2.3)	0.559 (0.268-1.166)	0.521 (0.241-1.124)

The odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated by multiple logistic regression models, and adjusted for smoking, alcohol consumption, and age. * $P < 0.05$.

compared to healthy controls.[43] It is well known that hypertension, diabetes, and obesity are risk factors of CAD, indicating that there may be an indirect effect for Angpt2 on the incidence of CAD. Therefore, further studies should be conducted that focus on investigating the underlying mechanism of the angiogenesis process in the pathogenesis of CAD.

A limitation of this study is that CAD is caused by multiple genes and factors, and not by a single gene locus. Moreover, the results of SNP analysis are limited by the number of samples available. The reliability of the experimental results can be improved by increasing the sample size, expanding the sample collection range, and exploring a greater number of Angpt2 gene loci to further provide evidence of angiogenesis in the treatment of CAD.

In conclusion, our findings demonstrated that *ANGPT2* SNPs are possibly associated with susceptibility to CAD. By analyzing polymorphisms of ANGPT2 in the population at risk for CAD, we may be able to predict the occurrence of disease and provide interventions. The involvement of *ANGPT2* SNPs in the function of CAD remains unclear; therefore, further studies are warranted to investigate the underlying mechanism.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

This study's protocol was approved by the Ethics Committee of Dongyang People's Hospital and all experiments were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants before study entry. Written consent was provided by the participants and this study was approved by the Ethics Committee and Institutional Review Board of Dongyang People's Hospital (2019-YX-21).

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Authors' Contribution

LL, CmS and WL designed the study and wrote the manuscript. LK, LL, MW and CmS performed the statistical analysis. LL, XG, HS and JP collected the data. The manuscript was approved by all authors.

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