The association of single nucleotide polymorphism rs189037C>T in ATM gene with coronary artery disease in Chinese Han populations

A case control study

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Abstract
Accumulated evidence has indicated that ataxia telangiectasia mutated (ATM) is closely related to atherosclerosis and cardiovascular diseases. So we aimed to examine potential association between a gene variant [single nucleotide polymorphisms (SNPs), i.e., rs189037C>T] in the promoter of ATM gene and coronary artery disease (CAD) in Chinese Han populations.

In this hospital-based case-control study, a total of 1308 participants were divided into CAD group (652 patients) and control group (656 subjects) after performing coronary angiography. The SNP rs189037 was genotyped by using polymerase chain reaction-restriction fragment length polymorphism.

The distribution of rs189037 genotypes and alleles showed a significant difference between CAD and control subjects (genotypes: P = .032; alleles: P = .028). The percentage of the TT genotype is much higher in control group than that in CAD group (22.0% vs 16.3%; P = .009). After adjustment of the major confounding factors, such difference remained significant (OR = 0.62, 95% CI = 0.43–0.89, P = .010). After analyzing data from different groups divided by genders and smoking status respectively, we found that the protective effect of TT genotype on CAD was significant in males (P = .007) and smokers (P = .031). The difference remained statistically significant after multivariate adjustment (adjusted in males: OR = 0.60, 95% CI = 0.38–0.93, P = .022; adjusted in smokers: OR = 0.47, 95% CI = 0.27–0.81, P = .006).

Our study suggests that ATM rs189037 polymorphism is associated with CAD in Chinese Han populations. The TT genotype of rs189037 seems to be associated with a lower risk of CAD and a protective genetic marker of CAD, especially in males and smokers.

Abbreviations: AT = ataxia telangiectasia, ATM = ataxia telangiectasia mutated, CAD = coronary artery disease, CIs = confidence intervals, DM = diabetes mellitus, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, ORs = odds ratios, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, ROS = reactive oxygen species, SNP = single nucleotide polymorphism, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride, UA = uric acid.

Keywords: ataxia telangiectasia mutated, coronary artery disease, rs189037, single nucleotide polymorphism
1. Introduction

Coronary artery disease (CAD) is the main cause of morbidity and mortality worldwide and continues to be the leading cause of disability and increased health-care expense in most societies.[1] CAD is a multifactorial disorder determined by complex interactions between genetic predisposition and various environmental factors.[2,3] Researchers estimate that the genetic factors may account for 40% to 60% in the occurrence and development of CAD.[4] Despite years of research, the genetic susceptibility of CAD has not been fully explained.

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder[5] manifesting cerebellar ataxia, oculocutaneous telangiectasia, immune deficiency, growth retardation, premature aging, insulin resistance, and cancer susceptibility.[6,7] Patients with AT lack functioning ataxia telangiectasia mutated protein (ATM), a member of the phosphatidylinositol 3-kinase family.[8,9] Evidence has indicated that AT is not only due to a defect in DNA-damage repair pathways and is also partly an oxidative stress sensor.[6,10,11] Researchers have demonstrated that ATM plays a critical role in DNA damage- repair pathways and is also partly an oxidative stress sensor.[6,12-15] ATM is immediately activated by autophosphorylation at Ser1981,[16] and it is in turn rapidly phosphorylates a number of substrates to coordinate their repairs in response to DNA damage caused by either endogenous or exogenous factors.[16-20] Moreover, ATM is activated by oxidants like H2O2.[21] When ATM is deficient, its ability to repair DNA damage will be weakened. And, ATM-deficient cells are in a constant state of oxidative stress.[22] As chronic oxidative stress and DNA damage are involved in the pathogenesis of cardiovascular disease and atherosclerosis, and ATM is a sensor of DNA damage and oxidative stress.[12] So ATM deficiency will lead to cell arrest, apoptosis, and mitochondrial dysfunction, which in turn results in hyperlipidemia, promoting atherosclerosis and the metabolic syndrome.[23] Currently, there is indirect evidence that ATM deficiency may be involved in occurrence and development of CAD. One study demonstrates that ATM heterozygosity has an increased risk of developing atherosclerosis-related cardiovascular diseases and dying from ischemic heart disease in humans.[24] AT patients have increased cholesterol and triglyceride levels,[25] which are 2 major risk factors for atherosclerosis. Furthermore, in apolipoprotein E (apoE) null mice, ATM haploinsufficiency accelerates diet-induced atherosclerotic lesions.[26]

A number of studies have reported associations of single nucleotide polymorphisms (SNPs) of the ATM gene with increased risk for several cancers, such as breast cancer, lung cancer, thyroid carcinoma, pancreatic cancer, and nasopharyngeal carcinoma.[27-31] However, to the best of our knowledge, a limited number of studies have addressed the relationship between ATM gene polymorphism and CAD.[32,33] Thus, in the present study, we performed a case-control study to analyze the potential association between the SNP rs189037C>T, located in the promoter region of the ATM gene, and CAD in Chinese Han people, which may provide new insights into the genetic mechanisms of CAD.

2. Materials and methods

2.1. Study subjects

In the case-control study, we consecutively recruited 1372 patients who were hospitalized for chest pain from 3 hospitals in Sichuan province, including West China Hospital of Sichuan University (Chengdu, China), the Third People’s Hospital (Chengdu, China), and the People’s Hospital of Suiying (Suiying, China) between October 2011 and August 2013. All participants were Han Chinese with no blood relationship and all of them underwent coronary angiography. They were assigned to either CAD group or control group based on their coronary angiogram. The coronary angiogram of each patient was interpreted by 2 experienced interventional cardiologists. The CAD group was defined as the presence of at least one significant coronary artery stenosis of ≥50% luminal diameter shown on coronary angiogram. The control group did not show coronary artery stenosis. Control subjects did not have any relevant regional wall motion abnormalities and cardiomyopathy detected by echocardiography, electrocardiographic signs of CAD, or a history of CAD. All patients with congenital heart diseases, valvular diseases, malignant tumors, or severe illness limiting life expectancy were excluded. After all, the study enrolled a total of 652 patients with CAD and 636 patients without CAD. The study was conducted in agreement with the basic principles of the Helsinki Declaration and was approved by the Institutional Review Boards at West China Hospital of Sichuan University. Written informed consent was obtained from all participants and their legal proxies.

2.2. Genotyping

Genomic DNA was isolated from whole blood using Blood Genomic extraction kits (DP319) from TIANGEN (Beijing, China) and performed according to standard procedures. SNP rs189037 of ATM gene was genotyped by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as previously described.[34] Forward primer was 5'-GCTGCTTGGCCTTGGCCT-3' and reverse primer was 5'-CATGGCATTTTGGGCCTGCG-3' (TaKaRa, Dalian, China). The PCR reaction was performed in 25 μL total volume containing 2 μL of genomic DNA. The PCR procedures were the following: 3 minutes at 94°C, followed by 30 cycles of 30 seconds at 94°C, 30 seconds at 55°C, and 30 seconds at 72°C, then 5 minutes at 72°C. The amplification products (287 bp) were visualized on a 2% agarose gel by staining with ethidium bromide (Fig. 1A). Computer software analysis showed that the ATM gene promoter region contains 2 restriction sites of Sac II restriction enzyme, and the SNP rs189037 is present at nucleotide CATGCGATTGGCGGTCTGG-3 at nucleotide 189037C>T, located in the promoter region of the ATM gene, and CAD in Chinese Han people, which may provide new insights into the genetic mechanisms of CAD.
determined using standard laboratory techniques performed by technicians in the biochemistry laboratories of West China Hospital, the Third People’s Hospital of Chengdu and the People’s Hospital of Suining. Because the number of ex-smoker was limited, we combined ex-smoker and current smoker into a single group (i.e., with a history of smoking). The diagnosis of hypertension was made if patients were under treatment of antihypertensive medication or the mean blood pressure of 3 measurements was >140/90 mm Hg. DM was defined on the basis of the American Diabetes Association. In addition, if patients were under treatment of anti-diabetic medication or fasting glucose levels were >7.0 mmol/L, they were also considered DM.

2.4. Statistical analyses
All statistical analyses were performed using SPSS software (version 19.0, SPSS, Inc., Chicago, IL). Hardy–Weinberg equilibrium of the genotype frequencies in both groups were tested by the Chi-square test. Chi-square test was used to analyze the differences in categorical variables; and continuous data were analyzed by the unpaired Student t test (for variables with normal distribution) or Mann–Whitney U test (for variables with nonnormal distribution). Genotypes and alleles frequencies were compared between the 2 groups using Chi-square test. Unconditional multiple logistic regression analyses were performed to estimate unadjusted and adjusted odds ratios (ORs), as well as 95% confidence intervals (CIs). Comparisons of each of the 3 genotypes were made with a Type 1 error at 0.017 for each comparison (adjusted for 3 primary comparisons). Adjusted ORs and P values were corrected for the risk factors of CAD, including gender, age, FPG, UA, blood lipid levels, cigarette smoking status, histories of DM, and hypertension. Statistical significance was determined by a P-value < .05. P values were 2-sided.

3. Results
Among 1308 patients, 867 males and 441 females, the mean age was 66.36 ± 9.65 years (range 24–92 years). Of these, 652 patients with CAD (525 males and 127 females, mean age 65.08 ± 10.05 years, range 34–92 years), and 656 patients without CAD (342 males and 314 females, mean age 67.63 ± 9.10 years, range 24–90 years). The basic demographic and clinical characteristics of the study participants are presented in Table 1. There was a significant difference in the aforementioned variables except LDL-C between the patient and control groups.

The distributions of genotypes frequencies in CAD patients and control subjects were compatible with Hardy–Weinberg equilibrium (P = .69 for the CAD group; P = .08 for the control group) (Table S1, http://links.lww.com/MD/C90). Table 2 demonstrates the genotypes and alleles distribution of SNP rs189037 and its associations with CAD in these Chinese Han populations. In the total population, the frequencies of the CC, CT, and TT genotypes of SNP rs189037 were 34.7%, 49.0%, and 16.3% in cases and 31.9%, 46.1%, 22.0% in controls, respectively. The frequency of the T allele was 40.8% in the CAD group and 45.1% in control group. We found significant differences in the frequencies of genotypes and alleles of the SNP rs189037 between patients with and without CAD (genotypes: P = .032; alleles: P = .028). And TT genotype carrier state was more frequent in controls in comparison to the CAD group (22.0% vs 16.3%, P = .009). After adjusted for covariates associated with CAD, including age, gender, FPG, UA, TG, TC, LDL-C, HDL-C and histories of smoking, DM, and hypertension, a significantly decreased risk of CAD was observed among the participants with TT homozygote (adjusted OR = 0.62, 95% CI = 0.43–0.89, P = .010), compared with the C carriers (CC+CT).
Moreover, similar significant association was observed in male populations. Gender stratification revealed that there was an association between genotypes and alleles of SNP rs189037 and CAD (genotypes: \( P = .007 \); alleles: \( P = .011 \)) in male patients.

Compared with those carrying CC and CT genotypes, males with TT genotype exhibited a significant decrease in terms of the incidence of CAD (unadjusted: OR = 0.58, 95% CI = 0.41–0.81, \( P = .002 \); adjusted: OR = 0.60, 95% CI = 0.38–0.93, \( P = .022 \)).
interactions with such factors of CAD as age, gender, FPG, UA, and smoking lifestyle for CAD susceptibility.

There may be an interaction between the SNP rs189037 genotype and smoking lifestyle for CAD susceptibility. The SNP rs189037 genotypes and alleles were tested for interactions with such factors of CAD as age, gender, FPG, UA, blood lipid profile, smoking, DM, and hypertension but no any notable interaction was identified (Table S3, http://links.lww.com/MD/C90).

We found that TT homozygote of SNP rs189037 is a protective factor of CAD in Chinese Han males, while no such protective effect was found in the female subgroups (Table S2, http://links.lww.com/MD/C90).

The present study showed that the genotype and allele frequencies of SNP rs189037 have significant differences between CAD and control groups, suggesting that the polymorphism rs189037 in the promoter region of ATM gene is significantly associated with CAD in Chinese Han populations. Moreover, carriers of the TT genotype were more frequent in control group than in CAD group. This indicates an association between TT genotype and a decreased risk for CAD, suggesting that this polymorphism could be a genetic preventive factor for CAD, which is consistent with the study conducted by Li et al.[32] They recruited 366 patients with significant coronary stenosis and 196 patients without significant coronary stenosis, and concluded that the TT genotype of ATM rs189037 is associated with less severe coronary stenosis.[32] Our study is the first demonstrating a significant association of SNP rs189037 with CAD in male subgroups, but not for females. The different results between males and females might be explained by the following factors. First, it is possible that estrogen plays a protective effect. Mounting evidence has shown that premenopausal women have a lower risk of CAD occurrence compared with men of the same age, while the increased risk begins after menopause.[40,41] This means that estrogen plays a protective role against the development of CAD. Thus, it is easy to show the positive effect in such a higher risk population. Second, the number of males is approximately equal to four times that of females in CAD group, so the small sample size of females might be another reason.

Considering smoking status, to the best of our knowledge, this is the first study evaluating the interaction of ATM rs189037 polymorphism with CAD from 2 groups stratified by smoking status. As for the observation of the joint effects of genetic (the genotypes of SNP rs189037) and lifestyle (a history of smoking) factors on CAD risk, we found that the frequency of those patients with TT genotype was significantly higher in control group than that in the CAD group (22.9% and 15.1%, respectively) among smokers. However, there was no such difference for the nonsmokers. The specific mechanisms about the different results between smokers and nonsmokers are not clear. It might be associated with cigarette smoke-oxidative stress.

We found that TT homozygote of SNP rs189037 is a preventive factor for the occurrence of CAD, but the exact mechanism is unknown. SNP rs189037 is located in the promoter

| Genotypes and alleles distribution of ATM rs189037 between coronary artery disease (CAD) and control groups in smokers. | CAD group (n=425, %) | Control group (n=258, %) | P |
|---|---|---|---|
| CC | 145 (34.1) | 85 (32.9) | .031† |
| CT | 216 (50.9) | 114 (44.2) | .042† |
| TT | 64 (15.1) | 50 (22.9) | .010‡ |
| Dominant model | | | .753 |
| CC | 145 (34.1) | 85 (32.9) | .031† |
| CT + TT | 280 (65.9) | 173 (67.1) | .010‡ |
| Recessive model | | | .989 |
| TT | 64 (15.1) | 50 (25.3) | .010‡ |
| CC + CT | 361 (84.9) | 199 (77.1) | .010‡ |
| Alleles | | | .103 |
| C | 506 (59.5) | 284 (55.0) | .103 |
| T | 344 (40.5) | 232 (45.0) | .103 |

Adjusted OR and 95% CI

TC vs others†

| Unadjusted | 0.95 (0.68–1.32) | .753 |
| Adjusted | 0.67 (0.35–1.36) | .535 |

TT vs others†

| Unadjusted | 1.31 (0.96–1.78) | .093 |
| Adjusted | 1.40 (0.91–2.16) | .125 |

Adjusted α ORs and P values were corrected for age, gender, FPG, UA, TG, HDL-C, LDL-C, history of DM, and hypertension.

ATM = ataxia telangiectasia mutated, CI = confidence interval, DM = diabetes mellitus, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglycerides, UA = uric acid.

† CT and TT.

‡ CC and TT.

§ CC and CT.

P <.05.

P <.017.

4. Discussion

CAD is one of the major health problems in most societies, which is the consequence of atherosclerotic plaques formation in coronary arteries.[36,37] DNA damage and oxidative stress could contribute to the development of atherosclerosis.[112] ATM is a major sensor of DNA damage and oxidative stress.[112]

Therefore, ATM deficiency causes the failure of DNA repair and increases of ROS production that further result in metabolic disorder and atherosclerosis. Schiekofer et al.[131] reported that the rs11212617 variant near the ATM gene is associated with CAD in the German men. Li et al.[32] found that the rs189037 polymorphism in the promoter of ATM gene is connected with coronary stenosis in Chinese populations. Our previous study suggested that ATM rs189037 polymorphism is related to type 2 diabetes mellitus (T2DM) in Chinese old people.[131] And CAD is a common complication of T2DM in which plaque formation narrows the coronary arteries. We conducted a case-control study to explore the relationship between the polymorphism rs189037 of ATM gene and CAD in Chinese Han people. We found that genetic factor, ATM rs189037 polymorphism, plays a crucial role in the CAD development.

The present study showed that the genotype and allele frequencies of SNP rs189037 and CAD control. COMPARISON WITH CAD GROUP.

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region (noncoding region) of ATM gene, which cannot directly encode the amino acids of ATM protein. It is possible that ATM rs189037 polymorphism is involved in RNA splicing and the stability of RNA and thereby affecting the expression level of ATM protein.[32] People carrying TT genotype in their genome may have a higher capacity in DNA double-strand repair, leading to a lower susceptibility for CAD development. To illuminate how this polymorphism regulates the mRNA expression level of ATM gene. Chen et al[43] observed a transcription factor AP-2a binding site around the SNP rs189037 and demonstrated that AP-2a suppresses ATM gene expression by specifically binding to the SNP rs189037 site. Among the genotypes, ATM mRNA expression level is higher in TT homozygote than in CC or CT genotype[43] which is in line with Li et al’s study.[32] These studies indicate that higher ATM expression level (like TT genotype of sclerosis. Mercer et al[23] reported that accelerated atherosclerosis Activation of ATM with low-dose chloroquine decreases atherogenesis. It is critically binding to a lower susceptibility for CAD development. To illuminate the effect of high expression of ATM gene on atherogenesis. It is reported that the ATM deficiency worsens the features of metabolic syndrome including hypertension, hyperglycemia, obesity, and dyslipidemia, and causes insulin resistance and DM[26,44,45]. However, no association was found between SNP rs189037 and DM, hypertension or lipidprotein levels in this study. A major strength of this study is that it was performed in multicenter (participants from 3 hospitals) and a large number of individuals, and first analyzed the relationship between ATM rs189037 polymorphism and CAD from different groups stratified by gender and smoking status. Conversely, this study has several limitations. First, this is a cross-sectional study. Second, all of the patients in our study are Han Chinese. Third, the study exists some potential confounders, such as nutrition status and different medications that patients took. However, after adjustment for the conventional CAD risk factors in multivariate logistic regression, the same results still remained. Fourth, there is no significant association between genotypes and alleles distribution of ATM rs189037 and CAD in different centers, which is incompatible with our results in the whole sample, suggesting the association was not robust. Fifth, our study lacked the association between rs189037 polymorphism and CAD in the protein level. So further studies are needed to confirm them. Meanwhile, we will conduct multietnic studies to validate our findings. Long-term follow-up studies between the SNP rs189037 in the ATM gene and CAD are also warranted.

5. Conclusions
In conclusion, our study suggests that ATM rs189037 polymorphism is associated with CAD in Chinese Han populations. The TT genotype of rs189037 appears to lower CAD susceptibility and may serve as a new protective genetic marker, especially in males and smokers.

Acknowledgments
The authors thank the staff of the Department of Cardiology, West China Hospital, Sichuan University, the Third People’s Hospital of Chengdu, the People’s Hospital of Sining and Laboratory of Stem Cell Biology, State Key Laboratory of Biotherapy, Sichuan University and all participants (as well as their legal proxies) for their great contribution, especially the corresponding investigators of the Third People’s Hospital of Chengdu (Dr. Han Wang) and the People’s Hospital of Sining (Dr. Dahong Gao). We also thank Dr. Hui Lan who is an epidemiologist for the guidance of statistics. Dr. Shizhang Ling critically read the manuscript and edited the language. We appreciate their help.

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