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ORIGINAL ARTICLE – OPEN ACCESS

Association of Angiotensin II Type 1 Receptor A1166C Gene Polymorphisms with Coronary Artery Disease in Thrace Region of Turkey

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ABSTRACT

Objective: Although the risk factors for coronary artery disease (CAD) are well established, a significant gap still exists in understanding the pathology of atherosclerotic heart disease evolving without conventional risk factors. Therefore, genetic factors are considered to play a significant role in this setting. The present study aimed to assess the relationship between angiotensin 2 type 1 receptor (AT1R) A1166C gene polymorphism and CAD.

Materials and Methods: Patients with documented CAD (n=121) were compared with controls with normal coronary arteries (n=121). CAD was diagnosed using a coronary angiography. The median age of participants was 59±12 years with an equal sex distribution. A comparison between the two groups with regard to the AT1R A1166C gene polymorphism was made through the amplification of DNA using polymerase chain reaction.

Results: This study demonstrated that adenine-adenine and cytosine-cytosine (CC) genotypes were more frequent, yet adenine-cytosine genotype was less frequent among patients with CAD compared with controls [p=0.003), 95% confidence interval (CI)]. The AT1R A1166C gene polymorphism along with the CC genotype and C allele was found to be associated with CAD. Further, gender, hypertension, family history, age, and low levels of serum high-density lipoprotein also had a significant relationship with AT1R A1166C gene polymorphism.

Conclusion: The present study suggested AT1R A1166C gene polymorphism, CC genotype, and C allele as potential risk factors for atherosclerotic CAD. Patients harboring these genetic variants should be under close supervision for the development of CAD.

Keywords: A1166C, angiotensin, coronary artery disease, gene polymorphism

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INTRODUCTION

In the clinical setting, even though risk factors for coronary artery disease (CAD) are well established, a significant gap still exists in the conception of pathological insights regarding atherosclerotic heart disease evolving without conventional risk factors. Atherosclerotic process is well known to be mediated through genetic as well as environmental factors. In the previous studies, multiple genetic locations associated with CAD were identified (1). Detection of gene polymorphisms and their roles in the development of CAD may help better comprehend the fundamental metabolic pathways and; hence pathophysiology of the disease. Recent studies have identified chromosomal mutations in which gene polymorphism has been shown to result in CAD (2–4). One such mutation was reported to be angiotensin II type 1 receptor (AT1R) adenine (A) 1166 cytosine (C) gene polymorphism. This polymorphism was the one of most studied for CAD.

Renin–angiotensin system (RAS) primarily constitutes angiotensinogen, renin, angiotensin I (AT-I), angiotensin-converting enzyme (ACE), AT-II along with AT-II receptor subtypes 1, 2, 3, and 4 (AT1R, AT2R, AT3R, and AT4R). In recent studies, various genes have been identified in RAS (5, 6). Polymorphisms in these genes have been shown to play a role in the pathophysiology of CAD possibly through potent vasoconstrictive and other multifaceted effects of AT-II. Regarding AT-II receptor subtypes, AT1R A1166C gene polymorphism has been widely studied and has been suggested to be associated with CAD (7). AT1R gene is located on the 3. chromosome (3q21-q25). It is 45.123 kb long and comprises five exons with four introns. AT1R gene polymorphism appears to be a single-nucleotide polymorphism (SNP) characterized by the transversion of adenine/cytosine at nucleotide 1166 (8). This situation theoretically does not have an impact on the coding process of the AT1R protein. However, it might still have the potential to influence the stability of the gene mRNA expression.

As a striking example of RAS impact on atherosclerosis, a recent study has demonstrated increased levels of ACE and AT-II expression in various vascular lesions, particularly in regions with a higher risk of atherosclerotic plaque rupture (9). Within this context, the present study aimed to make a comparison between patients with CAD and with normal coronary arteries (detected on coronary angiogram [CAG]) in terms of AT1R A1166C gene polymorphism.

MATERIALS and METHODS

Patient Selection

The study was planned to comprise a population of 248 patients who had undergone CAG between 2013 and 2014 at the Department of Cardiology in Trakya University. Patients suggestive of having CAD and without previous diagnoses of CAD or malignancy were recruited as study subjects. Six of the patients were excluded based on the following exclusion criteria: Presence of conditions including chronic renal failure, liver disease, migraine, epilepsy, multiple sclerosis, cerebrovascular event with neurological sequelea, malignancy, or refusal to participate in the study. Institutional Ethical Committee approval and written informed consent of the patients were obtained.

In CAG, a luminal stenosis of >50% in left anterior descending, circumflex, right coronary, and left main coronary arteries was defined as critical stenosis (10, 11). To evaluate the extent of CAD, Syntax scores were also calculated Table 1. Patients with normal coronary arteries were assigned as the control group.

DNA Isolation and Genotyping

Blood samples were drawn after a 12-h fasting. Hemogram was calculated using a Sysmex device, and biochemical analyses were implemented with Architect c16000 (Abbott Core Laboratory, USA). DNA was isolated from the blood samples using a high-purity polymerase chain reaction (PCR) template kit from Roche Company (K11796828001 Roche, Germany). DNA was separated using agarose gel electrophoresis and quantified using an ultraviolet (UV) spectrophotometer device (Shimadzu UV-1280). DNA samples were kept at –20°C. After isolation, DNA was amplified using PCR. The sequences used in PCR were as follows: A1166C F: 5′-GCAGCACTTCACTACCAAATGGGC-3′; A1166C R: 5′-CAGGACAAAAGCAGGCTAGGGAGA-3′.

PCR conditions were as follows: 5 min at 94°C, 1 min at 94°C, 1 min at 55°C, 1 min at 72°C, and 7 min at 72°C; 35 cycles of these conditions were applied. The restriction enzyme HaeIII (BsuRI) intersects where the sequence of 5′-…..G G↓C C….-3′ is present (5′-…….G G↓C C……..-3′ and 3′-…….C C↑G G……..-5′). The A1166C gene polymorphism was determined as a result of cutting PCR products with HaeIII (BsuRI) restriction enzyme for 30 min at 37°C, executing in 3% agarose gel and examining them under UV light after the PCR stage. In the AA genotype, no cut is observed and a single band of 255 bp is formed behind. In the AC genotype, a single allele is cut. Three bands of 255 bp, 231 bp, and 24 bp are formed. In the CC genotype, two alleles are cut and two bands of 231 bp and 24 bp are formed (Fig. 1).

Statistical Analysis

As a case–control study, the moderate effect size (d) 0.25 recommended by Cohen (1988) was determined for power analysis performed in the light of the information obtained from the literature. According to the results of the power analysis, it was decided to take at least 120 observations in both groups at the level of 80% power and 5% significance. Hence, 121 patients diagnosed with CAD were enrolled in the CAD group, and 121 participants with normal coronary arteries were enrolled in the control group. The results were evaluated using the Statistical Package for the Social Sciences (SPSS) package program.

Table 1. Relationship between AT1R A1166C genotypes and coronary artery disease severity

Genotypes	n	Syntax score Mean±SD	p
AA	71	18.00±9.21	
AC	42	19.74±9.54	0.689
CC	8	19.25±10.99	
Total	121	18.68±9.40	

AA: Adenine-adenine; AC: Adenine-cytosine; CC: Cytosine-cytosine; AT1R: Angiotensin II type 1 receptor; A1166C: Adenine 1166 cytosine; n: Patient number; SD: Standard deviation

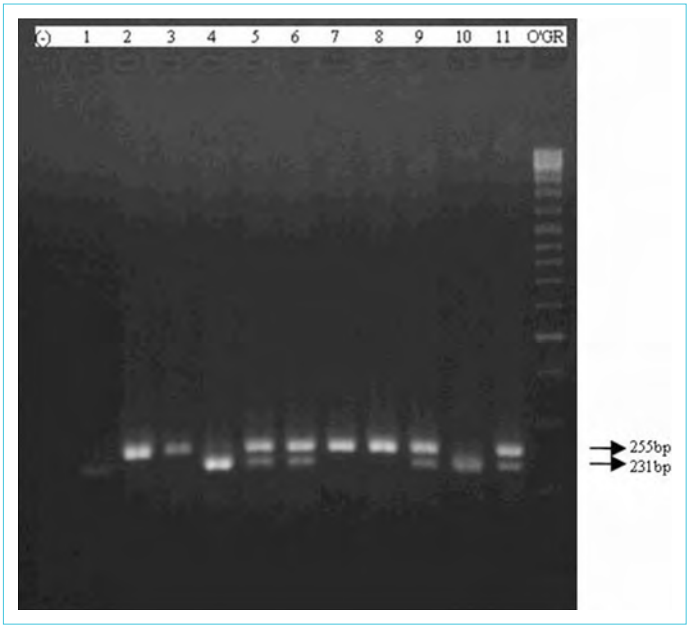

Figure 1. Agarose gel image stained with EtBr showing ATIR A1166C polymorphism. AA (255 bp: 2, 3, 7, and 8), AC (255 bp, 231 bp, and 24 bp) (do not appear): (5, 6, 9, and 11) and CC (231 bp and 24 bp) (do not appear): (1, 4, and 0), O'GR; 100 bp DNA marker (O'GeneRuler 100 bp DNA ladder Fermentas life scienes)

Continuous variables were expressed as mean±standard deviation and median and minimum-maximum and categorical variables expressed as frequency and percentage. The Kolmogorov–Smirnov test was used as a normality test for binary comparison of continuous variables. For two independent group comparisons, the Student t test was used for parameters with a normal distribution, whereas the non-parametric Mann–Whitney U-test was used for parameters with no normal distribution. Kruskal–Wallis test was used to compare more than two independent groups. The Chi-square test and Fisher's exact test were used for comparing categorical variables. The binary univariate and multiple logistic regression analysis was used to explore the risk factors (both known risk factors and gene polymorphisms) for CAD. A stepwise approach was used to detect independent risk factors in binary multiple logistic regression analysis. $P<0.05$ was accepted as the statistical significance limit.

RESULTS

The genotype frequencies observed for the study groups were analyzed using the Hardy–Weinberg calculation (12). The Pearson Chi-square test was used to evaluate the compatibility to Hardy–Weinberg distributions and did not exhibit any statistical difference in our study population might. The demographic characteristics of participants are presented in Table 2. No statistically significant difference in variables including body mass index, diabetes mellitus, smoking and serum levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) was found between the study groups. However, variables including age, gender, hypertension (HT), high-density lipoprotein (HDL), and a family history of CAD significantly differed between the groups.

Adenine-adenine (AA) and cytosine-cytosine (CC) genotypes were more frequent in patients with CAD than those in the control group (p=0.003) (Table 3). Similarly, no significant relationship was observed between AT1R A1166C gene polymorphism and CAD severity (p=0.689) (Table 1).

The binary univariate logistic regression analysis was performed for each independent risk factor separately. Then, binary multiple logistic regression analysis was performed to select independent risk factors. As a result of binary multiple logistic regression analysis, male gender (OR=5.008, 95% confidence interval [CI]: 2.492–10.064), HT (OR=2.685, 95% CI: 1.254–5.748), family history (OR=3.237, 95% CI: 1.455–7.197), and age (OR=1.080, 95% CI: 1.046-1.115) found to be significantly associated with CAD. On the other hand, high level of HDL shows a protective effect against CAD (OR=0.951, 95% CI: 0.925–0.978). There were no significant associations between AT1R A1166C gene polymorphisms and CAD risk factors. The binary univariate and multiple logistic regression analyses result summarized in Table 4.

Table 2. Baseline demographic parameters of the study population

Variables	Control groups (n=121)	CAD groups (n=121)	p
Age	54.32±10.77	63.76±12.15	<0.001
Gender			<0.001
Female	77 (63.6%)	44 (36.3%)	
Male	44 (36.3%)	77 (63.6%)	
BMI	26.76±3.84	26.51±3.34	0.594
HT	60 (49.6%)	95 (78.5%)	<0.001
DM	26 (21.5%)	37 (30.6%)	0.107
Smoking	47 (38.8%)	59 (48.8%)	0.120
Family history	16 (13.2%)	35 (28.6%)	0.003
Total cholesterol	184.21±39.69	175.80±50.17	0.149
Triglyceride	123 (39–487)	126 (47–497)	0.608
HDL	48.40 (21–111)	38.80 (13.7–80)	<0.001
LDL	117.12±36.11	112.74±43.89	0.397

BMI: Body mass index; CAD: Coronary artery disease; HT: Hypertension; DM: Diabetes mellitus; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; n: Patient number. Descriptives expressed as mean±standard deviation, median (minimum-maximum) and frequency (percentage)

Table 3. Angiotensin II type 1 A1166C genotypes between study groups

Genotypes	Groups				p
	CAD		Control		
	n	%	n	%	
AA	71	52.6	64	47.4	
AC	42	42.4	57	57.6	0.003
CC	8	100	0	0.0	

A1166C: Adenine 1166 cytosine; AA: Adenine-adenine; AC: Adenine-cytosine; CC: Cytosine-cytosine; CAD: Coronary artery disease

DISCUSSION

To date, SNPs have been the most frequently encountered genetic polymorphisms in clinical practice. However, it should be borne in mind that SNPs might not invariably elicit disease. On the other hand, they have the potential to help determine the likelihood of a specific disease in a given person. In general, gene polymorphisms appear to be associated with ethnicity along with genetic and environmental factors (13). The potential explanation to the issue of why Hardy-Weinberg analysis did not exhibit any statistical difference in our study population might, in part, be based on the consecutive random selection of the spouses by the individuals and impact of migration to the society.

The present study has clearly demonstrated that the AA genotype appeared to be the commonest variant in both groups. On the other hand, CC genotype was observed exclusively in the CAD group and was associated with the presence of CAD (Table 3). These results also uncovered a significant association of AT1R polymorphism with the C allele in patients with CAD potentially implying that C allele might, in part, play a role in the etiopathogenesis of CAD. However, no statistical significance in genotypes was found in the regression analysis (Table 4). In a previous study, Berge et al. (14) demonstrated a low risk of CAD in Norwegian males. However, myocardial infarction was closely associated with AT1R CC genotype polymorphism exclusively in male patients potentially suggesting the impacts of alcohol consumption and dietary habits in the northern countries. Similarly, the present study has also demonstrated a statistically significant association of male gender with AT1R genotypes and CAD. In another study, Feng et al. (15) demonstrated a significant association between C allele and AMI risk in their meta-analysis comprising approximately 7000 patients and controls for A1166C gene polymorphism. However, CC genotype was not associated with AMI risk for overall population. This finding is quite contradictory to our findings. In general, these results might be in close correlation with CAD risk factors that are well known to significantly vary according to the region (16–18). Sekuri et al. (19) reported a relation of premature CAD with AA genotype. However, only CC genotype was found to be statistically significant in terms of CAD evolution along with no statistically significant relationship between AA genotype and CAD in this study. On the other hand, Nakauchi

Table 4. Binary univariate and multiple logistic regression analysis between coronary artery disease risk factors and AT1R A1166C gene polymorphisms

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Gender (male)	3.062 (1.864–5.171)	<0.001	5.008 (2.492–10.064)	<0.001
A1166C (AC)	0.15 (0.01–10.128)	0.999		
A1166C (CC)	0.664 (0.394–1.120)	0.125		
HT	3.175 (2.119–6.512)	<0.001	2.685 (1.254–5.748)	<0.001
DM	1.609 (0.900–2.878)	0.109		
Smoking	1.498 (0.899–2.497)	0.121		
Family history	2.671 (1.385–5.150)	0.003	3.237 (1.455–7.197)	0.004
Age	1.073 (1.047–1.100)	<0.001	1.080 (1.046–1.115)	<0.001
Triglyceride	1.001 (0.998–1.004)	0.592		
Total cholesterol	0.996 (0.990–1.002)	0.150		
HDL	0.946 (0.924–0.969)	<0.001	0.951 (0.925–0.978)	<0.001
LDL	0.997 (0.991–1.004)	0.396		
BMI	0.981 (0.914–1.053)	0.592		

AT1R: Angiotensin II type 1 receptor; A1166C: Adenine 1166 cytosine; AC: Adenine-cytosine; CC: Cytosine-cytosine; BMI: Body mass index; DM: Diabetes mellitus; HDL: High-density lipoprotein; HT: Hypertension; LDL: Low-density lipoprotein; OR: Odds ratio; CI: Confidence interval

et al. (20) demonstrated a significant association of Adenine-cytosine (AC) genotype (in comparison to AA genotype) with high prevalence of CAD (along with null association of the CC genotype). Of note, C allele was also found to be associated with CAD (20). In a similar manner to our study, Araujo et al. (21) reported no significant association of AT1R genotypes with AMI incidence and severity of CAD. On the other hand, Freitas et al. (22) previously suggested significant associations of ACE11860 GG and ACE I/D DD genotypes with CAD. Interestingly, in a previous study by Gruchala et al., (23) co-existing characteristics including ventricular dimensions and performance in the setting of significant CAD were demonstrated to have no significant association with ACE I/D and AT1R A1166C polymorphisms. However, our study was not designed to investigate ventricular characteristics, and hence we cannot currently elaborate on this association based on our findings. In another study by Canavy et al. (24), the presence of C allele was found to be significantly associated with AMI and vasospastic angina. However, as we exclusively focused on angiographically determined CAD, we cannot further speculate on this issue (24). Interestingly, certain CAD risk factors including HT were also previously suggested to be associated with G-6A and M235T polymorphisms of the angiotensinogen gene (25). Since HT has been a well-known risk factor for CAD, these findings (25) might also have important implications in the setting of CAD evolution as well. In a previous study from our country, Berdeli et al. (26) have demonstrated significant contributory roles of certain RAS gene polymorphisms including AGT T/M, AT1R T/C, and ACE I/D along with the endothelial nitric-oxide gene polymorphism Glu-298Asp in the evolution of premature CAD. Taken together, there exist various studies with different designs and results in the literature. However, studies with a larger sample size are still warranted to validate implications of RAS gene polymorphisms in the setting of CAD evolution, and draw firm conclusions (27). Importantly, the association of CC genotype with CAD in the current study might potentially be ascribed to ethnic and environmental factors on genetic polymorphisms. Of note, participants of the study were recruited from the Thrace region of Turkey. Over many centuries, this region had served as a homeland for various civilizations whose ethnic origin dates back to B.C suggesting its variegated ethnic roots. Moreover, smoking and salt consumptions are more prevalent in the general population of Thrace. Accordingly, the prevalence of HT was found to be higher in Thrace compared with other regions of Turkey (16, 17). Certain genotypes of ACE DD, AGT TT, and AT1R CC are well known to increase the propensity of an individual for premature CAD. Within this context, the association of these risky RAS genotypes with CAD risk factors was reported to augment the susceptibility for premature CAD development in an Egyptian population (18). Similarly, the present study has also demonstrated that the relationship of AT1R CC genotype with certain risk factors including gender, family history of CAD, age, and low HDL (<40 mg/dL) was statistically significant and was of crucial significance in terms of susceptibility to CAD evolution. On the other hand, DM, HT, smoking, and family history of CAD were found to be more frequent in the CAD group. However, among these, the association of HT and family history of CAD with AT1R gene polymorphisms exclusively remained statistically significant in the binary logistic regression analysis. This was evaluated in accordance with the ethnic origin and environmental factors (salt consumption, etc.) of the Thrace region previously reported. It was also previously suggested that the C allele in AT1R A1166C gene polymorphisms increased the risk of CAD evolution in patients with hypercholesterolemia (elevation of total and LDL cholesterol) and in smokers (28, 29). Besides a variety of largely acquired factors including abdominal obesity, and low physical activity genetic and ethnic differences might also be associated with low HDL levels. According to a Turkish study on

adults with a 12-year follow-up, mean HDL cholesterol values were 20% lower than those in the Western population in both sexes mostly suggesting ethnic background of HDL metabolism (30). The mean total cholesterol and LDL levels were found to be slightly higher in the control group (and statistically insignificant) possibly due to the genetic factors and the presence of patients receiving statin therapy in the CAD group. In summary, it seems highly plausible that polymorphisms in RAS genes, besides their possible direct impact on atherogenesis, might elicit CAD evolution through their potential effects on CAD risk factors.

This study had several limitations. First; vasospastic angina or endothelial dysfunction was not evaluated in those with apparently normal coronary arteries. In other terms, normal CAG findings might not fully exclude an existing CAD suggesting vasospastic angina, microvascular dysfunction, etc., as important etiologies of CAD as well. Second; even though several confounders were adjusted, the potential impact of certain factors including gender could not be completely eliminated largely due to the obligation of recruiting all consecutive patients in an effort to mirror a real life data. In addition, premature coronary atherosclerosis and non-critical CAD were not evaluated in the current study.

CONCLUSIONS

CAD has been the most important etiology of mortality and morbidity worldwide suggesting the need for early diagnosis and proper treatment strategies along with identification of risk factors and underlying mechanisms as well. In the recent years, gene polymorphisms have been suggested to be associated with CAD evolution as part of multiple and complex mechanisms of atherogenesis. Of note, the relationship between AT1R gene polymorphism and CAD was found to be of particular relevance in this setting. In the current report, we were able to demonstrate a significant association of AT1R A1166C gene CC genotypes and C allele with CAD evolution (but not CAD severity) and certain risk factors including age, HT, family history of CAD, male sex, and low HDL levels. To the best of our knowledge, the present study is the first one from the Thrace region in our country. However, our findings should be substantiated through future studies on this issue.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – GT, NS; Design – GT, NS, YA; Supervision – GT, YA, NS; Materials – GT, OP, FÖ; Data Collection and/or Processing – GT, OP, MAY; Analysis and/or Interpretation – GT, YA, MAY, OP; Literature Search – GT, NS, YA, MAY; Writing – GT, FÖ, MAY; Critical Reviews – GT, OP, FÖ, MAY.

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