Original Article

Association of the rs236918 variant of PCSK7 with the prevalence of the metabolic syndrome and its components in population from Ahvaz cohort study: A case-control study in Iran

Negar dinarvand[1], Mojdeh Rahimi[2], Hajieh Shahbazian[2], Maryam Tahmasebi Birgani[3], Bahman cheraghian[4], Narges Mohammadtaghvaei [1,5*]

[1] *Hyperlipidemia Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
[2] *Diabetes Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
[3] *Department of Medical Genetics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
[4] *Alimentary Tract Research Center, Department of Biostatistics & Epidemiology School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*
[5] *Department of Laboratory Sciences, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.*

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[*] **Corresponding Author:**

Dr. Narges Mohammadtaghvaei, Dept of Laboratory Sciences, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Email: Ntaghvaie@gmail.com

ABSTRACT

Objectives: The proprotein convertase subtilisin/kexin type 7 (PCSK7) enzyme is encoded by the PCSK7 gene and is involved in the processing and activation of latent precursor proteins. Previous studies have reported that some PCSK7 variants are associated with markers of body iron stores and lipid profiles, as well as obesity and insulin resistance. The aim of this study was to investigate the association of the rs236918 variant of PCSK7 with metabolic syndrome (MetS) and its related components.

Methods: In this cross-sectional study, 325 participants in the age group of 25 to 86 years were examined. Standard protocols were employed to measure body mass index, blood pressure, fasting blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Individuals with metabolic syndrome (MetS) were identified in accordance with the guidelines set by the National Cholesterol Education Program. Genotype was determined using the PCR-RFLP method.

Results: The findings revealed that there was no association between the rs236918 variant and increased risk of MetS or its components and also plasma lipid profile.

Conclusion: Overall, the findings exhibit no significant association between the PCSK7 rs236918 polymorphism and MetS in this population. Although these results may be due to sample size and power issues, the role of lifestyle factors and other genes in the development of MetS appears to be more important in this population. Therefore, further research is required to validate these results.

Keywords: Metabolic syndrome, PCSK7, rs236918, RFLP

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Introduction

Metabolic syndrome (MetS) is defined by a combination of metabolic risk factors that increase the risk of developing diabetes and cardiovascular diseases (1). These factors include low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, abdominal obesity or high body mass index (BMI), glucose intolerance or insulin resistance, high blood pressure, and microalbuminuria (2). Global data show that MetS prevalence is increasing in Asian and European nations. According to reports, the prevalence of MetS in Iran is thought to be between 21.9% and 31.1% (3, 4). It is now well known that MetS mostly affects populations with high caloric intake and low levels of physical activity, even though the exact pathophysiology of the condition is still unknown. Its development is also significantly influenced by genetic predisposition (5, 6). However, many MetS-related genes are still unknown.

The proprotein convertase subtilisin–kexin type 7 (PCSK7) is a member of the PCSK family that have 9 calcium-dependent serine proteases. These proproteins are involved in the activation/inactivation of various proteins and peptides by breaking the peptide bond (7, 8). These proteins include receptors, ligands, enzymes, viral glycoproteins, or growth factors (7). Several studies have reported various functions for PCSK7, including the regulation of Apo-A5, iron homeostasis, adipocyte differentiation, obesity, insulin resistance, and lipid metabolism (7, 9, 10). In addition, some single nucleotide polymorphisms (SNPs) of the PCSK7 gene affect HDL-C and/or triglyceride (TG) levels and are associated with hypertriglyceridemia (7). Recent studies have reported that SNP rs236918 C/G PCSK7 is associated with the risk of atherosclerosis and liver disease, however, whether PCSK7 genotype is related to MetS risk, remains unclear. Considering that the early identification and appropriate treatment can be effective in managing the complications of MetS (11), this study was conducted with the aim of determining the relationship between PCSK7 rs236918 variant and the prevalence of MetS and its related components in the Ahvaz cohort population.

Materials and methods

Study design and participant characteristics

The data utilized in this study were acquired from a five-year follow-up cohort of adults ranging from 25 to 86 years old in Ahvaz. The research included 142 male and 183 female participants. Approval for the study protocol was granted by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (HLRC-9505), and informed consent was obtained from all participants. The identification of MetS adhered to the Adult Treatment Panel III (ATP III) criteria, requiring at least three of the following five criteria: abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), TG ≥ 150 mg/dl or the use of medications for triglyceride management, HDL ≤ 40 mg/dl in men and ≤ 50 mg/dl in women, systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or the use of antihypertensive medication, and fasting blood glucose (FBS) ≥ 100 mg/dl or the use of blood sugar-lowering drugs (12-14).

Clinical Analysis

Anthropometric and biochemical information was extracted from the five-year follow-up cohort of the adult population in Ahvaz. The details regarding the measurement of anthropometric and biochemical parameters have been previously presented by Shahbazian et al. in 2013 (11).

DNA Isolation and Genotyping

Sure, here's the edited text:

The rs236918 variant was identified through genotyping using the PCR-RFLP method. Genomic DNA was isolated from leukocytes in EDTA blood samples utilizing the QIAamp DNA Mini Kit (Qiagen, Germany), following the instructions provided by the manufacturer. The integrity and purity of the extracted DNA were assessed through 1% agarose gel electrophoresis and NanoDrop (Thermo Scientific, USA) at wavelengths of 260 and 280 nm, respectively. The PCR reaction proceeded as follows: Step one involved a 5-minute incubation at 95°C for enzyme activation; Step two comprised 35 cycles, including denaturation at 95°C for 45 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s; and a final extension step at 72°C for 5 minutes. The primer sequences used for PCR are detailed in Table 1.

After PCR amplification, a 490-bp fragment was obtained. Subsequent digestion of the PCR product with the RsaI enzyme resulted in specific fragments corresponding to different genotypes. Specifically, the GG genotype (does not break) produced a 490-bp fragment, the CC genotype resulted in 320-bp and 188-bp fragments, and the GC heterozygous genotype produced all three fragments (490-bp, 302-bp, and 188-bp). Electrophoresis on a 2.5% agarose gel was used to

Table 1: The sequences of the primers used in the study.

Forward sequences: 5'-CAACGATCCAAGTGCCATAGAG-3'
Reverse sequences: 5'-TATCCCAACTCCCAACTCCAAA-3'

Table 2: Clinical Characteristics of the study participants according to PCSK7 rs236918 genotype

Clinical Data	Mean/percent data level by genotype			p value [a]
	GG	GC	CC	
Number of participants (%)	59.38%	36.92%	3.69%	
Age (years)	42.2 ± 13.7	41.0± 12.1	45.16 ± 14.3	0.55
Sex (Male/female)	106/87	73/47	4/8	0.15
BMI (kg/m^2)	27.6± 4.6	28.0 ± 5.0	26.5±3.7	0.69
Waist circumference(cm)	88.5 ± 12.3	88.0± 11.4	85.0±9.7	0.73
Systolic blood pressure (mmHg)	114.6±17.6	116.0±16.0	113.7±18.7	0.74
Diastolic blood pressure (mmHg)	70.0±13.0	70.4±.13.2	66.0±12.4	0.99
Fasting plasma glucose (mg/dL)	104.5 ± 38.0	109.1±46.7	107.±52.7	0.44
Triacylglycerol (mg/dL)	161.0± 104.0	162.1±108.0	139.6±49.0	0.17
HDL-cholesterol (mg/dL)	59.0± 14.6	57.5± 13.4	53.3 ± 10.3	0.11
Smoking (%)	10.9%	6.7%	25.0%	0.09
Abdominal Obesity (%)	26.9%	30.0%	8.3%	0.44
Hypertriglyceridemia (%)	38.9%	38.3%	33.3%	0.36
Low HDL- cholesterol (%)	13.5%	14.2%	16.7%	0.45
Hypertension (%)	18.7%	17.5%	25.0%	0.65
Hyperglycemia (%)	40.4%	40.0%	33.3%	0.78
Metabolic syndrome, NCEP-ATPIII	16.1%	20.0%	8.3%	0.62

[a] All p values are for univariate logistic regression model and $P < 0.05$ indicate significant differences.
[b] The comparison between groups was based on the means ± standard deviation.
BMI: body mass index

separate the digestion products, and visualization was achieved using a safe stain (Yektatajhiz Inc., Iran) under a UV transilluminator (Quantum ST4, France).

Statistical analysis

SPSS version 23.0 (IBM Corporation) was utilized for statistical analysis. The Hardy-Weinberg equilibrium was evaluated through a simple chi-square test. Comparisons of anthropometric and biochemical characteristics among genotypic groups involved chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. To determine the independent association of various genotypes and alleles of rs236918 with the prevalence of MetS, multivariable binary logistic regression, adjusted for age and gender, was conducted. The associations were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. The comparison focused on the GG genotype (as the dominant model) versus carriers of the minor alleles (GC and CC) in the analysis.

Results

Characteristics of the study participants based on PCSK7 rs236918 genotype

At the initiation of the study, the anthropometric and clinical characteristics of the study participants were examined according to their PCSK7 rs236918 genotype. The distribution of genotypes was consistent with Hardy-Weinberg equilibrium ($p>0.05$). However, no significant difference was observed in the examined variables based on genotype (Table 2).

Association between PCSK7 rs236918 and MetS

Logistic regression analysis (Table 3) showed that individuals with the GG, GC, and CC genotypes had no significant difference in the prevalence of MetS and its components ($P>0.05$).

Association between PCSK7 rs236918 and MetS components

As shown in Table 4, individuals with the GG, CG, and CC genotypes exhibited no significant difference in the prevalence of MetS components, including high blood pressure, low HDL cholesterol, abdominal obesity, high triglycerides, and hyperglycemia.

Discussion

MetS is characterized by a combination of metabolic abnormalities including insulin resistance, abnormal lipid profile, and high blood pressure (12, 15-17).

Table 3: Association between PCSK7 rs236918 polymorphism and MetS based on logistic regression analysis

Rs236918	Crude model		Adjusted model [b]	
	OR (95% CI)	p-value	OR (95%CI)	p-value
GG	reference	-----	reference	-----
CG	1.06(0.61-1.82)	0.82	1.09(0.63-1.90)	0.73
CC	1.16(0.30-4.40)	0.82	1.13(0.28-4.47)	0.85
GC+CC vs. GG(D)	1.07(0.63-1.81)	0.80	-----	-----
CC vs. GG+GC(R)	1.13(0.30-4.30)	0.85	-----	-----

[b] Adjusted model: adjusted for age, gender.
Abbreviations: D, dominant; R, recessive; OR, Odds Ratios; CI, confidence interval.

Table 4: The association between *PCSK7 rs236918* polymorphism and MetS components.

PCSK7 rs236918	abdominal obesity (W.C ≥ 102 cm in men ≥ 88 cm in women)		High triglycerides (TG ≥ 150 mg/dl)		Low HDL cholesterol HDL ≤ 40 mg/dl in) men, ≤50 mg/dl in (women		High blood pressure (systolic BP ≥130 mmHg and or diastolic BP ≥85mmHg)		Hyperglycemia (FBS ≥100 mg/dl)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p- value	OR (95% CI)	p-value
GG	reference	----	reference	----	reference	---	reference	-----	reference	-----
CG	0.98(0.60-	0.88*	1.18(0.59-	0.64*	1.15(0.71-	0.55*	0.88(0.48-	0.69*	0.0	0.99*
CC	1.10(0.31-	0.95*	1.63(0.33-	0.54*	2.09(0.64-	0.22*	1.46(0.36-	0.59*	1.17(0.63-	0.60*
GC+CC vs.	1.0(0.63-	0.97	1.22(0.63-	0.54	1.24(0.78-	0.35	0.90(0.51-	0.73	1.05(0.56-	0.87
CC vs.	1.0(0.29-	0.99	1.44(0.30-	0.64	1.78(0.56-	0.32	1.43(0.37-	0.59	0.0	0.99

*Data are adjusted according to age and sex.

Several studies have shown that genetic variants play an important role in the prevalence of these risk factors and indicated significant associations between single SNPs in genes such as FTO, TCF7L2, APOA5, APOC3, and PCSK7 and MetS risk factors (7, 12, 18-20).

PCSK7 variants have been reported to be associated with dyslipidemia, which is one of the risk factors of MetS (8). PCSK7 also affects obesity and insulin resistance by regulating adipocyte differentiation (9, 21). However, in this study, no association was found between the rs236918 variant of PCSK7 and the prevalence of the MetS and its related components in a population from the Ahvaz cohort study. Our findings are consistent with the study conducted by Eshraghian A et al., which indicated that there is no association between PCSK7 rs2277287 genotype and hepatic steatosis in liver transplant recipients (22). In contrast, studies conducted by Furuhashi M et al., showed that the PCSK7 variant was associated with an elevated TG level and obesity in the Japanese general population without taking medication (8). Vargas-Alarcón G et al., have also indicated that the rs236918 variant was associated with a lower plasma HDL-C level (7). In addition, Zheng X et al. reported the association of PCSK2 and type 2 diabetes in the Han Chinese population (23). However, it is important to note that the effects of some genetic variants can be effectively reduced by lifestyle intervention (24), and it should be noted that MetS is a multifactorial condition caused by several factors, while our study focused on the role of PCSK7 rs236918 polymorphism alone. Therefore, further studies are necessary to evaluate other related genes and to consider lifestyle, diet, and nutrition factors in the study population.

In conclusion, our study indicated no association between PCSK7 rs236918 polymorphism and the MetS or its related components. Therefore, further research is necessary to find the effective genes or polymorphisms in the study population.

Conflict of Interest

The authors have nothing to declare.

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