The Relationship Between Coronary Artery Disease and Genetic Polymorphisms of Melanoma Inhibitory Activity 3

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Abstract

Background: Melanoma Inhibitory Activity 3 regulates the plasma level of LDL cholesterol. The c.3169 + 315G > A single-nucleotide polymorphism of the MIA3 gene has been reported to be associated with serum coronary artery disease (CAD). However, there have been no studies analyzing the association of this polymorphism with CAD in Iranian individuals with CAD.

Objectives: Therefore, in the present study we have investigated the potential protective effect of the rs3008621 MIA3 polymorphism in 188 subjects with and without CAD.

Materials and Methods: Genotyping of the MIA3 gene was undertaken using TaqMan real-time PCR in all subjects. Anthropometric and biochemical features, including HDL, LDL, and TG were assessed in all subjects.

Results: The CAD patients had significantly (P < 0.05) higher BMI and significantly higher levels of TG, LDL, SBP, and DBP, while the level of HDL was lower compared to that of the control group. the MIA3 gene polymorphism was not associated with CAD in our population sample.

Conclusions: The MIA3 polymorphism is unlikely to play an important role in CAD in the Iranian population. However, further studies are needed in a larger population to confirm this.

Keywords: Proprotein Convertase Subtilisin/Kexin Type 9, Polymorphism, Coronary Artery Disease

1. Background

Coronary artery disease (CAD) is a leading cause of death worldwide. Serum low-density lipoprotein-cholesterol (LDL-C) concentrations are an established risk factor for CAD (1). Abnormal levels of serum lipids may enhance the rate of atherosclerosis and the development of CAD (2-4). Currently, HMG-CoA reductase inhibitors (statins) are widely used as a therapeutic agent for reducing LDL-C levels and cardiovascular complications. However, identification of new signaling pathways and markers that can regulate LDL-C metabolism might provide a novel strategy for identifying subjects at high risk of developing CAD (5). Melanoma Inhibitory Activity 3 is a potential target that has been shown to modulate plasma LDL-C concentration (6, 7). PCSK9 is a circulating protein that has been suggested as reducing the half-life of the LDL-receptor (LDL-R), thereby controlling the plasma level of LDL-C (8). Mutations in the PCSK9 gene are associated with both gene overexpression and gene deficiency. It has been reported that the upregulation of this gene in mice could reduce the amount of LDL-R in the liver. Conversely, mice deficient in PCSK9 demonstrated a correspondingly increased level of LDL-R (9-12). PCSK9 is a glycoprotein with 692 amino acids, and causative mutations in the gene are known to be highly associated with familial hypercholesterolemia (5, 13). Recent genome-wide association studies (GWAS) have revealed an association between rs3008621 T > G in the MIA3 gene and LDL-C levels and risk of CAD (1, 2, 5, 8, 14-16).

2. Objectives

The aim of the present study was to explore the association of the rs3008621 MIA3 polymorphism in an Iranian population with and without CAD.
3. Materials and Methods

3.1. Population

The research protocol was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences. Written consent was obtained from all subjects. The study included 188 subjects, including 94 CAD patients who underwent coronary angiography.

3.2. Anthropometric and Biochemical Measurements

Anthropometric parameters, including height and body weight, were evaluated. Body mass index (BMI) was determined as body weight (kg) divided by squared height in meters (m$^2$). Systolic and diastolic blood pressures were measured. TC, HDL, LDL, TG, and fasting blood glucose (FBG) concentrations were determined in all the samples.

3.3. Genotyping

Genomic DNA was extracted using high pure PCR template preparation kits (Roche; Germany). The quantified and purity of DNAs were evaluated by Nanodrop 1000 (Thermo Fisher Scientific; USA) and gel electrophoresis. The polymorphism, rs11591147 T > G, was genotyped using TaqMan probe real-time PCR (LightCycler 96; Roche; Germany).

3.4. Statistical Analysis

Data were analyzed using SPSS-20 software (SPSS Inc. IL, USA). Descriptive statistics, including mean ± standard deviation (SD), were determined for normally distributed variables. Median ± inter-quartile range (IQR) were determined for those variables not normally distributed. The student’s t-test was used for normally distributed variables, and the Mann-Whitney U-test was used for those not normally distributed. The statistical differences in genotype distribution and allele frequencies between groups were assessed by the $\chi^2$ test. Compliance of genotypes was evaluated by Hardy-Weinberg equilibrium. A 2-sided P < 0.05 was considered significant.

4. Results

4.1. Demographic Features and Clinical Characteristics of the Study Population

Table 1 summarizes the clinical and biochemical characteristics of the study population. The CAD subjects had significantly higher BMIs and significantly higher SBP, DBP, triglycerides, fasting blood sugar, and LDL, while their level of HDL was lower compared to the control group.

4.2. Association of SNP rs3008621 with CAD

Genotyping was performed successfully, and the polymorphism followed the Hardy-Weinberg equilibrium. All the CAD patients were homozygous for the G allele, while the genotype frequencies of the MIA3 polymorphism for AA, AG, and GG in the control group were 0%, 19% and 81%, respectively (Table 2).

5. Discussion

To the best of our knowledge, this is the first study evaluating the association of the rs3008621 MIA3 polymorphism in an Iranian population with CAD. Results showed...
that this genetic polymorphism was not associated with CAD. In agreement with these findings, several other studies have shown the lack of an association between this genetic polymorphism and CAD (17).

Accumulating evidence shows an association between the MIA3 polymorphism and CAD (2, 15, 18-20). In particular, Benn et al. showed a protective value of rs11591147 in ischemic heart disease and myocardial infarction (MI) patients (21). In addition, Guella et al. showed a positive association between rs11591147 and lower LDL-C, as well as the reduced risk of developing MI in an Italian population (OR = 0.67; 95% CI = 0.46 - 0.97; P = 0.036) (2). Another study revealed a correlation between circulating level of PCSK9 and LDL level in 5,722 subjects in Stockholm (8). In line with these observations, several other studies have shown an association between circulating level of PCSK9 and LDL-C levels (14, 15). Several studies have also reported the functional role of protein in the lipid pathway. In particular, Lalanne et al. enforced the expression of PCSK9 in mice and cultured HuH7 hepatoma cells. They measured the catabolism of LDL particles and the endogenous synthesis of very low density lipoprotein (VLDL) and/or apolipoprotein B (apoB). In addition, they showed that PCSK9 overexpression inhibited LDL expression and activity in mice and in cultured cells. Furthermore, they suggested that the S127R mutation in patients increased VLDL and apoB levels (11, 12). However, the present study did not identify a relationship between the PCSK9 polymorphism and CAD, supporting further investigations of the role of this genetic polymorphism in a larger population. Samani et al. performed a genetic study, evaluating the role of rs3008621 located on chromosome 1q41 from the Wellcome Trust Case Control Consortium with 1926 cases and 875 CAD patients. They identified SNP rs3008621 in MIA3 gene as a putative genetic variant on 1q41 locus with a high possibility of an association with CAD (2). Another study by the Myocardial Infarction Genetics Consortium in 2009 confirmed the probability of the existence of an association between this SNP with CAD (7). Similarly, another investigation showed the association of this SNP with CAD cases (OR = 1.10 [1.04-1.17], P = 1.02 × 10 [U+02D7] 3) (8). A recent study by Koch et al. 2011 analyzed rs3008621 in 3,657 MI patients. They failed to show the association of this SNP with MI (16). This lack of relationship can be explained at least in part by variations in lifestyle, diet, medication, and ethnic background and the small sample size used.

In conclusion, data from the present study suggest that rs3008621 MIA3 single-nucleotide polymorphisms are unlikely to play a key role in CAD in the Iranian population, although further investigations are warranted in a larger sample size in both the Iranian population and in other ethnicities to confirm these findings.

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Footnotes

Authors’ Contribution: Study design: Hooshang Zaimkohan, Mohammad Keramatipour, Majid Ghyour-Mobarhan, Javad Tavakkoly-Bazzaz and Seyed Mohammad Hossein Ghaderian; experimental part: Hooshang Zaimkohan, Mohammad Keramatipour, Majid Ghyour-Mobarhan, Javad Tavakkoly-Bazzaz and Seyed Mohammad Hossein Ghaderian; data analyses: Hooshang Zaimkohan, Seyed Reza Mirhafez, Javad Tavakkoly-Bazzaz, Azadeh Tahooni, Mohammad Piryaie, Majid Ghyour-Mobarhan, and Seyed Mohammad Hossein Ghaderian; manuscript preparation: Hooshang Zaimkohan, Mohammad Keramatipour, Javad Tavakkoly-Bazzaz, Azadeh Tahooni, Mohammad Piryaie, Majid Ghyour-Mobarhan, and Seyed Mohammad Hossein Ghaderian.

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