The effect of SORT1 rs: 599839 polymorphism on lipid profiles in Turkish population Runing Title: Relationship of rs599839 and lipid profiles

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Research Article

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Abstract

Objective

The SORT1 gene encoding Sortilin-1 (SORT1), a receptor of the VPS10p family, is localized at 1p13.3. SORT1 has been associated with the risk of developing cardiovascular disease in genome wide association studies (GWAS) due to its association with hepatic lipid metabolism and low-density lipoprotein-cholesterol (LDL-C) levels. Various variations on the SORT1 gene region cause different effects on lipid profiles. Our aim in this study; To determine whether the SORT1 (599839) gene variants have an effect on CHD development and lipid parameters in Turkish population.

Materials and Method

In this case-control study, the study group consisting of 396 men (209 CHD/187 controls) was genotyped in terms of SORT1 rs: 599839 polymorphism using TaqMan 5 'Allelic Discrimination Test.

Results

There is no statistically significant difference between the patient and control groups in terms of SORT1 rs599839 genotypes (p = 0.81). The presence of the G allele caused lower Total-C (p = 0.005, p = 0.032, respectively) and LDL-C (respectively; p = 0.005, p = 0.040) levels in both patient and control groups, while higher HDL-Cholesterol (p = 0.001, p = 0.006) levels were observed, respectively.

Conclusion

Our findings suggest that the SORT1 rs599839 polymorphism does not contribute directly to the pathogenesis of CHD. However, the presence of the minor G allele lowered Total-cholesterol and LDL-C levels and caused an increase in HDL-cholesterol levels. This situation gave the impression that the presence of the minor G allele has a positive effect on the lipid profile and is protective against CHD.

Introduction

Coronary heart disease (CHD) and its subsequent complications remain the most common cause of death globally, with death rates falling (1). Atherosclerotic CHD (ACHD) is an inflammatory disease characterized by non-resolving plaque inflammation triggered and sustained by lipoprotein retention and cholesterol accumulation. Although the underlying mechanisms of the disease are not fully understood, the increased incidence of CHD is attributed to various environmental and genetic factors (2). Numerous studies have shown that the underlying process of atherosclerosis is lipoprotein injection, and the accumulation of cholesterol in the arterial wall leads to a chronic inflammatory disorder that causes the formation and activation of atherosclerotic lesions (3–5). According to recent genome-wide association

studies (GWAS) and their meta-analysis data, Sortilin is recommended as the new regulator of lipid metabolism (6–8). The SORT1 gene, which encodes Sortilin-1 (SORT1), a receptor of the VPS10p family, is localized at 1p13.3 (9). This locus contains the CELSR2-PSRC1-SORT1 gene cluster and it has been reported that the functional gene in this locus is SORT1 (10). The data we have obtained from epidemiological studies, cohort studies, and animal experiments have proven to us the strong relationship between sortie and lipid parameters (11–13). In addition, the effect of sortilin on the inflammatory process has been reported, independent of lipid parameters. According to the experimental study data, sortilin plays a role in the regulation of the secretion of proinflammatory cytokines such as IL-6 and IFN-y, and it has been shown that targeting sortilin in immune cells reduces inflammation-induced atherosclerosis (14). In addition, the report that sortilin promotes lipid accumulation in macrophages and the formation of foam cells has drawn attention to the central role of sortilin in the pathogenesis of CHD (12). Various variations on the SORT1 gene region cause different effects on lipid profiles. Single nucleotide polymorphisms (TNPs) can be used to examine whether a genetic biomarker is causally linked to disease risk. Many studies have reported that SORT1 rs: 599839 variant has a downregulation effect on Total-K and LDL-K and is a protective factor against CHD. However, there are no studies on this subject in Turks. Our aim in this study; To determine whether SORT1 (rs599839) gene variants have an effect on CHD development and lipid parameters in the Turkish population.

Method

Study Population

This case-control study consisted of 396 male individuals who applied to Giresun University Giresun and Research Hospital Department of Cardiology. The study population of the SORT1 rs599839 polymorphism consisted of 209 CHDs and 187 voluntary healthy controls. Coronary angiography was applied to all groups. Coronary angiography was performed by an experienced cardiologist in all groups due to suspected CHD-related symptoms or the results of non-invasive tests. The severity and prevalence of CHD were evaluated according to the Gensini score. A diagnosis of CHD was made with clinical findings such as unstable angina, myocardial infarction (MI) or presence of previous myocardial infarction (OMI), electrocardiograms, examination of cardiac enzymes, or coronary angiography defined as ≥50% stenosis of vessels larger than 1.5 mm. The control group with angio (-) (no luminal stenosis on coronary angiography; Gensini score = 0) was selected from healthy volunteers without any evidence of chronic disease, including hepatic, renal, or thyroid. In addition, this group was not taking any drugs known to affect serum lipid levels such as statins or fibrates at the time of blood sampling. All procedures performed in this study comply with the ethical standards of the institutional and/or national research committee and the Declaration of Helsinki (2013) (15). Ethical approval for this study was obtained from the Giresun University Local Ethics Committee (KAEK-83). The informed consent form was obtained from all individuals included in the study.

SORT1 Genotyping

DNA isolation was performed with a commercial kit (Roche high pure isolation kit, Germany) from the peripheral blood taken from the cases included in the study, purity was determined and DNA levels were calculated and stored at $+4^0$C until the time of study. Allelic variations rs599839 were genotyped by Real-time Polymerase Chain Reaction (RT-PCR) using the bi-directional quantitative TaqMan 5' Allelic Discrimination Test (Applied Biosystems, Foster City, CA) using established protocols according to the manufacturer's instructions. For the control, 10% of randomly selected samples were double genotyped and the accuracy of the results was reconfirmed.

Statistical analysis

Statistical analysis of this study was made using the SPSS 20 package program. Statistical significance was taken as $p<0.05$. Allele and genotype frequencies were calculated by direct counting. Hardy-Weinberg balance (HWE) was calculated using Arlequin V3.0 software (16). The Chi-square ($\chi 2$) test was used to evaluate the intergroup differences in the frequency of genotypes and alleles. Odds ratio (OR) and 95% confidence interval (95% CI) are given to determine the risk factor between groups.

Results

396 male (209 patients + 187 control) individuals were included in our study. The demographic information of our working groups is given in Table 1. There was no statistically significant difference between the patient (age = 50.14 ± 13.39) and control (age = 49.72 ± 12.80) groups in terms of age, triglyceride, LDL-Cholesterol, and smoking ($p > 0.05$). In addition, there is a statistically significant difference between the patient and control groups in terms of HDL-Cholesterol, Total-Cholesterol, hypertension, hyperlipidemia, and diabetes ($p < 0.001$).

Table 1
Demographic data of study groups

Parameters	Case (n = 209)	Control (n = 187)	p Value
Age	50.14 ± 13.39	49.72 ± 12.80	NS
Triglyceride (mg/dl)	153.34 ± 90.171	152.80 ± 90.171	NS
LDL- cholesterol (mg/dl)	107.47 ± 38.115	110.09 ± 29.081	NS
HDL- cholesterol (mg/dl)	41.97 ± 11.464	52.21 ± 14.253	**< 0.001**
Total- cholesterol (mg/dl)	181.22 ± 47.524	163.36 ± 42.502	**< 0.001**
Hypertension (HT)			
HT-	77(36.8%)	147(78.6%)	**< 0.001**
HT+	132(63.2%)	40(21.4%)	
Type 2 Diyabetes Mellitus			
DM-	121(84.0%)	157(84.0%)	**< 0.001**
DM+	88 (57.9%)	30 (16.0%)	
Hyperlipidemia (HL)			
HL-	90(43.1%)	152(81.3%)	**0.001**
HL+	119(56.9%)	35(18.7%)	
Smoking			
Smoking -	85(40.7%)	92(49.2%)	0.08
Smoking +	124(59.3%)	95(50.8%)	

Data are presented as mean ± S.D and n (%). Bold values were statistically significant ($p < 0.05$). n: number of samples. Mean values were compared between patients and controls using the Student's t-test. Qualitative data were analyzed using the chi-square test.

SORT1 rs599839 genotype and allele distributions of the study groups are shown in Table 2. Both groups were compatible with HWE in terms of SORT1 rs599839 genotypes ($p < 0.05$). There is no statistically significant difference between the patient and control groups in terms of SORT1 rs: 599839 genotypes ($p = 0.81$).

Table 2
Genotype and allele distributions in study groups.

Genotypes	Case(n = 209)	Control(n = 187)	χ^2	*p* Value
AA	119(16.6%)	112(59.9%)	0.421	0.810
AG	73(65.1%)	62(33.2%)		
GG	17(8.1%)	13(7.0%)		
HWE	p < 0.05	p < 0.05		
A allele fraction	0.91	0.93	0.197	0.657
G allele fraction	0.43	0.40	0.355	0.552

Genotypes and allele fractions were analyzed by chi-square test. Data are presented as n (%). n: number of samples. HWE: Hardy - Weinberg Equilibrium

The effect of the minor G allele on the lipid profile in the study groups is shown in Table 3. The presence of minor G allele did not affect triglyceride levels in both patient and control groups (p > 0.05). On the other hand, the presence of the G allele resulted in lower Total-Cholesterol (p = 0.005, p = 0.032, respectively; p = 0.005, p = 0.040) and higher HDL-Cholesterol levels in both the patient and control groups. (p = 0.001, p = 0.006, respectively) levels were observed.

Table 3
Effect of SORT1 rs599839 G minor allele on lipid profile

Parameters	Case (n = 209)	p Value	Control (n = 187)	p Value
Triglyceride (mg/dl) G allele +	149.64 ± 78.231	NS	156.24 ± 54.181	NS
G allele -	156.16 ± 98.545		150.49 ± 60.691	
LDL-cholesterol (mg/dl) G allele +	98.97 ± 29.933	**0.005**	104.77 ± 18.625	**0.040**
G allele -	113.91 ± 42.286		113.65 ± 33.970	
HDL- cholesterol (mg/dl) G allele +	44.77 ± 10.983	**0.001**	55.56 ± 12.196	**0.006**
G allele -	39.64 ± 11.426		49.97 ± 15.121	
Total- cholesterol (mg/dl) G allele +	153.91 ± 34.494	**0.005**	171.89 ± 50.073	**0.032**
G allele -	170.50 ± 46.554		187.46 ± 44.888	

Data are presented as mean ± S.D. Bold values were statistically significant (p < 0.05). n: number of samples. Mean values were compared between patients and controls using the Student's t-test.

Discussion

CHD represents a clinical phenotype in which inflammatory mediators are involved, including environmental risk factors and genetic susceptibility. Management of lipid parameters is very important in the clinical management of the disease. Therefore, the identification of gene regions known to have genetic effects on lipid profiles and their functional variants is very important in order to reduce the comorbidities of the disease by establishing early treatment protocols. In recent years, in studies conducted to determine predictors in CHD pathogenesis, a new candidate locus has been associated with CHD due to its effect on 1p13.3 lipid parameters (11–13, 17). Although the complex scenario of sortilin's role in lipid metabolism has not been explained yet, according to the information we have obtained from experimental and functional studies, hepatic sortilin can act as a receptor for LDL-C, independent of its LDLR (18). Interestingly, the SORT1 gene has been shown to bind the LDL receptor-associated protein (RAP) in vitro, thus providing a potential functional link to lipoprotein metabolism (19). In their experimental study using Sort1 (- / -) mice, Patel et al. Reported that Sort1 deficiency significantly reduced atherosclerosis by reducing LDL uptake of macrophages without creating any change in LDL-C levels (12). Another important task of Sortilin is its effect on inflammatory cytokines whose contribution to the atherosclerotic process is well known. It has been reported that sortilin deficiency alleviates inflammation by affecting the secretion of interleukin-6 (20). Due to its lipid regulation and inflammatory effects, sortie appears to be a very powerful mediator in the atherogenic process and a strong predictor of CHD risk. The SORT1 rs599839 polymorphism has been frequently associated with lipid levels and has been reported to be protective against CHD, usually due to the decrease in LDL-C levels (21, 22). However, there is no study conducted in the Turkish population related to this variant. Our study is the first Turkish study to examine the relationship between the SORT1 rs599839 polymorphism and lipid profile and CHD. According to our study data, the SORT1 rs599839 polymorphism does not appear to be effective in the pathogenesis of CAD. Our study data is Zhou. and Sánchez Muñoz-Torrero (21, 23, 24). Zou et al. reported that rs599839 and rs464218 variants were not effective in CHD pathogenesis in their case-control study in patients with CHD and ischemic stroke. Similarly, the data of a study conducted in the Spanish familial hypercholesterolemia cohort have recently published their studies reporting that there is no relationship between rs599839 alleles and CHD. Inconsistent with the data of these studies, the LURIC study data also reported that the AG and GG genotypes were more represented in the control groups compared to the CHD group, and this difference was statistically significant ($p = 0.004$). Studies conducted in the Chinese Han population also reported that the minor G allele was higher in the control group compared to the premature coronary heart disease group ($p = 0.004$) (25). Inconsistent data among the results of the studies may be related to sample size, ethnic differences, different genotypic frequencies, gene-environment interactions. The SORT1 rs599839 polymorphism; It can increase HDL-C level while decreasing the level of Total-K and LDL-C (21, 26, 27). Functional studies have demonstrated that the 1p13.3 rs599839 variants regulate cholesterol metabolism through regulation of sortilin expression and LDL-C uptake in hepatocytes and affect the diameter of circulating LDL-C particles of nature (28, 29). While the presence of the G allele did not affect triglyceride levels in accordance with the literature, a statistically significant decrease was observed in LDL-C and Total-C levels (30). This decline is consistent

with data from studies in the Arab population (27), Austrians (31), Indians (32), Japanese (33), Chinese (34), Pakistanis (35), and Mexicans (36). We think that this decrease in LDL-C levels is due to the increase in intracellular uptake of LDL caused by the increased SORT1 expression in the presence of minor G allele, which is consistent with the previous study data (28). The 46% increase in Total-C levels caused by the reduction of SORT1 expression by siRNA and the more than the two-fold increase observed in LDL-C levels also support this idea (10). However, our study data are inconsistent with the study data reporting high Total-C levels observed in the Dutch population (37). An additional finding in this study is the high HDL-C levels we observed in the presence of the G allele. While this finding is consistent with the study of Zhou et al., It is inconsistent with the study data of Gigante et al. (30, 38). The differences in these results can be explained by the high linkage imbalance in allele frequency and sample size between different ethnic populations, with additional variants in genes involved in the lipid metabolism pathway of this SNP (27). We found that other cardiovascular risk factors HDL-C, Total-C, hypertension, diabetes ($p < 0.001$) and hyperlipidemia examined in our study had significant effects on the development of CHD (39–47). Our study confirms the importance of hypertension and hyperlipidemia in the pathogenesis of male CHD disease. Based on our findings from our study, we would like to report that the rs599839 variant does not contribute directly to the pathogenesis of CHD in Turks. However, considering the positive effect of this variant on lipid profiles, we think that the presence of a minor G allele is an important protective factor for the development of CHD. Therefore, investigation of SORT1 variations as potential risk modifier genetic factors in Turks may lead to the discovery of better biomarkers for personalized cardiovascular risk assessment.

Limitation

Our study population was relatively small, and larger population studies are needed to define and clarify our findings. In addition, while we could not find any difference between genotype distributions in our study groups, we discovered the positive effect of the minor G allele on lipid profile. A larger sample group will allow an analysis of the frequencies of missing alleles and genotypes in the current study. Moreover, we think that for the analysis of gene-gene and gene-environment interactions, it is necessary to examine the interaction of more variations in the 1p13.3 locus with each other. Therefore, more studies with larger sample sizes and including multivariate analyzes are needed.

Declarations

Conflict of interests.

Authors declare that no conflict of interests exist.

Financial Resource

No financial resources have been used for this article.

Contributions

Design—ABAT; data collection and/or processing—ABAT, ET; analysis and/or interpretation—ABAT,ET; literature search—ABAT; writing manuscript—ABAT; English language editing—ABAT.

Ethical approval

Ethical approval for this study was obtained from the Giresun University Local Ethics Committee (KAEK-83).

Informed consent

Written and signed informed consent form was obtained from all of the case and control subjects before the study.

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