Research Article

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Investigation of *SR-BI* gene rs4238001 and rs5888 polymorphisms prevalence and effects on Turkish patients with metabolic syndrome

Metabolik sendromlu Türk hastalarında *SR-BI* geni rs4238001 ve rs5888 polimorfizmlerinin prevalansı ve etkilerinin araştırılması

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Abstract

Aim: Metabolic syndrome (MS) is associated with dyslipidemia such as hypertriglyceridemia and high-density lipoprotein (HDL) levels. Scavenger receptor BI (*SR-BI*) is the transmembrane receptor that regulates selective intake of cholesterol esters by the liver and it binds to HDL with high affinity. This study was aimed to determine the effects of *SR-BI* gen variations upon proatherogenic and antiatherogenic lipid profiles in the patients with metabolic syndrome.

Methods: The patient group was consisted of 104 (30–65 years) male subjects who were diagnosed with MS and 100 healthy male subjects were included in control group. DNA was isolated from blood samples. *SR-BI* gene rs4238001 and rs5888 variants were examined by SNaPshot multiplexing system. SPSS 18 was used for statistical analysis and $p < 0.05$ considered as statistically significant.

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Results: It was found that *SR-BI* gene rs4238001 T allele increased the risk of metabolic syndrome 1.61 fold ($p = 0.02$). Subjects with TT genotype 2.847 fold increased the risk of metabolic syndrome according to subjects with CC genotype ($p = 0.017$).

Conclusions: *SR-BI* rs4238001 variation may be related to an increased risk of metabolic syndrome.

Keywords: Metabolic syndrome; *SR-BI*; rs5888; rs4238001; Polymorphism.

Öz

Amaç: Metabolik sendrom (MS) hipertrigliseridemi ve yüksek yoğunluklu lipoprotein (HDL) seviyeleri gibi dislipidemi ile ilişkilidir. Çöpçü reseptörü BI (*SR-BI*) karaciğer tarafından kolesterol esterlerin selektif alımını düzenleyen ve yüksek afinite ile HDL'ye bağlanan transmembran reseptörüdür. Bu çalışmada, metabolik sendromlu hastalarda *SR-BI* gen varyasyonlarının proterojenik ve antiaterojenik lipid profilleri üzerine etkilerinin belirlenmesi amaçlanmıştır.

Yöntemler: Hasta grubuna MS tanısı konulmuş 104 (30–65 yaş) erkek ve kontrol grubuna 100 sağlıklı erkek dâhil edilmiştir. DNA kan örneklerinden izole edildi. *SR-BI* geni rs4238001 ve rs5888 varyantları SNaPshot multiplexing sistemi ile incelendi. İstatistiksel analiz için SPSS 18 kullanıldı ve $p < 0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: *SR-BI* geni rs4238001 T alelinin metabolik sendrom riskini 1.61 kat arttırdığı bulundu ($p = 0.02$). TT genotipinin CC genotipine göre metabolik sendrom riskini 2.847 kat arttırdığı belirlendi ($p = 0.017$).

Sonuç: *SR-BI* rs4238001 varyasyonu artmış metabolik sendrom riski ile ilişkili olabilir.

Anahtar kelimeler: Metabolik sendrom; *SR-BI*; rs5888; rs4238001; Polimorfizm.

Introduction

Metabolic Syndrome (MetS) is defined as a set of risk factors including hyperglycemia, dyslipidemia and an atherosclerotic cardiovascular disease characterized by insulin resistance, subsequent hyperinsulinemia, abdominal obesity, hypertension and low levels of high-density lipoprotein (HDL) and high levels of triglyceride (TG) [1–3]. The prevalence of MetS increases with age and it was found 7% in the age group of 20–29, whereas 44% in the age group of 60–69 in United States of America (USA) [4–6]. The prevalence of metabolic syndrome rose from 24.4% to 36.2% between 1990 and 2000 in Turkey [7]. The mean value of HDL-cholesterol (HDL-C) levels was found 37.2 mg/dL in 1211 men and 44.9 mg/dL in 1261 women in the TEKHARF study. The value of <40 mg/dL is identified as low HDL-C level and two-thirds of Turkish adults had low HDL levels [8]. Environmental and genetic determinants effect plasma lipid concentrations. It is thought that approximately the half of the variations in HDL-C and TG might be genetic [9–11].

The *class B type scavenger receptor (SR-BI)* binds HDL-C with high affinity and transfers lipids from HDL-C in the reverse cholesterol transport pathway [9, 12, 13]. *SR-BI* gene is localized in the long arm of chromosome 12 at q24.31–32 in the human and contains 13 exons [14, 15]. *SR-BI* is a 509-amino acid glycoprotein on the cell surface with a molecular weight of 82 kD and expressed essentially in the non-placental steroidogenic tissues and liver [16, 17]. *SR-BI* also mediates selective cholesterol uptake [18].

Previous studies showed that single nucleotide polymorphisms (SNPs) in the *SR-BI* gene are associated with plasma lipids [19, 20]. The minor allele of c.1050 C>T (rs5888, A350A, silent mutation) in the *SR-BI* gene was observed in Caucasians up to 40–49% [21]. The minor allele of rs4238001 (G2S, G>A at 4. base pair that encodes a glycine-to-serine) was significantly found associated with high HDL-C and low LDL-cholesterol (LDL-C) levels in men. However, this effect was not observed in women [19]. This difference between men and women can be stem from estrogen response element in the *SR-BI* gene indicating a regulation by estrogen [22, 23]. Thus, we aimed to evaluate the effects of the *SR-BI* gene rs5888 and rs4238001 variants on the male patients with metabolic syndrome.

Materials and methods

Patient selection

The study protocol was approved by the Ethical Committee of Selçuk University (No: 2015/19) and all participants gave written informed consent. Since *SR-BI* is regulated by estrogen [22, 23], we preferred male participants for our study. Two groups were studied as MetS and control groups. The MetS group was formed by 104 male subjects who were diagnosed with metabolic syndrome to the criteria's of MetS followed by Department of Family Medicine, Selçuk University. The control group consisted of 100 male subjects with no cardiovascular disease, hypertension and metabolic diseases including diabetes mellitus, renal failure, liver failure and lipid metabolism disorder in the age range of 30–65 years.

Genotyping

DNA was isolated from the remaining blood and serum samples which were taken during the routine blood tests of the two groups and QIAzol lysis reagent 200 mL (Cat. No. 79306® QIAGEN, Hilden, Germany) was used for DNA isolation. The purity and concentration of DNA samples were determined by NanoDrop spectrophotometer (ThermoFisher, Waltham, MA, USA) at 260 nm and 280 nm. In the obtained DNA samples, C>T (rs5888) change in exon 8 and C>T (rs4238001) change in exon 1 in *SR-BI* gene were examined by SNaPshot multiplex system. Primer sequences for amplify *SR-BI* gene rs5888 and rs4238001 variations were sense 5'-TGGTTATCTT-GTCATCGCCA-3' and antisense 5'-GTGCTCCAACCAG-GAATCAC-3'; sense 5'-TTAAGGACCTGCTGCTTGAT-3' and antisense 5'-CATAAAACCACTGGCCACCT-3', respectively for polymerase chain reaction (PCR). PCR amplifications were performed in a thermal cycler (®Applied Biosystems, Waltham, MA, USA). PCR reactions were carried out with a total volume of 25 µL containing 100 ng genomic DNA, 10×Taq buffer (with KCl), 25 mM MgCl₂, 1 mM dNTPs, 50 pmol/µL of each primer and 1.5 U Taq DNA polymerase (®Fermentas, ThermoFisher, Waltham, MA, USA). Thermal conditions consisted of an initial denaturation step of 5 min at 95°C followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s and extension at 72°C for 30 s with a final extension step for 5 min at 72°C. To genotyping *SR-BI* gene rs5888 and rs4238001 variations, primer sequences were 5'-CTCCATCCTCACTTCTCAACGC-3' and 5'-AGCCAGCGCGCTTTGCGGAGCAGC-3', respectively. Genotyping reactions

were carried out with a total volume of 10 μ L containing PCR product, SnaPshot multiplex reaction buffer (ABI PRISM® Applied Biosystems), primers and pure water. Thermal conditions for genotyping of *SR-BI* gene variations consisted of an initial denaturation step of 5 min at 95°C followed by 25 cycles of denaturation at 96°C for 10 s, annealing at 50°C for 5 s and extension at 60°C for 30 s. The PCR product was incubated at 37°C for 1 h with 1 unit of Calf Intestinal Phosphatase (CIP) (Cat. No. 18009019® Thermo Fisher Scientific) and inactivated at 75°C for 15 min and stored at +4°C. For capillary electrophoresis, 0.5 μ L of the PCR product was mixed with 0.5 μ L of GeneScan™ 120 LIZ (®Thermo Fisher Scientific) solution loaded into wells and denatured at 95°C for 5 min and performed on electrophoresis.

Statistical analysis

The statistical analyses of this study were done by using Statistical Package of Social Science (SPSS, version 18; SPSS Inc., Chicago, IL, USA). The results were evaluated in 95% confidence interval and statistical significance limit of $p < 0.05$. Hardy-Weinberg equilibrium (HWE) was examined by Fisher Exact test. The relationship between genotypic distributions of other data was firstly examined by Shapiro-Wilk test whether these data were a normal distribution. The Student's t-test was used for binary comparison of normal distribution data and One-way analysis of variance (ANOVA) analysis was used for triple comparison. Mann Whitney U-test for binary comparisons and Kruskal Wallis for more groups were used for the data analysis in non-normal distribution.

Results

Clinical investigation

MetS and control groups were compared in terms of clinical parameters and the obtained data are shown in Table 1. The metabolic syndrome group was consisted of 104 patients with mean age 45 ± 9.8 , while control group was consisted of 100 healthy individuals with mean age 47.2 ± 10.3 . It was observed that the patient and control groups were significantly different in terms of weight, body mass index, waist circumference, HDL and triglyceride ($p < 0.001$).

The distributions of *SR-BI* rs4238001 and rs5888 genotypes and alleles

The HWE analysis showed that both polymorphisms for the control group were in HWE ($p = 0.82$ for rs4238001, $p = 0.104$ for rs5888). General genotype distributions are shown in Tables 2 and 3. In the *SR-BI* rs4238001 variation, the major C allele frequency was 55.8% and the minor T frequency was 44.2% in the MetS group, while 67% and 33% were found in the control group, respectively. In the *SR-BI* rs5888 variation, the major C allele frequency was 59.1% and the minor T frequency was 40.9% in the MetS group, while 55.5% and 44.5% were found in the control group, respectively.

When the effects of these polymorphisms on susceptibility to disease were examined by comparing the genotype distributions of patients with metabolic syndrome and healthy controls; it was observed that rs4238001 polymorphism increases the risk of susceptibility to disease. On the

Table 1: Clinical characteristics of metabolic syndrome and control groups.

Parameters	Mean $\pm$ SD		
	Metabolic syndrome (n = 104)	Control (n = 100)	Total (n = 204)
Age (years)	45 ± 9.8	47.2 ± 10.3	46.1 ± 10.1
Height (cm)	174.8 ± 6.8	173.3 ± 6.2	174.1 ± 6.6
Weight (kg)	87.6 ± 10.7^a	79.5 ± 12.4	83.6 ± 12.2
HDL (mg/dL)	33.1 ± 3.9^a	44.9 ± 7.2	38.9 ± 8.2
TG (mg/dL)	284.5 ± 179.3^a	116.7 ± 25.9	202.2 ± 153.9
Waist circumference (cm)	104.9 ± 9.4^a	94.6 ± 8.1	99.8 ± 10.2
HbA1C (%)	5.9 ± 1.5	5.6 ± 1	5.7 ± 1.3
FBG (mg/dL)	113.2 ± 51.4	101.9 ± 34.9	107.7 ± 44.4
BMI (kg/m ²)	28.7 ± 3.1^a	26.5 ± 3.8	27.6 ± 3.6

SD, Standard deviation; HDL, high density lipoprotein; TG, triglyceride; HbA1C, hemoglobin A1C; FBG, free blood glucose; BMI, body mass index; ^a $p < 0.001$.

Table 2: The distributions of the genotypes and alleles for rs4238001.

<i>SR-BI</i> rs4238001	Metabolic syndrome		Control		p-Value
	n	%	n	%	
Genotype					
CC	34	32.7	44	44	0.017
CT	48	46.2	46	46	
TT	22	21.1	10	10	
Allele					
C	116	55.8	134	67	0.02
T	92	44.2	66	33	

Table 3: The distributions of the genotypes and alleles for rs5888.

<i>SR-BI</i> rs5888	Metabolic syndrome		Control		p-Value
	n	%	n	%	
Genotype					
CC	39	37.5	35	44	Reference
CT	45	43.2	41	46	0.96201
TT	20	19.2	24	10	0.44637
Allele					
C	123	59.1	111	55.5	Reference
T	85	40.9	89	44.5	0.45804

other hand, rs5888 polymorphism had no effect. Among the variants, rs4238001 T allele increased 1.61 fold MetS risk (95% CI=1.077–2.407; OR=1.610; $X^2=5.42$; $p=0.02$), while the risk of metabolic syndrome is increased 1.35 fold in those with the CT heterozygous genotype (95% CI: 0.739–2.468; OR=1.35; $X^2=0.95$; $p=0.33$). It was determined that subjects with TT genotype 2.847 fold increased risk of metabolic syndrome according to subjects with CC genotype (95% CI: 1.191–6.804; OR=2.847; $X^2=5.75$; $p=0.017$).

The rs4238001 polymorphism was examined with clinical features in the metabolic syndrome group and MetS group's genotypes are shown in Table 4 including

the demographics, waist circumference, HDL and TG levels. When these clinical characteristics were compared according to the genotypes, no relation was determined between the genotypes ($p_{\text{Weight}}=0.952$, $p_{\text{BMI}}=0.659$, $p_{\text{Waist}}=0.303$, $p_{\text{HDL}}=0.622$, $p_{\text{Triglyceride}}=0.661$).

Discussion

Our results show that rs4238001 polymorphism increases the risk of susceptibility to MetS. Among the variants, subjects with rs4238001 TT genotype had 2.847 fold increased risk of MetS compared to subjects with CC genotype (95% CI: 1.191–6.804; OR=2.847; $X^2=5.75$; $p=0.017$). However, these effects were not observed in rs5888 polymorphism.

In Turkey, it is estimated that 28% of men and 40% of women have MetS. The 53% of the coronary artery patients are also affected by the metabolic syndrome [24]. Two of the components in the MetS definition are directly related to dyslipidemia (high TG levels and low HDL levels). Furthermore, low HDL levels are a risk factor for major cardiovascular disease (CVD) and coronary artery disease (CAD) [25, 26]. The most important function of HDL to protect against atherosclerosis is HDL-mediated reverse cholesterol transport. HDL takes cholesterol from surrounding tissues including macrophages and arterial wall and leaves the cholesterol in the liver. The discovery of *SR-BI* increased the interest of the molecular infrastructure involved in reverse cholesterol transport and the control of serum HDL cholesterol levels influencing by this transport system [27]. Apo-B and Apo-E are ligands of *SR-BI* which affects recognition of these lipoproteins and taking into the cell [28–30]. Thus, *SR-BI* variants may have a key role in lipid levels containing Apo-B and Apo-E lipoproteins and may contribute to development of MetS.

Juárez-Meavepeña et al. found that the *SR-BI* rs5888 T allele was associated with MetS in pediatric patients ($p=0.02$) [31]. In another study, researchers found that hypercholesterolemic (HC) individuals carrying C allele had a lower change in total cholesterol, LDL-C, apoB

Table 4: Average of the patient's characteristics according to the genotype for rs4238001.

Genotype	n	Weight (kg)	BMI (kg/m ²)	Waist circumference (cm)	HDL (mg/dL)	Triglyceride (mg/dL)
CC	34	86.9 ± 1.9	28.22 ± 0.45	103.5 ± 1.44	33.08 ± 0.53	262 ± 23.5
CT	48	87.1 ± 1.4	28.60 ± 0.42	105.6 ± 1.46	32.93 ± 0.63	289.6 ± 22.2
TT	22	89.6 ± 2.7	29.42 ± 0.86	105.6 ± 2.03	33.54 ± 0.88	308 ± 57.8
p-Value		0.952	0.659	0.303	0.622	0.661

BMI, Body mass index; HDL, high density lipoprotein.

and apoB/apoAI ratio ($p=0.05$) response to atorvastatin [32]. Wu et al. reported that the genotypic frequencies of rs5888 were different between CAD patients and controls [33]. The subjects with TT genotype had a higher CAD risk ($p=0.036$). Furthermore, the subjects with the TT genotype in controls had higher serum LDL-C and Apo-B levels than the subjects with the CC genotype ($p<0.05$) and the subjects with the TT genotype in the total population had lower levels of HDL-C than C allele carriers ($p<0.05$). Rodriguez-Esparragon et al. found that CC major allele increased coronary heart disease by 50% independent of serum lipid levels in a patient-controlled trial [26]. Morabia et al. reported that the minor allele frequencies of the *SR-BI* gene exons 1 (rs4238001) and exon 8 (rs5888) variation were found 12% and 49% in the case-control study, respectively [34]. *SR-BI* rs5888 polymorphism showed atherosclerotic protective effect ($p<0.03$) in men but not in women. *SR-BI* rs5888 genotypes had a protective HDL-C effect in men ($p=0.0062$) and a deleterious LDL-C effect in women ($p=0.014$). Thus, they suggested that *SR-BI* rs5888 variation had gender-specific and age-related effects on HDL and LDL. However, in our study, *SR-BI* rs5888 major C allele frequency was 59.1% and the minor T frequency was 40.9% in the MetS group ($p>0.05$), while 55.5% and 44.5% in the control group, respectively ($p>0.05$). Moreover, we observed rs5888 variant had no statistically significant effect on MetS or HDL, either TG levels.

Cerda et al. reported that rs4238001 C>T polymorphism minor allele frequency was 14% in normolipidemic individuals and 12% in individuals with hypercholesterolemia [32]. Another study conducted in the United States found that *SR-BI* protein levels are independent predictors of HDL-C. Carriers with rs4238001 A allele had low *SR-BI* levels and rs4238001 variation was reported as independent predictors of *SR-BI* protein levels [35]. Acton et al. found that the *SR-BI* rs4238001 was statistically significant with high HDL-C and low LDL-C levels in men [19]. A meta-analysis showed that rs4238001 T allele had higher risk of coronary heart disease (CHD) under a consistent and formally adjudicated definition of CHD events [36]. AA genotype was associated with an increased risk of significant coronary stenosis (SCS) in diabetics and metabolic syndrome. Furthermore, the exon 1 polymorphism AA genotype, in other words TT genotype of rs4238001 was found no associated with lipids or apolipoproteins. Researchers also found the AA genotype is associated with an increased risk of SCS in diabetics and patients with MetS [37]. In our study, the rs4238001 variation major C allele frequency was 55.8% and the minor T frequency was 44.2% in the MetS group, while alleles were found 67% and 33% in control group, respectively ($p=0.002$). The frequency of

rs4238001 T allele was higher than Brazilian populations [32]. It was determined that rs4238001 T allele increases the risk of MetS 1.61 fold and the patients with TT genotype have 2.847 fold increased this risk of MetS compared to CC genotype. No significant relationship was observed between TG, HDL levels and rs4238001. However, the subjects with T allele (CT+TT) had higher triglyceride levels, BMI, and weight but that was not statically significant.

Our study population was limited and patients were used statin derivative drugs in the treatment. Thus, this therapy may prevent the association between HDL, TG and the variations. We also did not replicate our results in independent materials. In the Turkish population with TEKHARF study [8], the polymorphisms in *ATP binding cassette transporter A1 (ABCA1)*, *Apolipoprotein A1 (APOA1)*, *Apolipoprotein C3 (APOC3)*, *Apolipoprotein A5 (APOA5)*, *Lipoprotein lipase (LPL)* genes involved in HDL metabolism and reverse cholesterol metabolism were also studied for the determination of polymorphisms and haplotypes of candidate genes in relation to cardiovascular and metabolic events [8]. Especially, It has been emphasized that the *APOC3*-482TT genotype and the T1131>C and c.56C>G polymorphisms of the *APOA5* gene might be related with the MetS. Thus, *SR-BI* gene variations can be assessed with other genes related to the MetS such as *APOC3* and *APOA5* to determinate MetS risk [38, 39].

Conclusion

We found that the *SR-BI* rs4238001 gene variation might be related with metabolic syndrome. This research is the first report about *SR-BI* gene variations in Turkish patients with metabolic syndrome. However, we believe that the investigation of *SR-BI* gene variations is important for diseases requiring dyslipidemia treatment and we intend to continue to contribute to the work in this area.

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References

1. Alshehri AM. Metabolic syndrome and cardiovascular risk. *J Family Community Med* 2010;17:73–8.
2. Paoletti R, Bolego C, Poli A, Cignarella A. Metabolic syndrome, inflammation and atherosclerosis. *Vasc Health Risk Manag* 2006;2:145–52.
3. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989;149:1514–20.

4. Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. *Endocrinol Metab Clin North Am* 2004;33:351–75.
5. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008;28:629–36.
6. Balkau B, Charles MA, Drivsholm T, Borch Johnsen K, Wareham N, Yudkin JS, et al. Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab* 2002;28:364–76.
7. Onat A, Sansoy V. Halkımızda Koroner Hastalığın Başşuçuşu Metabolik Sendrom: Sıklığı, Unsurları, Koroner Risk ile İlişkisi ve Yüksek Risk Kriterleri. *Türk Kardiyol Dern Arş* 2002;30:8–15.
8. Onat A, Can G, Yüksel H, Ademoğlu E, Erginel Ünaltuna N, Kaya A, et al. TEKHARF 2017: Tıp Dünyasının Kronik Hastalıklara Yaklaşımına Öncülük. İstanbul, Turkey: Logos Yayıncılık, 2017:48–9.
9. Perusse L, Rice T, Despres JP, Bergeron J, Province MA, Gagnon J, et al. Familial resemblance of plasma lipids, lipoproteins and postheparin lipoprotein and hepatic lipases in the HERITAGE Family Study. *Arterioscler Thromb Vasc Biol* 1997;17:3263–9.
10. Rice T, Vogler GP, Perry TS, Laskarzewski PM, Rao DC. Familial aggregation of lipids and lipoproteins in families ascertained through random and nonrandom probands in the Iowa Lipid Research Clinics family study. *Hum Hered* 1991;41:107–21.
11. Austin MA, King MC, Bawol RD, Hulley SB, Friedman GD. Risk factors for coronary heart disease in adult female twins. Genetic heritability and shared environmental influences. *Am J Epidemiol* 1987;125:308–18.
12. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-B1 as a high density lipoprotein receptor. *Science* 1996;271:518–20.
13. Rigotti A, Trigatti BL, Penman M, Rayburn H, Herz J, Krieger M. A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism. *Proc Natl Acad Sci USA* 1997;94:12610–5.
14. Acton SL, Osgood D, Donoghue M, Corella D, Pocovi M, Cenarro A, et al. Association of polymorphisms at the SR-BI gene locus with plasma lipid levels and body mass index in a white population. *Arterioscler Thromb Vasc Biol* 1999;19:1734–43.
15. Tang Y, Taylor KT, Sobieski DA, Medved ES, Lipsky RH. Identification of a human CD36 isoform produced by exon skipping. Conservation of exon organization and pre-mRNA splicing patterns with a CD36 gene family member, CLA-1. *J Biol Chem* 1994;269:6011–5.
16. Calvo D, Vega MA. Identification, primary structure, and distribution of CLA-1, a novel member of the CD36/LIMPII gene family. *J Biol Chem* 1994;268:18929–35.
17. Acton SL, Scherer PE, Lodish HF, Krieger M. Expression cloning of SR-BI, a CD36-related class B scavenger receptor. *J Biol Chem* 1994;269:21003–9.
18. Varban ML, Rinninger F, Wang N, Fairchild-Huntress V, Dunmore JH, Fang Q, et al. Targeted mutation reveals a central role for SR-B1 in hepatic selective uptake of high density lipoprotein cholesterol. *Proc Natl Acad Sci USA* 1998;95:4619–24.
19. Acton S, Osgood D, Donoghue M, Corella D, Pocovi M, Cenarro A, et al. Association of polymorphisms at the SR-B1 gene locus with plasma lipid levels and body mass index in a white population. *Arterioscler Thromb Vasc Biol* 1999;19:1734–43.
20. McCarthy JJ, Lewitzky S, Reeves C, Permutt A, Glaser B, Groop LC, et al. Polymorphisms of the HDL receptor gene associated with HDL cholesterol levels in diabetic kindred from three populations. *Hum Hered* 2003;55:163–70.
21. Tanaka T, Delgado Lista J, Lopez-Miranda J, Perez-Jimenez F, Marin C, Perez-Martinez P, et al. Scavenger receptor class B type I (SCARB1) c.1119C>T polymorphism affects postprandial triglyceride metabolism in men. *J Nutr* 2007;137:578–82.
22. Graf GA, Roswell KL, Smart EJ. 17 beta-estradiol promotes the up-regulation of SR-BII in HepG2 cells and in rat livers. *J Lipid Res* 2001;42:1444–9.
23. Lopez D, McLean MP. Estrogen regulation of the scavenger receptor class B gene: antiatherogenic or steroidogenic, is there a priority? *Mol Cell Endocrinol* 2006;247:22–33.
24. Binici DN, Kayabekir M, Timur O, Sanıbas AV, Tasar PT, Baydar I. Prevalence of metabolic syndrome in patients with obstructive sleep apnea syndrome: a single center experience. *Ann Clin Exp Metabol* 2016;1:1010.
25. Lavie CJ, Milani RV, O'Keefe JH. Dyslipidemia intervention in metabolic syndrome: Emphasis on improving lipids and clinical event reduction. *Am J Med Sci* 2011;341:388–93.
26. Rodriguez-Esparragon F, Rodriguez-Perez JC, Hernandez-Trujillo Y, Macias-Reyes A, Medina A, Caballero A, et al. Allelic variants of the human scavenger receptor class B type 1 and paraoxonase 1 on coronary heart disease: genotype-phenotype correlations. *Arterioscler Thromb Vasc Biol* 2005;25:854–60.
27. Van Eck M, Pennings M, Hoekstra M, Out R, Van Berkel TJ. Scavenger receptor BI and ATP-binding cassette transporter A1 in reverse cholesterol transport and atherosclerosis. *Curr Opin Lipidol* 2005;16:307–15.
28. Murao K, Terpstra V, Green SR, Kondratenko N, Steinberg D, Quehenberger O. Characterization of CLA-1, a human homologue of rodent scavenger receptor BI, as a receptor for high density lipoprotein and apoptotic thymocytes. *J Biol Chem* 1997;272:17551–7.
29. Gu X, Lawrence R, Krieger M. Dissociation of the high density lipoprotein and low density lipoprotein binding activities of murine scavenger receptor class B type I (mSR-BI) using retrovirus library-based activity dissection. *J Biol Chem* 2000;275:9120–30.
30. Bultel Brienne S, Lestavel S, Pilon A, Laffont I, Tailleux A, Fruchart JC, et al. Lipid free apolipoprotein E binds to the class B type I scavenger receptor I (SR-BI) and enhances cholesteryl ester uptake from lipoproteins. *J Biol Chem* 2002;277:36092–9.
31. Juárez-Meavepeña M, Carreón-Torres E, López-Osorio C, García-Sánchez C, Gamboa R, Torres-Tamayo M, et al. The Srb1+1050T allele is associated with metabolic syndrome in children but not with cholesteryl ester plasma concentrations of high-density lipoprotein subclasses. *Metab Syndr Relat Disord* 2012;10:110–6.
32. Cerda A, Genvigir FD, Arazi SS, Hirata MH, Dorea EL, Bernik MM, et al. Influence of SCARB1 polymorphisms on serum lipids of hypercholesterolemic individuals treated with atorvastatin. *Clin Chim Acta* 2010;411:631–7.
33. Wu DF, Yin RX, Cao XL, Chen WX, Aung LH, Wang W, et al. Scavenger receptor class B type 1 gene rs5888 single nucleotide polymorphism and the risk of coronary artery disease and ischemic stroke: a case-control study. *Int J Med Sci* 2013;10:1771–7.
34. Morabia A, Ross BM, Costanza MC, Cayanis E, Flaherty MS, Alvin GB, et al. Population-based study of SR-BI genetic variation and lipid profile. *Atherosclerosis* 2004;175:159–68.

35. West M, Greason E, Kolmakova A, Jahangiri A, Asztalos B, Pollin TI, et al. Scavenger receptor class B type I protein as an independent predictor of high-density lipoprotein cholesterol levels in subjects with hyperalphalipoproteinemia. *J Clin Endocrinol Metab* 2009;94:1451–7.
36. Manichaikul A, Wang XQ, Musani SK, Herrington DM, Post WS, Wilson JG, et al. Association of the lipoprotein receptor SCARB1 common missense variant rs4238001 with incident coronary heart disease. *PLoS One* 2015;10:e0125497.
37. Rejeb J, Omezzine A, Boumaiza I, Rebhi L, Kacem S, Rejeb NB, et al. Association of three polymorphisms of scavenger receptor class BI gene (exon8, exon1, intron5) with coronary stenosis in a coronary Tunisian population. *Gene* 2012;511:383–8.
38. Onat A, Erginel-Unaltuna N, Hergenç G, Çoban N, Yüksel H. APOC3 -482C>T polymorphism, circulating apolipoprotein C-III and smoking: Interrelation and roles in predicting type-2 diabetes and coronary disease. *Clin Biochem* 2011;44:391–6.
39. Komurcu-Bayrak E, Onat A, Poda M, Humphries SE, Palmen J, Guclu F, et al. Gender-modulated impact of apolipoprotein A5 gene (APOA5) -1131T>C and c.56C>G polymorphisms on lipids, dyslipidemia and metabolic syndrome in Turkish adults. *Clin Chem Lab Med* 2008;46:778–84.