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Polymorphisms in ABC transporters (ABCA1 and ABCC8) in metabolic syndrome

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Aim: To identify important single nucleotide polymorphisms (SNPs) in the ABCA1 and ABCC8 (SUR1) genes and determine if they are associated with metabolic syndorome (MetS).

Materials and methods: Fifty-eight subjects fulfilling all 5 MetS criteria were chosen from 4809 subjects who participated in our screening study (Trabzon MetS study). Forty-three subjects who did not fulfill any MetS criteria were chosen as the control group. Genotyping of the samples after DNA isolation was performed by direct sequencing. For SNP analysis, exons 7, 15, 19, 36, 41, and 49 for ABCA1 and exons 16 and 18 for ABCC8 were selected.

Results: The most important SNPs in the present study were R219K (AGG-AAG for codon 219 in exon 7) for ABCA1, and 16-3t (CTT-TTT for codon 723 in exon 16) and GAC-GAG for codon 760 in exon 18 for ABCC8.

Conclusion: It was concluded that MetS may be associated with polymorphisms in ABCA1 and ABCC8.

Key words: Metabolic syndrome, ATP-binding cassette transporters, ABCA1, ABCC8 (SUR1, sulfonylurea receptor), polymorphisms

1. Introduction

Metabolic syndrome (MetS) has been described as a "clustering" of several risk factors for cardiovascular disease (CVD) such as hypertension, dyslipidemia [specifically, high triglycerides, low levels of high-density lipoprotein (HDL), and increased small dense low-density lipoprotein (LDL)], obesity (particularly central or abdominal obesity), insulin resistance, and impaired glucose tolerance or diabetes mellitus (DM) (1). Insulin resistance or hyperinsulinemia has been suggested to be the underlying characteristic of MetS (2). Previously we reported that the MetS prevalence was 26.9% in a study done in Trabzon, Turkey (3).

Transmembrane transport is mediated by specific proteins associated with the membrane. The ATP-binding cassette (ABC) transporters are known as the most important members of transmembrane proteins. This type of protein has ATP-binding sites and uses energy to manage the transport of various molecules across cell membranes. ABC transporters participate in many important biological processes. In addition, they are associated with clinical problems such as cystic fibrosis and multidrug resistance. Over 50 ABC transporters are known (4–6).

The ABCA1 gene, a member of the ATP-binding cassette A (ABCA1) transporter superfamily, is reported to encode a membrane protein that facilitates the cellular efflux of cholesterol and phospholipids. Mutations in ABCA1 are seen in familial HDL deficiency and Tangier disease. Santamarina-Fojo et al. found that the *Homo sapiens* ATP-binding cassette, subfamily A (ABC1), member 1 (ABCA1) gene, spans 149 kb and contains 50 exons. In addition, they reported that the fragment spanning 220 to 280 bp of the ABCA1 gene promoter contains a cholesterol-regulatory element that modulates ABCA1 expression in macrophages. Their findings provided insight into the mechanisms that regulate the expression of this key receptor involved in cellular cholesterol efflux (7). The roles of ABCA1 include regulation of the apolipoprotein A1-dependent cellular export of cholesterol and phospholipids (8) (thus, ABCA1 participates in the initial steps in HDL formation and in reverse cholesterol transport); engulfment of apoptotic cells by macrophages (9); secretion of macrophage cytokines (9); and caveolar processing (10).

The ABCC subfamily contains 12 full transporters. They have various functions, including ion transport, cell surface receptor, and toxin-secretion activities.

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The ABCC8 (SUR1) gene is on chromosome 11p15.1 and encodes transporter protein with a high-affinity receptor for the drug sulfonylurea. *Homo sapiens* ATP-binding cassette, subfamily C, member 8 (ABCC8), is 11,246 bp long and contains 39 exons. Sulfonylureas are a class of drugs widely used to increase insulin secretion in patients with type 2 DM. These drugs bind to the ABCC8 protein and inhibit associated potassium channel Kir6.2 (KCNJ11). Familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is an autosomal recessive disorder in which subjects have defects in regulation of insulin secretion. The disease has been mapped by linkage analysis, and mutations in the ABCC8 gene were found in PHHI families (11,12).

Our major aim is to identify important polymorphisms in the ABCA1 and ABCC8 genes and determine if they are associated with insulin resistance and dyslipidemia in MetS. Important polymorphisms in the ABCA1 and ABCC8 genes have been investigated here for the first time.

2. Materials and methods

2.1. Subjects

A total of 4809 subjects (2601 women and 2208 men, >20 years old) were screened in an epidemiological study titled "Prevalence of metabolic syndrome and associated risk factors among Turkish adults" (Trabzon MetS study) (3). MetS is defined by the National Cholesterol Education Program Adult Treatment Panel III criteria (13,14), which include abdominal obesity (waist circumference of >88 cm for women and >102 cm for men), high triglyceride levels (>150 mg/dL), decreased HDL-cholesterol (HDL-C) levels (<50 mg/dL for women and <40 mg/dL for men), impaired fasting blood glucose (≥100 mg/dL), and hypertension (blood pressure of >130/85 mmHg). Fifty-eight subjects (32 women and 26 men) who fulfilled all 5 MetS criteria were chosen for the study. Twenty-three subjects with MetS (40%) had type 2 DM or had been newly diagnosed in the Trabzon MetS study. In addition, 43 subjects (24 women, 19 men) who did not fulfill any MetS criteria were chosen for the control group. Routine biochemical and some demographical parameters of the subjects are shown in Table 1. All the parameters were found to be significantly different between the MetS group and the control group, except for sex. The study protocol was approved by the ethics committee of the Faculty of Medicine, Karadeniz Technical University.

2.2. Biochemical analyses

Serum total cholesterol, triglycerides, HDL-C, LDL-C, and glucose determinations were made by the cholesterol oxidase, glycerol phosphate oxidase cholesterol oxidase/esterase modified by polyethylene glycol, homogeneous enzymatic colorimetric, and glucose oxidase methods, respectively. All commercial reagents were supplied by Roche (Turkey).

Table 1. Biochemical and some demographical parameters of the subjects [mean ± SD (ranges)].

	Control (n = 43)	Patients with MetS (n = 58)	P
Sex, women/men	24/19	32/26	
Age (years)	43 ± 12 (22–75)	51 ± 14 (21–80)	0.003*
Glucose (mg/dL)	82 ± 9 (66–105)	131 ± 60 (64–345)	0.001*
Total cholesterol (mg/dL)	173 ± 17 (140–210)	196 ± 50 (104–297)	0.001*
Triglycerides (mg/dL)	85 ± 29 (37–155)	241 ± 99 (79–506)	0.001**
HDL-C (mg/dL)	60 ± 12 (40–99)	41 ± 8 (28–70)	0.001*
LDL-C (mg/dL)	107 ± 20 (26–141)	133 ± 43 (60–222)	0.001*
Systolic blood pressure (mmHg)	115 ± 12 (90–140)	149 ± 22 (110–200)	0.001*
Diastolic blood pressure (mmHg) 75 ± 11	89 ± 12 (50–100)	0.001* (60–120)	
Waist circumference (cm)	84 ± 11 (66–104)	(106 ± 16) (50–165)	0.001*

* Student t-test, **Mann–Whitney U test

All analyses were performed using the Roche modular autoanalyzer with daily internal quality controls.

2.3. Genotyping

Genomic DNA was isolated from peripheral blood in accordance with standard procedures (Invisorb Spin Blood Mini Kit; Invitek). Genotyping of the samples was performed by direct sequencing, reacted with a BigDye Terminator v3.1 cycle sequencing system (Applied Biosystems), and analyzed with an ABI 3100 capillary sequencer (Applied Biosystems). For single nucleotide polymorphism (SNP) analysis, exons 7, 15, 19, 36, 41, and 49 for ABCA1 and exons 16 and 18 for ABCC8 were selected. Forward (F) and reverse (R) primary sequences of these exons are shown in Table 2. Distributions of genotype frequency did not deviate from Hardy–Weinberg equilibrium.

2.4. Statistical analysis

The genotype frequencies obtained were tested for Hardy–Weinberg equilibrium by the chi-square test. The allele and genotype frequencies were compared between MetS and control subjects by the chi-square test. Statistical comparisons of routine biochemical parameters between groups or alleles were tested by either the Student t-test or the Mann–Whitney U test using SPSS for Windows 11.5.0. $P < 0.05$ was considered to be statistically significant.

3. Results

The types of SNPs found in the study are shown in Table 3. Statistically significant frequencies of genotypes and alleles are shown in Table 4. According to the results obtained, the most important polymorphisms include AGG-AAG for codon 219 in exon 7 (R219K variant), GCA-GCT for codon 920 in exon 19, CGG-AGG for codon 1860 in exon 41, and AGG-AAG for codon 1877 in exon 41 for ABCA1; and CTT-TTT for codon 723 in exon 16 (16-3t variant) and GAC-GAG for codon 760 in exon 18 for ABCC8. All of the SNPs in MetS have been reported here for the first time. In addition, ATC-ATA for codon 680 in exon 15 was found in only 2 subjects for MetS, and 6 insertions were found in exons 7, 19, and 49 for ABCA1. The ACC-ACT polymorphism for codon 759 in exon 18 was found in 1 control subject and in 2 subjects with MetS; ACC-AGC for codon 759 in exon 18 for ABCC8 was found in only 1 subject with MetS.

4. Discussion

ABCA1 is an effective exporter of cholesterol from macrophages and other cells. Therefore, it is a major determinant of plasma HDL-C levels. Due to its role in reverse cholesterol transport, it is a potent cardioprotective factor (15).

Relationships between the ABCA1 gene and human diseases have been investigated. In particular, ABCA1

Table 2. Primary sequences of the exons.

Protein	Exon no.	Primary sequence
ABCA1	7	F: 5'-AAGGACCCAGCTTCCAATCTTC-3'
		R: 5'-GCCTCACATTCCGAAAGCAT-3'
	15	F: 5'-GGTCAATGCCCCTCTTCATG-3'
		R: 5'-GCTATTTCGGAGTTTCCTGGC-3'
	19	F: 5'-CTCCTGCCTGCCTGAGAAAC-3'
		R: 5'-CCCTCCTGTGGCTGATTCTG-3'
	36	F: 5'-TTTCTGAGGTTTATGGGCATGG-3'
		R: 5'-GAGCTGCTGCTTGGTGAGATT-3'
	41	F: 5'-TTTTCCTTGTCATGGGTGATAGC-3'
		R: 5'-CAGGTGCTCCACGGGTTCTA-3'
	49	F: 5'-GGGCCGCCCTTTTTCAT-3'
		R: 5'-TCGCTTTTTGCTCTGGGAGA-3'
ABCC8	16	F: 5'-GGTAATGGTTGTTCAGACTCCCC-3'
		R: 5'- TGAACACAGAGTGGG CCCTC-3'
	18	F: 5'- AGGCTTCCCCAAGATGGG-3'
		R: 5'- GCAGGGTGATGTGGCTCC-3'

Table 3. SNPs found in ABCA1 exon 7, exon 15, exon 19, exon 36, exon 41, and exon 49 and in ABCC8 exon 16 and exon 18.

Location	Codon	Nucleotide mutation	Amino acid alteration
ABCA1 exon 7	192	CAT-CGT	His-Ala
	219	AGG-AAG	Arg-Lys
	231	TCC-TTC	Ser-Phe
ABCA1 exon 15	680	ATC-ATA	- -Iso
ABCA1 exon 19	901	ATT-TTT	Iso-Phe
	904	CTG-TTG	- -Leu
	919	CTG-TTG	- -Leu
	920	GCA-GCT	- -Ala
	935	AAT-AAG	Asp-Lys
ABCA1 exon 36	1590	CAG-CAA	- -Glu
ABCA1 exon 41	1855	GCC-TCC	Ala-Ser
	1858	GTG-GAG	Val-Glu
	1860	GGG-AGG	Gly-Arg
	1861	GTG-GAG	Val-Glu
	1877	AGG-AAG	Arg-Lys
ABCA1 exon 49	2161	GAC-GAA	Asp-Glu
ABCC8 exon 16	723	CTT→TTT	Leu-Phe
ABCC8 exon 18	759	ACC→ACT	Thr-Thr
	759	ACC→AGC	Thr-Ser
	760	GAC→GAG	Asp-Glu
	761	TTG→GTG	Leu-Val

gene mutations and SNPs have been found in patients with Tangier disease and in subjects with familial HDL deficiency (hypoalphalipoproteinemia) associated with reduced cholesterol efflux (16–18). Marcil et al. (17) found that C2665T in exon 18, T3212C in exon 22, C6370 in exon 49, and a double deletion in exon 41 polymorphisms in the ABCA1 gene in familial HDL deficiency were related with low HDL-C levels. Changren and Oram reviewed recently that over 70 mutations in ABCA1 have been identified in subjects with low plasma HDL-C levels, more than half of which are missense mutations. Although these mutations occur throughout the gene, they tend to cluster in the extracellular loops, the NBD domains, and the C-terminal region. Furthermore, SNP analyses have identified over 20 common polymorphisms (>1% allelic frequency) in the coding, promoter, and 5'-UTR regions of ABCA1 (15). Iida et al. (19) reported variants of R219K and I680 in 48 healthy Japanese individuals. Clee et al. (20) found that the R219K variant has a carrier frequency of 46% in Europeans; carriers have a reduced severity of CAD, decreased focal and diffuse atherosclerosis, and fewer coronary events. They also reported that carriers have decreased triacylglycerol levels and a trend toward increased HDL-C. Benton et al. (21) concluded in their "Multi-Ethnic Study of Atherosclerosis (MESA)" that the AA genotype of the variant is associated with slightly higher HDL-C and lower prevalence of coronary artery calcification, and thus may protect against subclinical cardiovascular disease. Therefore, the R219K variant has been recognized as a putative antiatherogenic polymorphism, and the A allelic form of the variant has been associated with increased HDL-C levels. Hodoğlugil et al. (22) reported that a combination of R219K with –C-14T was associated with high HDL-C in both Turkish males and females. However,

Table 4. Frequencies of genotypes and alleles.

SNPs	n	Control 43	MetS 58	χ^2	P
ABCA1 exon 7 codon 219 AGG → AAG	Genotype				
	G/G	30 (0.70)	28 (0.48)		
	G/A	10 (0.23)	22 (0.38)		
	A/A	3 (0.07)	8 (0.14)	6.998, df = 1	0.008
	Allele				
	G	70	78		
	A	16	38		
ABCA1 exon 19 codon 920 (W) GCA→GCT	Genotype				
	A/A	43 (1.00)	52 (0.90)		
	A/T	0	6 (0.10)		
	T/T	0	0	4.729, df = 1	0.03
	Allele				
	A	86	110		
	T	0	6		
ABCA1 exon 41 codon 1860 GGG→AGG	Genotype				
	G/G	43 (1.00)	55 (0.95)		
	G/A	0	3 (0.05)		
	A/A	0	0	2.292, df = 1	0.130
	Allele				
	G	86	113		
	A	0	3		
ABCA1 exon 41 codon 1877 AGG→AAG	Genotype				
	G/G	43 (1.00)	52 (0.90)		
	G/A	0	6 (0.10)		
	A/A	0	0	4.729, df = 1	0.03
	Allele				
	G	86	110		
	A	0	6		
ABCC8 exon 16 codon 723 CTT→TTT	Genotype				
	C/C	43 (1.00)	39 (0.67)		
	C/T	0	18 (0.31)		
	T/T	0	1 (0.02)	44.446, df = 1	0.001
	Allele				
	C	86	96		
	T	0	20		
ABCC8 exon 18 codon 759 ACC→ACT	Genotype				
	C/C	42(0.98)	55 (0.95)		
	C/T	1(0.02)	3 (0.05)		
	T/T	0	0	89.356, df = 1	0.001
	Allele				
	C	85	113		
	T	1	3		
ABCC8 exon 18 codon 760 GAC→GAG	Genotype				
	C/C	43 (1.0)	43 (0.74)		
	C/G	0	15 (0.26)		
	G/G	0	0	55.693, df = 1	0.001
	Allele				
	C	86	101		
	G	0	15		
ABCC8 exon 18 codon 761 TTG→GTG	Genotype				
	T/T	43 (1.0)	53 (0.91)		
	T/G	0	1 (0.02)		
	G/G	0	4 (0.07)	178.772, df = 1	0.001
	Allele				
	T	86	107		
	G	0	9		

Table 5. Association of SNPs with type 2 DM (a: exon 16-3t, b: exon 18, codon 759 for ABCC8).

Association with type 2 DM		
SNP a	SNP b	Ref.
+	+	Inoue (27)
-	+	Hansen (28)
+	-	't Hart (29,30)
+	-	Rissanen (31)
-	-	Reis (32)
-	-	Gloyn (33)
-	-	van Dam (34)
+	-	Yokoi (35)

these associations have not been found in all studies. Frikke-Schmidt et al. (23) suggested that variants of R219K and I680 did not affect HDL-C levels in the general population. Li et al. (24) pointed out that the R219K polymorphism was not significantly associated with CAD. Singaraja et al. (25) reviewed ABCA1 mutations and SNPs, especially the R219K variant, and concluded that the R219K variant is antiatherogenic. The R219K polymorphism was found in 30 (52%) of 58 subjects with MetS in the study. Of these, 8 were homozygotes (A/A) and 22 were heterozygotes (G/A). According to Oram's recent review (15), ABCA1 has become a new therapeutic target for developing drugs designed for clearing cholesterol from arterial macrophages and preventing CVD. For example, prevention of oxidative damage to apolipoproteins in the artery wall could also be an important therapeutic approach for enhancing the ABCA1 pathway. Factors that are elevated in individuals with MetS and diabetes, such as fatty acids and glycoxidation products, destabilize ABCA1 in cultured macrophages, raising the possibility that damaged ABCA1 contributes to the increased CVD that is prevalent in patients with these common disorders (15).

The physiological roles of ABCC8 channels include contribution to glucose homeostasis by regulating insulin secretion from pancreatic β cells, glucagon secretion from pancreatic α cells, somatostatin secretion from D cells, and GLP-1 secretion from L cells (26). Association studies on variants of exon 16-3t and exon 18 in codon 759 for ABCC8 in type 2 DM are shown in Table 5 (27–35). As can be seen there, conflicting results were obtained for these SNPs. The ABCC8 exon 18 variant was associated with glucose intolerance (36), with lower C-peptide levels (37), and with lower insulin secretion (38), but other studies did not report associations with insulin secretion (28,31). For the exon 16 variant, association with insulin secretion has not been reported clearly (30,37,39). Zychma et al. (40) reported that when the frequency of the TT homozygotes, showing a slight majority among patients with short diabetes duration treated with insulin, was compared to the frequency of the T allele carriers, no significant differences were observed. Recently, van Dam et al. (34) conducted a metaanalysis of reported association studies in Caucasian populations for common variants in ABCC8 (exons 16 and 18). The metaanalysis was based on 7768 subjects. They concluded that the ABCC8 exon 16 or exon 18 variant was not consistently associated with type 2 DM.

Mutations or SNPs for ABCA1 and ABCC8 in MetS have not been studied to date. There have been a few studies on MetS genetics. Robitaille et al. (41) found that the PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and MetS components in the Quebec Family Study including 720 adults. Akkiprik et al. (42) suggested that low acid phosphatase (ACP1) enzyme activity genotypes seem to be associated with a protective effect for the development of MetS. In the present study, the exon 16 variant was found in 19 subjects (33%) with MetS, whereas the exon 18 variant was found in 2 subjects (4%). In addition, a SNP was found in 15 subjects (26%) with MetS in exon 18 in codon 760, which is adjacent to codon 759. The total SNP count in exon 18 was found to be 23.

The sample size seems to be relatively small for such a study, but it should be pointed out that all MetS cases in the present study fulfilled all 5 criteria of MetS.

Known and new SNPs in the ABCA1 and ABCC8 transporters were found in the present study for subjects with MetS chosen from our national screening study; 40% of the subjects had type 2 DM. Some studies on the high prevalence of MetS in Turkey have been reported (3,43). It was concluded that MetS may be associated with polymorphisms in ABCA1 and ABCC8. Further studies including many subjects with MetS are required to investigate associations among ABC proteins and lipids, carbohydrates, and other metabolic parameters and to determine which factors destabilize ABC proteins.

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