Negative results in screening for possible new sequence variations on ATP-binding cassette transporter A1 gene in Turkish adults with metabolic syndrome

Metabolik sendromlu Türk yetişkinlerinde ATP bağlayıcı kaset taşıyıcı A1 (ABCA1) genindeki olası yeni dizi varyasyonlarının taramasında negatif sonuçlar

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ABSTRACT

Objectives: ATP binding cassette transporter A1 (ABCA1) plays a pivotal role in the reverse cholesterol transport. Some mutations in the ABCA1 gene have correlation with changes in serum high-density lipoprotein-cholesterol (HDL-C) and other lipids concentrations. The role of genetic factors in susceptibility to metabolic syndrome (MetS) is not clear. The aim of this study was to explore the relationship between ABCA1 gene and the MetS.

Study design: Therefore, to investigate probable new mutations in the functional regions of the ABCA1 gene, 14th, 19th and 49th exons were analyzed using single strand conformational polymorphism method in 220 subjects, 110 of whom had MetS, selected from the Turkish Adults Risk Factor study.

Results: No significant relationship was found between the functional region of ABCA1 and MetS. The risk for low HDL-C-high triglyceride levels and MetS are not associated with selected functional regions of the gene, 14th, 19th and 49th exons, which code for the first extracellular loop, the nucleotide binding domain and the C-terminal region, respectively.

Conclusion: These data indicate that the mutations and polymorphisms in ABCA1 gene are not associated with MetS in Turks.

ÖZET

Amaç: ATP bağlayıcı kaset taşıyıcı A1 (ABCA1) ters kolesterol transferinde önemli bir rol oynar. ABCA1 genindeki bazı mutasyonlar serum yüksek yoğunluklu lipoprotein-kolesterol (HDL-K) ve diğer lipit konsantrasyonlarındaki değişiklikler ile korelasyon göstermektedir. Buna karşın, metabolik sendrom (MetS) yatkınlığında genetik faktörlerin rolü açık değildir. Bu çalışmada ABCA1 geni ve MetS arasındaki ilişkinin gösterilmesi amaçlandı.

Çalışma planı: ABCA1 geninin işlevsel bölgelerindeki olası yeni mutasyonları araştırmak için 14., 19. ve 49. ekzonları SSCP (tek iplik konformasyon polimorfizmi) yöntemi kullanılarak incelendi. Türk Yetişkinleri Risk Faktörü (TEKHARF) çalışmasından seçilen 110 tanesi MetS ve 110 tanesi sağlıklı olmak üzere toplam 220 birey incelendi.

Bulgular: İncelenen fonksiyonel bölgelerde, MetS ve sağlıklı gruptaki tarama sonucunda bu ekzonlarda herhangi bir farklılık saptanmadı. Düşük HDL-C, yüksek trigliserit seviyeleri ve MetS riski ile ABCA1 geninin seçilmiş fonksiyonel bölgeleri olan ilk hücre dışı ilmek, nükleotid bağlama alanı ve C-terminal bölgesine denk gelen, 14., 19. ve 49. ekzonları ilişkili değildi.

Sonuç: Bu veriler ABCA1 genindeki mutasyonlar ve polimorfizmlerin Türk yetişkinlerinde MetS ile ilişkili olmadığını göstermektedir.

The metabolic syndrome (MetS) is characterized by abdominal obesity, insulin resistance, hyperglycemia, elevated blood pressure and a dyslipidemia consisting of elevated plasma triglyceride and decreased plasma high-density lipoprotein cholesterol (HDL-C) levels. Patients with the MetS are at high risk for cardiovascular disease.[1-3] Reduced serum HDL-C is a powerful established risk factor for coronary heart

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Abbreviations:

ABCA1	*ATP binding cassette transporter A1*
Apo	*Apolipoprotein*
BMI	*Body mass index*
CHD	*Coronary heart disease*
HDL-C	*High-density lipoprotein cholesterol*
MetS	*Metabolic syndrome*
NBD	*Nucleotide binding domain*
PCR	*Polymerase chain reaction*
RCT	*Reverse cholesterol transport*
SNPs	*Single nucleotide polymorphisms*
SSCP	*Single strand conformational polymorphism*
TARF	*Turkish Adult Risk Factor*
TC	*Total cholesterol*

disease (CHD).[4] Although HDL-C concentration is strongly influenced by environmental factors,[5] research has been focused increasingly on genetic causes leading to reduced HDL-C. The antiatherogenic function of HDL is generally attributed to its pivotal role in reverse cholesterol transport (RCT), a process that delivers excess cholesterol from macrophages within the arterial wall to the liver for disposal.[6,7] The ATP binding cassette transporter A1 (ABCA1) has been identified as the mediator of the initial step of the RCT because it facilitates the efflux of cholesterol and phospholipids from peripheral cells to lipid-poor Apolipoprotein (Apo)-AI creating nascent HDL particles.[8,9] Although there are multiple mechanisms by which HDL can be atheroprotective, it is clear that the relative activity of ABCA1 plays a major role in this process.[10]

The ABCA1 gene consists of 50 exons, spans over 147 kb on chromosome 9q31.[11] ABCA1 is a 2261-amino-acid integral membrane protein that comprises two halves of similar structure.[12] The gene is highly expressed in leukocytes and macrophages and a wide range of other tissues including liver, lung, adrenal gland and placenta.[13] The mutations in the ABCA1 gene are known to cause Tangier disease and familial HDL deficiency, both of which are characterized by low plasma concentrations of HDL-C and Apo-AI, and increased risk for premature CHD. Therefore, it is suggested that ABCA1 is a protein that plays a key role in regulating plasma lipid metabolism and a major factor in CHD risk protection.[14-17] Over 70 mutations in ABCA1 have been identified in subjects with low plasma HDL-C concentrations, more than half of which are missense mutations.[18-21] Although mutations do occur throughout the gene, they tend to cluster in the extracellular loop, the nucleotide binding domain (NBD) and the C-terminal region.[18-20] Those regions, called as hotspot regions, are also functionally important regions, and some of those regions are encoded by 14th, 19th and 49th exons.[18]

ABCA1 plays a central role in many pathways involved in the onset of the MetS, especially in HDL-cholesterol metabolism.[18,22-24]

The aim of this study was to examine the relation of ABCA1 gene with MetS, as well as atherogenic dyslipidemia, in a sample of the Turkish Adult Risk Factor (TARF) study cohort, representative of Turkish adults.[25]

PATIENTS AND METHODS

Study population

Participants of this study are derived from the cohort of the TARF study, a prospective survey on the prevalence of cardiac disease and risk factors in a representative sample of adults in Turkey conducted periodically in 59 communities throughout all geographical regions of the country. Partial logistic support was provided by the Turkish Ministry of Health. The methodology of this paper, based on the survey 2003/2004, has been previously described in detail.[25] Data were obtained on history of the past years via a questionnaire, physical examination of the cardiovascular system and recording of a resting electrocardiogram. Economic restraints limited the sample of this nested case-control study to 220 participants who attended the survey period 2004 over a third of whom was randomly selected among those identified as MetS (all of the 110 subjects with atherogenic dyslipidemia), the remainder from participants without MetS or cardiovascular disease (n=110). Participants gave written informed. The study protocol was approved by the Ethics Committee.

Definitions

Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Individuals with diabetes were diagnosed with criteria of the American Diabetes Association,[26] namely when plasma fasting glucose was ≥126 mg/dL (or 2-h postprandial glucose >200 mg/dL) and/or the current use of diabetes medication. Oral glucose tolerance test was not performed. Individuals with MetS were identified when 3 out of the 5 criteria of the National Cholesterol Education Program (ATP III)[1] were met, modified for prediabetes (fasting glucose 100-125 mg/dL)[27] and further for abdominal obesity using as a cut point ≥95 cm (instead of 102 cm) in men, whereas ≥88 cm in women as assessed in the TARF study.[28] Atherogenic dyslipidemia was defined

by high (>150 mg/dL) fasting triglyceridemia and low concentrations (<40/<50 mg/dL) of HDL-C.[1]

Measurement of risk factors

Weight was measured without shoes in light indoor clothes using a scale. BMI was computed as weight divided by height squared (kg/m^2). Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest.

Blood samples were collected after 11-h or longer fasting. Samples were shipped on cooled gel packs to Istanbul to be stored at -75°C, until analyzed at a central laboratory. Serum concentrations of total cholesterol (TC), fasting triglycerides, glucose, and HDL-C (directly without precipitation) were determined using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer. Concentrations of Apo-AI and B were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA).

Genetics analysis

The mutation screening of the 14th, 19th and 49th exons using single strand conformational polymorphism (SSCP).

DNA was extracted from peripheral blood leucocytes using a QIAmp® DNA Maxi KIT (Qiagen, Hilden, Germany). Polymerase chain reaction (PCR) was used to amplify all 3 exons of ABCA1 using primers designed at homepage of Cybergene (http://www.cybergene.se/EazyPrimer.htm) (Table 1). PCR cycling conditions included an initial denaturation step of 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s. For mutation analysis of ABCA1, the PCR products were mixed with 6 X loading dye (95% formamide, 20-mM EDTA, 0.05% bromophenol blue, 0.05% xylene cyanol), denatured for 10 min at 95°C, and placed on ice for 2-5 min. The denatured product was performed for SSCP on non-denaturing 10% or 12% polyacrylamide gel electrophoresis at 5-15 W for approximately 20 h at room temperature. After electrophoresis, the gel was fixed in 10% acetic acid for 5 min, stained with silver nitrate solution for 25 min, washed in deionized water, and developed in sodium carbonate solution for 10-15 min. DNA samples with SSCP-shifts or differing band patterns were sequenced.

Statistical analysis

All statistical analyses were performed using Windows SPSS version 10.0 software. Two-tailed t-test and analysis of variance test were used to compare continuous variables expressed as means and standard deviation, whereas categorical variables were compared using the Chi-square test. P<0.05 was considered as statistically significant.

RESULTS

Study characteristics

The biometric parameters and characteristics of the participants of the study population are shown in Table 2. The sample comprised of selected 110 participants with MetS (mean age; 46.4±9.3, 51.6% male) and 110 without MetS (mean age; 45.5±9.2, 48.4% male). As expectedly, significant differences were observed between individuals with MetS and without MetS for anthropometrical-biochemical parameters and clinical status including, BMI, waist circumference, HDL-C, TC, triglyceride, glucose, Apo-B concentrations and systolic and diastolic blood pressure levels (Table 2).

Table 1. Primers used for on the amplification of ABCA1 gene fragments

Exon	Primers (5'-3')
Exon 14 (first extracellular loop)	F: GGAATGGTTGATTACCTG
	R: GGCTTGCAGGTAACTTAC
Exon 19 (nucleotide binding domain)	F: TGTCCTTACACTCCACTCC
	R: CAGGGATCAGCATGGTTTC
Exon 49 (C-terminal region)	F: CTGGAGATCCTCCATTTG
	R: CTGTTTTGACACTCAAAGC

F: Forward primer; R: Revers primer; ABCA1: ATP binding cassette transporter A1.

Table 2. Anthropometric characteristics and lipid profiles of control subjects and those with MetS

Characteristic	Metabolic syndrome	Control	*p*
	Mean±SD	Mean±SD	
n	(110)	(110)	
Male % (n)	51.6 (47)	48.4 (44)	NS
Age (years)	46.4±9.3	45.5±9.2	NS
Body mass index (kg/m^2)	29.4±4.3	25±2.6	**<0.001**
Waist circumference (cm)	95.8±10.1	82.3±7.4	**<0.001**
Total cholesterol (mg/dL)	201.2±41.4	185±31.4	**0.001**
HDL-C (mg/dL)	33.4±7.1	40.1±14.9	**<0.001**
LDL-C (mg/dL)	119.7±39.04	111.7±27.8	NS
Fasting triglyceride (mg/dL)*	240.5±97.1	168.3±94.02	**<0.001**
Fasting glucose (mg/dL)	93.3±11.1	87.0±9.5	**<0.001**
Apolipoprotein A-I (mg/dL)	129.6±27.6	130.5±25.6	NS
Apolipoprotein B (mg/dL)	126.8±41.6	108.3±29.6	**0.009**
Systolic blood pressure (mmHg)	117.8±10.7	112.3±11.02	**<0.001**
Diastolic blood pressure (mmHg)	77.5±7.3	73.7±7.8	**<0.001**
Current smokers	37.9 (33)	62.1 (54)	**0.007**

HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; NS: Not-significant; SD: Standard deviation; MetS: Metabolic syndrome. Continuous variables are presented as mean±SD and dichotomous variables as percentages. A two-tailed t-test was used for comparison of means. n: number of subjects.

Screening of possible new sequence variations

We selected the three exons that most likely could have an effect on the function of the ABCA1 gene (Figure 1), when altered (14th, 19th and 49th exons) and checked for new sequence variations in our study subgroup (110 samples with MetS and 110 healthy samples) using SSCP. No new sequence variations were observed.

DISCUSSION

Following the discovery that mutations in ABCA1 cause Tangier Disease or familial hypoalphalipoproteinemia,[14-17] more than 90 functional variants[19,21,29] have now been reported to cause the low HDL-C phenotype. The vast majority of these mutations are located in coding regions, whereas only a few involve intronic areas.[19,21,29] Homozygotes and heterozygotes for mutations in ABCA1 display a wide range of phenotypes. Subjects who are either homozygous or compound heterozygous for mutations in ABCA1 have Tangier disease,[30] characterized by defective cellular lipid efflux and almost complete HDL deficiency. Individuals who are heterozygous carriers of ABCA1 mutations also have defective cellular lipid efflux and HDL deficiency. Interestingly, subjects with heterozygous mutations in the ABCA1 gene often have severe HDL-C deficiency, suggesting that some ABCA1 mutations may behave as dominant-negative mutations.[30] Whether heterozygosity for genetic variation in ABCA1 also contributes to HDL-C levels in the general population is presently unclear.

The identification of genes associated with MetS is important to understand better the development of this disorder. In order to explore the role of ABCA1 gene on the predisposition to MetS in Turkish adults, we screened 220 selected individuals (110 with MetS) for unknown polymorphisms and mutations in analyzed 14th, 19th and 49th exons of ABCA1 gene using SSCP method. We screened the functional regions of the gene, exons 14, 19 and 49 which code for the first extracellular loop, the NBD and the C-terminal region, respectively. We examined three exons in the human ABCA1 gene, but we could find no mutations and/or polymorphisms in the ABCA1 gene associated with MetS in Turkish adults. Although we could not

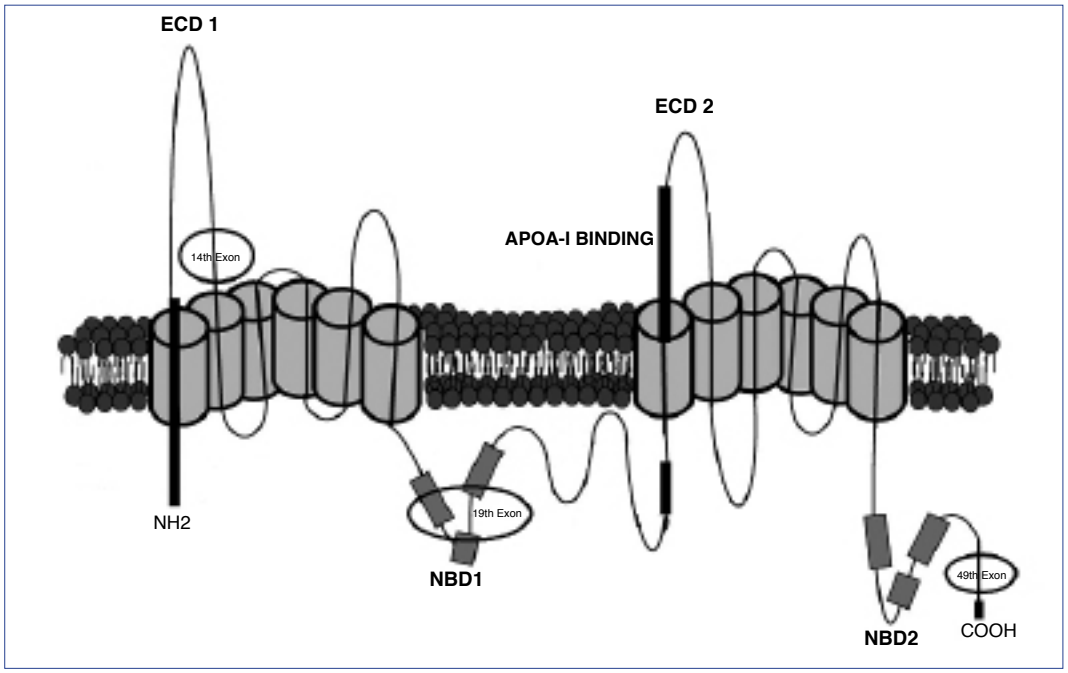

Figure 1. Location of the functional regions in the ATP binding cassette transporter A1 protein. The functional regions of the gene, exons 14, 19 and 49 which code for the first extracellular domain 1, the nucleotide binding domain 1 and the C-terminal region (black circle).

identify any mutation within the functional coding region of ABCA1 in subject with MetS, a common genetic variation (R219K) of ABCA1 gene is associated with both lipid concentrations and CHD in Turkish adults in a gender-specific manner, but not with metabolic syndrome.[31]

Moreover, Alenezi et al.[32] demonstrated that primary cellular lipid efflux defects do not contribute to the low HDL-C frequently encountered in the MetS. The extremely high correlation between phospholipid and cholesterol efflux in more than 15 mutations tested[18] indicates that ABCA1 influences efflux of both lipid types. Conversely, lipid efflux defects are a common heritable feature in subjects with low HDL-C even in the absence of coding sequence mutations in ABCA1.[33] A recent study demonstrated the molecular basis for non-ABCA1-mediated cellular lipid efflux defects leading to HDL deficiency.[34] They have demonstrated the strong potential of LXR agonists in enhancing RCT and raising HDL levels to decrease cardiovascular disease risk in humans, even when HDL deficiency is severe.[34] Thus, other genes are involved in the complex machinery of cellular lipid efflux pathways and can cause HDL deficiency.

A gender-specific modification of HDL profile was suggested by Catalano et al.[35] who demonstrated that the sera from both genders showed different capacity of cholesterol efflux in cell culture. Although SR-BI was found to be responsible for higher capacity to mediate cellular free cholesterol efflux of female plasma, ABCA1 was found to be responsible for enhanced free cholesterol efflux of male plasma. Therefore, this gender-specific quantitative difference in cholesterol efflux capacity of ABCA1 or SR-BI may lead to appear a male-or female-restricted association of single nucleotide polymorphisms (SNPs) or mutations in those genes.

This is the first report to examine ABCA1 gene in a selected sample of Turkish adults with MetS in the TARF study. We determined whether mutations or SNPs in ABCA1 were overrepresented in individuals with MetS in the general population by screening the coding region of ABCA1. The analyses were performed for screening of novel mutations using SSCP. No unknown genetic variants in 14th, 19th and 49th exons of ABCA1 gene were observed in this study group. The results demonstrated that the mutations and polymorphisms in ABCA1 gene were not associ-

ated with MetS in Turks. Further studies may still be needed in this area.

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Key words: ATP binding cassette transporter 1; atherogenic dyslipidemia; HDL-C; metabolic syndrome X; Turkish adults.

Anahtar sözcükler: ATP bağlayıcı kaset taşıyıcı 1; aterojenik dislipidemi; HDL-K; metabolik sendrom X; Türk yetişkinleri.