ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ASSOCIATION BETWEEN MDR 1 (ABCB1) GENE C3435T, C1236T, G2677T/A, A2956G POLYMORPHISMS AND THE RISK OF BREAST CANCER AMONG TURKISH WOMEN

TÜRK KADINLARINDA MDR1 (ABCB1) GENİ C3435T, C1236T, G2677T/A, A2956G POLİMORFİZMLERİ İLE MEME KANSERİ RİSKİ ARASINDAKİ İLİŞKİ

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Öz

Amaç
Meme kanseri dünya genelinde kadınlarda en yaygın rastlanan kanser türüdür. Farklı populasyonlarda yapılan daha önceki çalışmalarda MDR1 geni polimorfizmleri ile kadınlarda meme kanseri riski arasında ilişki olduğu öne sürülmüştür. Mevcut çalışmanın amacı Türk kadınlarında MDR1 geni C3435T, G2677A/T, C1236T, A2956G polimorfizmleri ile meme kanseri riski arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem
Bu çalışmaya 35 meme kanseri hastası ve 20 sağlıklı kontrol dahil edilmiştir. MDR1 genotiplerinin belirlenmesi amacıyla polimeraz zincir reaksiyonu/restriksiyon uzunluk polimorfizmi (PCR/RFLP) yöntemi kullanılmıştır.

Bulgular
Olgu ve kontrol grubu arasında C3435T polimorfizminin genotipleri açısından anlamlı bir fark gözlenmiştir (olgu grubu, CC %37.1, CT %28.6 ve TT %34.3; kontrol grubu CC %25, CT %65, TT %10, p: 0.023). Diğer taraftan, C1236T ve G2677A/T polimorfizmlerinin genotip ve allel sıklıkları gruplar arasında farklı bulunmamıştır. A2956G polimorfizmi için ise tüm çalışma grubunun AA genotipini taşıdığı belirlenmiştir.

Sonuç
Çalışmamızda değerlendirilen hasta sayısı az olmakla birlikte, elde ettiğimiz veriler MDR1 geni C3435T polimorfizminin Türk kadınlarında meme kanseri riskini artırabileceğini düşündürmektedir.

Anahtar Kelimeler: Meme kanseri, MDR1 geni, polimorfizm.

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Abstract

Objective
The most common malignancy in women is breast cancer worldwide. Previous studies performed in different populations have suggested an association between Multi-Drug Resistance (MDR1) gene polymorphisms and breast cancer risk in women. The purpose of the current study is to examine relationship between MDR1 polymorphisms (C3435T, G2677T/A, C1236T, A2956G) and the risk of breast cancer in Turkish women.

Material and Methods
In this study 35 breast cancer cases and 20 healthy controls were enrolled. Identification of MDR1 genotypes was performed with the polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP) technique.

Results
We observed significant difference in distribution of C3435T genotypes between the cases and the controls (cases, CC 37.1%, CT 28.6%, and TT 34.3%; controls, CC 25%, CT 65%, and TT 10%, p: 0.023). On the other hand, no significant differences in genotype and allele frequencies of C1236T and G2677T/A polymorphisms were observed between groups. We also found that all subjects carry AA genotype for A2956G polymorphism.

Conclusion
Although our study group is small, the results suggest that the MDR1 C3435T polymorphism may increase the breast cancer risk in Turkish women.

Keywords: Breast cancer, MDR1 gene, polymorphism.

Introduction

Breast cancer is the most common type of cancer and one of the most common leading cause of cancer related deaths among women in Turkey and worldwide (1-3). Complex interaction of genetic, epidemiological and epigenetic factors may predispose to breast cancer (4). The potential association between polymorphisms of numerous important candidate genes and breast cancer susceptibility has been investigated in many studies. Multi-Drug Resistance (MDR1) gene encoding a 170 kilo Dalton transmembrane glycoprotein called p glycoprotein (P-gp) is one of these important candidate genes due to its physiologic role. P-gp an ATP-driven transporter mediates to transportation of many metabolites and harmful substances from inside to outside through plasma membrane, so that intracellular levels of toxic compounds are kept low (4-6).

The MDR1 gene (also known as ABCB1), is located on chromosome 7q21.12. and comprises a core promoter region and 28 exons (7). MDR1 gene has many single nucleotide polymorphisms (SNPs) and these can affect expression and function of P-gp. Changes in P-gp transport function may trigger mutagenesis through accumulation of noxious substances and increase the risk of various disease including breast cancer (5, 8-13).

The most common, functional and clinically relevant SNPs of MDR1 gene are rs1045642 (C3435T) in exon 26, rs2032582 (G2677T/A) in exon 21 and rs1128503 (C1236T) in exon 12. Among these, C3435T and C1236T are synonym polymorphisms that decrease the mRNA expression level and P-gp activity whereas G2677T/A and A2956G are missense polymorphisms which cause changing of alanine to serine or threonine and methionine to valine respectively (4-6, 14, 15). The relationship between MDR1 gene SNPs and the breast cancer susceptibility have been explored previously in various population but the results of these studies are still inconclusive (4, 7-9). As far as we know, there is only one study that evaluates the association between one of MDR1 polymorphisms (C3435T) and breast cancer risk in Turkish population (8). In this study, it is intended to investigate possible association between MDR1 C3435T, G2677T/A, C1236T and A2956G polymorphisms and risk of breast cancer in Turkish female. We think that the results of this study may help better understanding of association between MDR1 polymorphisms and breast cancer risk in Turkish women.

Materials and Methods

Subjects
The approval of the present study was provided by the local ethics committee of Uludağ University (approval number: 2008-18/19). Signed informed consent was obtained from all participants before recruitment. A total of 35 women with breast cancer (thirty-three were invasive ductal carcinoma and two were ductal carcinoma in situ) and 20 healthy women were enrolled in this case-control study. Patients have a malign disease other than breast cancer were excluded. Gener-

al features of patients and disease related risk factors including age, smoking, duration of education, body mass index (BMI), age of menarche, number of pregnancies, age of first pregnancy, number of abortions, oral contraceptives consumption, age at onset of the disease, cancer stage, estrogen receptor status, presence of metastasis and family history of breast cancer were obtained from medical records.

DNA Isolation and Genotyping

High pure PCR template preparation kit (Roche Diagnostics, Mannheim, Germany) was used to isolate genomic DNA from whole blood by following the manufacturer's instructions. PCR-RFLP analysis was used for genotyping and it was performed twice for each sample. The details of primers, amplification fragment sizes, enzymes and fragment sizes of genotypes for each polymorphism were provided in table 1. The PCR amplifications were carried out in a total volume of 50 µl solution, containing 5 µl template DNA, 5 µl 10X Tsg reaction buffer, 5 µl MgSO4 (20mM), 0.5 µl primers (10µM), 0.5 µl dNTPs (10mM), and 0.5 µl Taq DNA polymerase (5u/µl, Bio Basic Inc., Markham, Canada), 33 µl water (PCR grade). The PCR protocol was 94 °C for 5 min, followed by 30 cycles of 94 °C for 1 min, 55 °C for 1 min, 72 °C for 1 min, and a final extension at 72 °C for 5 min. Restriction enzymes were utilized to digest the PCR amplicons, the digested amplicons were separated by agarose gel electrophoresis and then visualized under UV light. In the current study A allele of G2677T/A polymorphism was not genotyped because of low allele frequency (< 2% in Caucasians) (16,17).

Statistical Analyses

Statistical analyses were carried out by using a statistical software package (SPSS, Windows version release 15.0; SPSS Inc.; Chicago, IL, USA). Genotype and allele frequencies between the groups were compared by Fisher's Exact and Pearson Chi-Square Tests. P values below 0.05 were considered as statistically significant.

Results

The average age of the case and the control groups were 48,6 ± 13,3 and 62.45 ± 7,4 respectively. The clinical characteristics of the case group were shown in table 2. Except A2956G, all polymorphisms were tested for Hardy-Weinberg Equilibrium (HWE) (Table 3). Since there was no individual carrying AG or GG genotypes, HWE was not calculated for A2956G polymorphism. We found that genotype frequencies of C3435T are consistent with HWE in the control group (p= 0.14) but not in the case group (p= 0.01). In addition, genotype distribution is not in accordance with HWE for G2677T/A and C1236T polymorphisms in the case (p<0.001 for G2677T/A, p= 0.004 for C1236T) and the control groups (p=0.003 for G2677T/A, p= 0.025 for C1236T). C3435T, G2677T/A and C1236T polymorphism's genotype and allele frequencies were provided in Table 3. There is no individual carrying AG or AA genotype of A2956G genetic variant in the studied subjects. The genotype frequencies of C3435T are different for the cases and the controls (p= 0.023). On the other hand, there are no significant differences in the genotype frequencies of G2677T/A and C1236T between the groups. Also, allele frequencies of all studied polymorphisms are not different for the cases and the controls. In addition, no significant relationship between polymorphisms and the clinicopathological characteristics of the cases was observed.

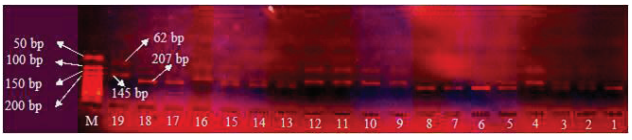

Figure 1
Fragments on agarose gel electrophoresis for C3435T polymorphism after PCR/RFLP analysis. M: Marker, bp: base pair.

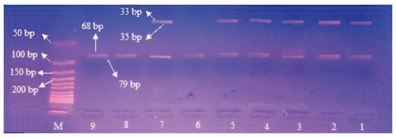

Figure 2
Fragments on agarose gel electrophoresis for C1236T polymorphism after PCR/RFLP analysis. M: Marker, bp: base pair.

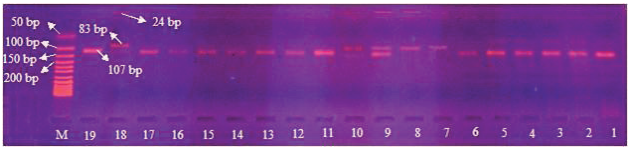

Figure 3
Fragments on agarose gel electrophoresis for G2677T/A polymorphism after PCR/RFLP analysis. M: Marker, bp: base pair.

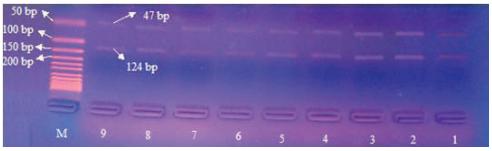

Figure 4
Fragments on agarose gel electrophoresis for A2956G polymorphism after PCR/RFLP analysis. M: Marker, bp: base pair.

Table 1 Primers, amplification fragment sizes, enzymes and fragment sizes of genotypes for each polymorphism

Variants	Primer Sequences	Amplification fragment size (bp)	Enzyme	Fragment sizes of genotypes (bp)
C3435T	5' TTGATGGCAAAGAAATAAAGC3'	207	MboI	CC: 62,145
	5' CTTACATTAGGCAGTGACTCG 3'			CT: 207, 145, 62
				TT: 207
G2677T/A	5' TACCCATCATTGCAATAGCAG 3'	107	XbaI	GG:107
	5' TTTAGTTTGACTCACCTTTCTAG 3'			GT:107, 83, 24
				TT: 83, 24
C1236T	5' TTTTTCTCACGGTCCTGGTAG 3'	147	HaeIII	TT: 79, 68
	5' CATCCCCTCTGTGGGGTCATA 3'			TC: 79, 68, 35, 33
				CC: 79, 35, 33
A2956G	5' TTGTGTTTGTGCTTTCCAGAG 3'	171	NcoI	AA: 124, 47
	5' TTAGGCCTTCCGTGCTGTAGC 3'			AG: 171, 124, 47
				GG: 171

Table 2 Baseline characteristics of breast cancer patients

Trait	Mean±SD or N (%) or Median (min-max)
Age, years	48.6±13.3
Median age at diagnosis(range), years	46 (19-77)
BMI, kg/m2	28.3±5.1
Age at first birth, years	21.4±3.5
Age at menarche, years	13±1
Nulliparous	4 (11.4)
Number of children	2.5±1.7

BMI: body mass index, SD: standard deviation

Discussion

P-gp encoded by human MDR1 gene is a transmembrane transporter protein that extrudes many active compounds out of the cell. It is expressed by wide variety of tissues and its physiological function is protection of cells from effects of harmful substances by decreasing their accumulation in the cells (4, 6, 7). MDR1 polymorphisms may cause impairment of P-gp expression or function and this results a reduction in the P-gp's protective effects (4, 18). Previous studies have proposed an relationship between MDR1 polymorphisms and risk of breast cancer development as well as other cancers because of decreased protective effect of P-gp (5, 8-13).

There are a couple of meta-analyses indicating relationship between MDR1 polymorphisms (especially C3435T) and breast cancer risk in the literature. The first meta-analysis carried out by Lu et al in 2011 gathering data from 7 studies revealed that C3435T polymorphism was not associated with risk of breast cancer (19). However, in a letter to the editor written by Jun Wang et al. it was claimed that there were methodological deficiencies and incorrect data provided by Lu et al. which likely to affect the results of the study (20). Jun Wang et al. performed the next meta-analysis in 2012 including many different type of cancer patients as well as breast cancer ones from 34 studies and they reported that cases carrying TT genotype had 1.66 fold (95% CI: 1.24-2.21) increased

Table 3 Genotype and allele frequencies of MDR1 polymorphisms in the cases and the controls.

Genotypes and alleles	Controls (n=20)	Cases (n=35)	p Value	OR (%95 CI)	p Value
C3435T			0.023		
CC	5 (25%)	13 (37.1%)		1[a]	
CT	13 (65%)	10 (28.6%)		0.30 (0.08-1.11)	0.066
TT	2 (10%)	12 (34.3%)		2.31 (0.38-14.21)	0.426
CT+TT[b]	15 (75%)	22 (62.9%)		0.56 (1.17-1.92)	0.356
CC+CT[c]	18 (90%)	23 (65.7%)		4.7 (0.93-23.71)	**0.047**
Alleles			0.718		
C	22 (55%)	36 (51.4%)		1[a]	
T	18 (45%)	34 (48.6%)		1.15 (0.53-2.52)	0.718
	HWE: 0.14	HWE: 0.01			
G2677T/A			0.253		
GG	12 (60%)	26 (74.3%)		1[a]	
GT	3 (15%)	1 (2.9%)		0.15 (0.01-1.64)	0.122
TT	5 (25%)	8 (22.9%)		0.74 (0.20-2.74)	0.738
GT+TT[d]	8(40%)	9 (25.8%)		0.52 (0.16-1.68)	0.270
GG+GT[e]	15 (75%)	27 (77.1%)		0.89 (0.25-3.21)	1.000
Alleles			0.352		
G	27 (67.5%)	53 (75.7%)		1[a]	
T	13 (32.5%)	17 (24.3%)		0.67 (0.28-1.57)	0.352
	HWE: 0.003	HWE: <0.001			
C1236T			0.962		
TT	8 (40%)	15 (42.9%)		1[a]	
TC	5 (25%)	9 (25.7%)		0.96 (0.24- 3.85)	1.000
CC	7 (35%)	11 (31.4%)		0.84 (0.23-3.01)	0.786
TC+CC[f]	12 (60%)	20 (57.1%)		0.89 (0.29-2.72)	0.836
TT+TC[g]	13 (65%)	24 (68.6%)		0.85 (0.27-2.73)	0.786
Alleles			0.745		
T	21 (52.5%)	39 (55.7%)		1[a]	
C	19 (47.5%)	31 (44.3%)		0.88 (0.40-1.92)	0.745
	HWE: 0.025	HWE: 0.004			

CI: Confidence interval, HWE: Hardy-Weinberg equilibrium, OR: Odds ratio,

[a]Reference Genotype/Allele

[b]Calculations were performed CC vs. CT+TT

[c]Calculations were performed TT vs. CC+CT

[d]Calculations were performed GG vs. GT+TT

[e]Calculations were performed TT vs. GG+GT

[f]Calculations were performed TT vs. TC+CC

[g]Calculations were performed CC vs. TT+TC

risk of breast cancer compared to ones carrying CC genotype. Also their results revealed that OR values for recessive and dominant models were 1.44 (95% CI: 1.14-1.82) and 1.41 (95% CI: 1.10-1.81) respectively (20). In 2013 another meta- analysis covering patients with different cancer types from 52 studies was conducted by Ling-Hui Wang et al. and results indicated that C3435T and G2677A/T polymorphisms were associated with increased risk of cancer, but not C1236T when all studies were evaluated together. On the other hand, if only breast cancer cases were assessed, there was no association between C3435T polymorphism and breast cancer risk (21). In 2013, the second meta-analysis that comprised of 10 case–control studies was published by Zhaoming Wang et al. They reported that there was a significant association between variant genotypes of MDR1 C3435T polymorphism and elevated risk of breast cancer (OR: 1.45 (95% CI: 1.14–1.30) for TT versus CC, OR: 1.13 (95% CI: 1.04–1.23) for recessive model, OR: 1.22, (95% CI: 1.02–1.46) for dominant model) (4).

In the following years individual studies in different population were performed. For example Abuhaliema et al. reported that the frequencies of C3435T and G2677A/T wild type genotypes (CC for C3435T, $p < 0.001$ and GG for G2677A/T, $p = 0.004$) were higher in the cases compared the controls and individuals carrying T allele of C3435T had a 2 fold decreased risk of breast cancer ($p< 0.0001$), opposite to the results of many previous studies. On the other hand, genotype and allele frequencies of C1236T were not different between the groups in their study (6).

In another study performed by Ghafouri et al. in Kurdish breast cancer patients, no significant association was observed between C3435T and elevated risk of breast cancer (22).

It was asserted by Macías-Gómez et al. C3435T polymorphism TT genotype may have a protective effect for benign fibrocystic changes, but there was no association between this polymorphism and infiltrating ductal breast cancer in Mexican women (23). But in another study performed by Gutierrez et al. it was reported that C3435T polymorphism T allele was a risk factor for development of breast cancer in Mexican premenopausal and triple-negative women (24).

In a Moroccan study performed by Tazzite et al. genotype and allele frequencies of C3435T polymorphism were not different between the breast cancer cases and the controls. Moreover, a meta-analysis comprising 16 studies was carried out by the authors in the same study. Their results indicated that there was no association between C3435T and breast cancer risk when all populations were taken into consideration. On the other hand, when they stratified this meta-analysis by ethnicity, results indicated that individuals carrying TT genotype had a significantly elevated risk of breast cancer in North Africans, Asians and Caucasians (25).

In this study, we analyzed the association between MDR1 C3435T, G2677T/A, C1236T and A2956G polymorphisms and risk of breast cancer among Turkish women. In addition, we evaluated the relationship between these polymorphisms and the clinicopathological characteristics of the patients. The genotype frequencies of C3435T polymorphism were consistent with HWE in the control group, but not in the case group. In addition, distribution of G2677T/A and C1236T genotypes were not in accordance with HWE both in the case and the control groups (Table 3). This inconsistency may be caused by small sample size of our study. Our results showed that the genotype frequencies of the C3435T polymorphism were different between the case and the control groups ($p= 0.023$). The frequency of TT genotype compared to CC+CT genotypes was higher in the cases than the controls ($p: 0.047$). No statistically significant differences were detected for the distribution of G2677T/A, C1236T and A2956G genotype and allele frequencies. Moreover, the clinicopathological characteristics of the patients were not associated with these polymorphisms.

There is still no consensus about relationship between C3435T polymorphism and risk of breast cancer. Similarly, our results are consistent with some previous studies (4, 20) but inconsistent with others (6, 22, 25). Like us, many researchers argued that conflicting results of these studies may depend on differences in genetic background and lifestyle of the studied populations. The findings obtained from stratification of meta-analyses by ethnicity seem to support this assumption. For example, in their meta-analysis Tazzite et al. showed that C3435T TT genotype significantly elevated risk of breast cancer in Caucasian, Asian and North African but not among mixed populations (25). That's why we think that it is important to evaluate the possible association between MDR1 polymorphisms and risk of breast cancer in different populations.

A previous study performed by Turgut et al. in Turkish breast cancer cases and healthy controls indicated that there was a significant difference between the cases and the controls in case of C3435T genotype (CC 12.3%, CT 57.9%, TT 29.8%, for cases, CC 36%, CT 46%, TT 18% for controls, $p= 0.013$) and allele frequencies (C 41.2%, T 58.8% for cases, C 59%,

T 41% for controls, p= 0.009) (8). Our findings are consistent with those of Turgut et al. Although sample size of the current study is very small, findings are important since; i. It provides supportive results to other study performed in Turkish women ii. The other MDR1 polymorphisms (C1236T, G2677T/A, A2956G) were investigated for the first time to assess breast cancer risk of Turkish women.

Conclusion

To conclude our results indicated that C3435T polymorphism may increase the risk of breast cancer development in Turkish women but G2677T/A, C1236T and A2956G not.

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