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ARAŞTIRMA / RESEARCH

Investigation of effects of PALB2 genetic variations on breast cancer predisposition

PALB2 genetik varyasyonlarının meme kanseri yatkınlığı üzerindeki etkilerinin araştırılması

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Abstract

Purpose: In this study, the effects of three different single nucleotide polymorphisms (rs249954, rs249935, and rs16940342) of partner and localizer of breast cancer gene 2 (PALB2) on breast cancer predisposition have been investigated.
Materials and Methods: For this purpose, 150 patients diagnosed to have breast cancer and 150 healthy individuals have been included. By using real time polymerase chain reaction (PCR) method isolated deoxyribonucleic acid (DNA) from each case has been investigated for the PALB2 genetic variations.
Results: The distribution of homozygote wild type (AA) and heterozygote (AG) genotypes at rs16940342 polymorphism has been observed to be 44.7% and 55.3% in breast cancer group and 32.7% and 67.3% in control group. The homozygote polymorphic (GG) genotype was not observed in both groups. The discrepancy between the groups in terms of genotype distribution regarding rs16940342 polymorphism has been found statistically significant. However, there was no significant difference in the frequencies of rs249954 and rs249935 polymorphisms comparing both groups.
Conclusion: These results show that rs16940342 polymorphism may be an important determinant in terms of breast cancer predisposition in the Turkish population.
Keywords: Breast cancer, genetic polymorphism, breast cancer gene 2, PALB2

Öz

Amaç: Bu çalışmada, meme kanseri geni partner ve lokalizeri-2'nin (PALB2) üç farklı tek nükleotid polimorfizminin (rs249954, rs249935 ve rs16940342) meme kanseri predispozisyonu üzerindeki etkileri araştırılmıştır.
Gereç ve Yöntem: Bu amaçla, çalışmamıza meme kanseri tanısı almış 150 hasta ve 150 sağlıklı birey dahil edilmiştir. Gerçek zamanlı polimeraz zincir reaksiyonu (PCR) yöntemi kullanılarak, her bir vakadan izole edilmiş deoksiribonükleik asit (DNA), PALB2 genetik varyasyonları için araştırılmıştır.
Bulgular: rs16940342 polimorfizminin homozigot yabanıl tip (AA) ve heterozigot (AG) genotip dağılımı meme kanseri grubunda sırasıyla % 44,7 ve % 55,3, kontrol grubunda ise % 32,7 ve % 67,3 olarak bulunmuştur. Her iki grupta da homozigot polimorfik (GG) genotip gözlenmemiştir. rs16940342 polimorfizmi için gruplar arasındaki genotip dağılımı açısından fark istatistiksel olarak anlamlı bulunmuştur. Bununla birlikte, her iki grup karşılaştırıldığında rs249954 ve rs249935 polimorfizmlerinin sıklığı bakımından istatistiksel olarak anlamlı bir fark bulunamamıştır.
Sonuç: Bu sonuçlar rs16940342 polimorfizminin Türk popülasyonunda meme kanseri yatkınlığı açısından önemli bir belirleyici rol üstlenebileceğini göstermektedir.
Anahtar kelimeler: Meme kanseri, genetik polimorfizm, meme kanseri geni 2, PALB2

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INTRODUCTION

Breast cancer is a multifactorial and devastating disease. It is characterized by its uncontrolled growth and spread of atypical breast cells[1]. Breast cancer represents the second main cause of cancer death in the world, which accounts for approximately 30% of all new cases of cancer diagnosed in female patients[2-4]. Age, early menarche, late menopause, obesity in postmenopausal women, high concentration of endogenous estrogen, and heredity are the main predisposing factors for developing breast cancer[3-7]. To date, approximately 5-10% of all breast cancer cases are caused by germline mutations in welldefined, dominantly acting breast cancer susceptibility genes, the majority of which can be accounted for by the major breast cancer susceptibility genes (*BRCA1* and *BRCA2*)[8-10]. However, additional susceptibility genes have been identified to confer an increased breast cancer risk, all of which can generally be classified according to the level of risk they confer: genes which confer a high risk for developing breast cancer which includes *BRCA1*, *BRCA2*, and *TP53*, those which confer a low to moderate risk of breast cancer, including partner and localizer of BRCA2 (*PALB2*) gene. Interestingly, the majority of these genes are intimately linked by their function in deoxyribonucleic acid (DNA) repair, cell cycle regulation and interaction with one or both of the BRCA genes[10-12].

PALB2, located on chromosome 16p12, is comprised of 13 exons coding for a 1,186 amino acid protein with a molecular mass of 130 kilo dalton. Immunohistochemical staining of a human osteosarcoma cell line illustrated the localization of *PALB2* with *BRCA2*13. The function of *PALB2* was further elucidated when Xia et al.[14] showed that immunodepletion of *BRCA2* codepleated a significant abundance of *PALB2*, whereas immunodepletion of *PALB2* codepleted almost all of *BRCA2*. Furthermore, the refocusing of both *PALB2* and *BRCA2*, after exposure to ionizing radiation, suggested that like *BRCA2*, *PALB2* participates in the DNA damage response. *PALB2* appeared to promote the stable interaction of *BRCA2* with nuclear structures[14]. Most recently, the first functional link between *BRCA1* and *BRCA2* has been illustrated by Zhang et al.[13], by showing that *PALB2* also physically interacts with *BRCA1*, linking *BRCA1* and *BRCA2* in a DNA damage response network through interaction with its NH_2 and COOH terminal ends. Due to the essential function of *PALB2* in DNA repair and tumor suppression, Reid et al.[12] suggested that monoallelic *PALB2* mutations could confer susceptibility to adult cancer. Following this hypothesis, Rahman et al.[15] fully sequenced the *PALB2* gene in affected individuals from breast cancer families with no mutations in *BRCA1* or *BRCA2*.

Several studies have shown that *PALB2* gene variations raise breast cancer risk in several societies[16-17]. Although there are lots of studies in literature on breast cancer and *BRCA1*, *BRCA2* and *p53* genes[8]; studies on *PALB2* are very limited and there is not any study regarding Turkish population. In this study, single nucleotide polymorphisms (SNP) at intron 6, intron 11 and intron 4 regions of the *PALB2* gene [SNP; rs249954 (C>T), rs249935 (A>G) and rs16940342 (A>G)] have been researched in breast cancer cases.

MATERIALS AND METHODS

Sample

150 newly diagnosed female patients with pathologically proven breast cancer were recruited between October 2010 and August 2011 from the Oncology Clinics, and as a control group 150 age-matched control women with no signs or symptoms of malignancy were randomly selected. Breast cancer was diagnosed based on the pathological examination and the relevant stage was assigned in accordance with the International Union against Cancer Tumor-Node-Metastasis (UICC-TNM) classification in all cases. All relevant clinical and pathological information was retrieved from their files, including menopausal state, family history of breast cancer, estrogen receptors (ER) and progesterone receptors (PR) expression in breast cancer tissue.

The study protocol was approved (approval number:21.06.2010/469) and informed consent for the experimental use of specimens was obtained from all participants.

Genomic DNA extraction

DNA isolation was carried out using High Pure PCR Template Kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

Real Time PCR assay

Genotyping of rs249954 (C>T), rs249935 (A>G) and rs16940342 (A>G) polymorphisms were performed by real-time polymerase chain reaction method using LightCycler 480 instrument (Roche Molecular Diagnostic, Manheim, Germany). Primers and probes were designed and prepared by Tib MolBiol (Berlin, Germany). The sequences of PCR primers and probes are given in Table 1[18-20]. The PCR mix contained 50 ng of the genomic DNA, 5 µL of LCTM FastStart DNA Master HybProbe kit (Roche Diagnostics, Mannheim, Germany), 0.5 µM of each primer and 0.2 µM of each probe. The initial 10 min denaturation at 95 °C was followed by 45 cycles–denaturation (95 °C; 10 s), annealing (54 °C; 20 s), and elongation (72 °C; 16 s). Melting curve analysis was done with an initial denaturating step at 95 °C for 30 s and 1 s at 40 °C, slow heating to 80 °C with a ramping rate of 0.15 °C/s and continuous fluorescence detection. Wild type, heterozygote, and polymorphic genotypes were detected by specific melting temperature (Tm) of amplicons.

Table 1. Sequences of primers or probes for PALB2 rs249954 (C>T), rs249935 (A>G) and rs16940342 (A>G) single nucleotide polymorphisms

SNP	Primers (forward, reverse), probes (sense, antisense)	Sequences
rs249954 (C>T)[18]	Forward Primer	5'_GGGTAATGCAGGCAGACATTA_3'
	Reverse Primer	5'_GAGAGCTCAAAACATAAACAGAGG_3'
	Sense Probe	5'_AATATTCTCTTCCAGTGTCTCGTGTCTTACAT--FL_3'
	Antisense Probe	5'-AAAACTTTAATGAACTGAAAAGAATTCA--P_3'
rs249935 (A>G)[19]	Forward Primer	5'_GGACCACTTTGTGTGTTACT_3'
	Reverse Primer	5'_GTCCTACAGCCAGAAAATTTA_3'
	Sense Probe	5'_CCCGTGGCATCTTTTTTCA—FL_3'
	Antisense Probe	5'_TTGGATAGCAATGTTTGTCCTTTCTTGAAA—P_3'
rs16940342 (A>G)[20]	Forward Primer	5'_CTGTGTTCCAACGCACC_3'
	Reverse Primer	5'_CCT6ACTTTTTGATGACTTTGTATCC_3'
	Sense Probe	5'_CATGTCCAATGGTACAGAGCA--FL_ 3'
	Antisense Probe	5'-CCTGCTACCTATTTTTGCACATAAAGTTG--P_3'

PALB2=Partner and Localizer of BRCA2, SNP=Single nucleotide polymorphism

Table 2. Clinicopathologic characteristics of the study population

Characteristics		Cases (*n*) (%)
Family history		
	Positive	24 (16)
	Negative	126 (84)
Menopausal state		
	Pre-menopause	51 (34)
	Post- menopause	77 (51.3)
	Unknown	22 (14.7)
ER status		
	Positive	123 (82)
	Negative	27 (18)
PR status		
	Positive	65 (43.3)
	Negative	85 (56.7)

n = number of individual, ER = estrogen receptor, PR = progesterone receptor

Statistical analysis

Data were analyzed using SPSS 11.5 package program (Stastistical Package for Social Sciences, SPSS Inc. Chicago, IL, United States). Descriptive statistics were expressed as mean ± standard deviation. Categorical data were shown as number of observations (n) and percent (%). Genotype distribution and allele frequencies were compared between groups using chi-square (χ^2) test. According to the reference categories, 95% confidence intervals and significance levels were calculated on the basis of both genotype and alleles between patients and control groups. p values smaller than 0.05 were considered statistically significant.

RESULTS

A total of 300 individuals consisting of 150 female patients diagnosed with breast cancer and a control group consisting of 150 women who and their relatives without any serious disease history comprising cancer were included into this study. The mean age of the control group, patient group and all individuals participated in the study were determined to be 47.75±8.14, 49.66±10.55 and 48.71±9.46, respectively. There was no statistical significant difference between the patient and control group in terms of age variance (p=0.081). The clinicopathologic characteristics of the cases of patient group included in this study were presented in Table 2.

When the patients were classified according to their menopausal state, it was determined that 51 patients (34.0%) were in premenopausal and 77 patients (51.3%) were in postmenopausal state. 24 patients (16%) were found to be with positive family history of cancer and 126 patients (84%) were found to be with no cancer story in their family. In 123 patients with breast cancer (82.0%) estrogen receptor positivity (ER+) and in 27 patients (18%) with breast cancer estrogen receptor negativity (ER−) were determined. In 65 patients (43.3%) and in 85 patients (56.7%) the cases were detected to be progesterone receptor positive (PR+) and progesterone receptor negative (PR-) breast cancer, respectively.

When the results of genotype belonging to *PALB2* intron 4 polymorphism were evaluated, in control group AA genotype and AG genotype were detected in 49 individuals (32.7%) and 101 individuals (67.3%), respectively. In patient group, AA genotype and AG genotype were detected in 67 patients (44.7%) and 83 patients (55.3%), respectively. Whereas GG genotype was not encountered in both patient and control groups, there was a statistically significant difference between the groups in terms of genotype distribution for *PALB2* intron 4 polymorphism ($p<0.05$) (Table 3). When the distribution of allele frequency of *PALB2* intron 4 polymorphism was examined, while incidence of A and G allele presence in control group were found to be 66% and 34%, for patient group incidence of the A and G allele presence were found to be 72% and % 28%, respectively (Table 3). There was no statistically significant difference between the groups ($p>0.05$).

As for the examination of *PALB2* intron 6 polymorphism, 150 patients (100%) with CC genotype were determined in patient group, however CT or TT genotypes were not encountered in this group. The frequency of the C allele and T allele were found to be 100% and 0%, respectively. Similar results were obtained in control group, as well (Table 3). According to the results of *PALB2* intron 11 polymorphism examination in patient group, AA genotype was detected in 150 patients (100%) but AG and GG genotypes were not detected. As the frequency of the A allele was 100%, it was 0% for the G allele. Similar results were obtained in control group (Table 3).

Considering the comparison of premenopausal and postmenopausal states, of patients with premenopausal breast cancer, AA genotype was detected in 23 patients and AG genotypes was detected in 28 patients. As for patients with postmenopausal breast cancer, AA genotype was detected in 34 patients and AG genotype was detected in 43 patients. The frequency of the A allele in premenopausal and postmenopausal groups were found to be 72.5% and 72.1%, respectively; however for the G allele it was 27.5% and 27.9%, respectively. There was no statistically significant difference between the distribution of genotype and allele frequency in *PALB2* intron 4 polymorphism of premenopausal and postmenopausal patients ($p>0.05$) (Table 4).

Of the patients having positive family history, in 13 patients AA genotype and in 11 patients AG genotype were determined. However, 54 patients carrying AA genotype and 72 patients carrying AG genotype were determined among the patients without a positive family history. The frequency of the A allele and G allele was determined to be 77.1%

and 22.9%, respectively. The *PALB2* intron 4 polymorphism of the patients with or without a positive family history, there was no statistically significant difference between the distribution of genotypes and allele frequencies (p>0.05) (Table 4).

Table 3. Genotype/allele frequency and odds ratio of PALB2 intron 4, intron 6 and intron 11 polymorphisms in control and breast cancer cases

		Controls (*n*) (%)	Patients (*n*) (%)	OR (95% CI)	p value
PALB2 intron 4 polymorphism					
	Genotype				
	AA	49 (32.7)	67 (44.7)	1.00 (referance)	0.033
	AG	101 (67.3)	83 (55.3)	1.66 (1.04-2.66)	
	Allele				
	A	199 (66.0)	217 (72.0)	1.00 (referance)	0.114
	G	101 (34.0)	83 (28.0)	1.33(0.94-1.88)	
PALB2 intron 6 polymorphism					
	Genotype				
	CC	150 (100)	150 (100)	N/D	N/D
	CT	0 (0)	0 (0)		
	Allele				
	C	300 (100)	300 (100)	N/D	N/D
	T	0 (0)	0 (0)		
PALB2 intron 11 polymorphism					
	Genotype				
	AA	150 (100)	150 (100)	N/D	N/D
	AG	0 (0)	0 (0)		
	Allele				
	A	300 (100)	300 (100)	N/D	N/D
	G	0 (0)	0 (0)		

n = number of individual, N/D = not defined, OR = odds ratio, PALB2=Partner and Localizer of BRCA2

Furthermore, 51 patients carrying the AA genotype and 72 patients carrying the AG genotype were detected among patients with ER positive breast cancer. As for patients with ER positive breast cancer, 16 patients carrying the AA genotype and 11 patients carrying AG genotype were detected. It was also ascertained that while the frequency of the A allele and G allele were 70.7% and 29.3% in patients with ER positive breast cancer, respectively. Whereas they were 79.6% and 20.4% in patients with ER negative breast cancer, respectively. There was no statistically significant difference between the distribution of genotype and allele frequency in PALB2 intron 4 polymorphism of patients with ER positive and ER negative breast cancer (p>0.05) (Table 4).

Table 4. Genotype/allele frequency of PALB2 intron 4 in control and breast cancer cases according to their clinicopathologic characteristics

	Menopausal state			
	Pre-menopause n (%)	**Post-menopause n (%)**	**Unknown n (%)**	**p value**
Genotype				
AA	23 (45.1 %)	34 (44.2 %)	10 (45.5 %)	0.991
AG	28 (54.9 %)	43 (55.8 %)	12 (54.5 %)	
Allele				
A	74 (72.5 %)	111(72.1 %)	32 (72.7 %)	0.995
G	28 (27.5 %)	43 (27.9 %)	12 (27.3 %)	
	Family history			
	Positive n (%)	Negative n (%)	p value	
Genotype				
AA	13 (54.2 %)	54 (42.9 %)	0.307	
AG	11 (45.8 %)	72 (57.1 %)		
Allele				
A	37 (77.1 %)	180 (71.4 %)	0.531	
G	11 (22.9 %)	72 (28.6 %)		
	ER status			
	Positive n (%)	Negative n (%)	p value	
Genotype				
AA	51 (41.5 %)	16 (59.3 %)	0.092	
AG	72 (58.5 %)	11 (40.7 %)		
Allele				
A	174 (70.7 %)	43 (79.6 %)	0.248	
G	72 (29.3 %)	11 (20.4 %)		
	PR status			
	Positive n (%)	Negative n (%)	p value	
Genotype				
AA	23 (35.4 %)	44 (51.8 %)	0.046	
AG	42 (64.6 %)	41 (48.2 %)		
Allele				
A	88 (67.7 %)	129 (75.9 %)	0.149	
G	42 (32.3 %)	41 (24.1 %)		

n = number of individual, ER = estrogen receptor, PR = progesterone receptor, PALB2=Partner and Localizer of BRCA2

Moreover, 23 patients carrying the AA genotype and 42 patients carrying the AG genotype were detected among the patients with PR positive breast cancer. As the AA genotype was detected in 44 patients with PR negative breast cancer, AG genotype was detected in patients with PR positive breast cancer. The frequency of the A allele and G allele in patients with PR positive breast cancer was found to be 67.7% and 32.3%, respectively.

Besides, the frequency of the A allele and G allele in patients with PR negative breast cancer was found to be 75.9% and 24.1%, respectively. Despite the fact that there was a statistically significant difference between the PR positive and PR negative groups in point of genotype distribution ($p<0.05$), there was no statistically significant difference between the frequency of allele distribution ($p>0.05$) (Table 4).

DISCUSSION

Family history, gender, age, radiation, obesity, hormonal and environmental factors are considered as the main causes in the etiology of the breast cancer[21]. Beside the various environmental factors contributing to the carcinogenesis of breast cancer, there is a general consensus that the disease may originate from genetic variations such as gene polymorphisms. 10 different genes responsible for hereditary breast cancer, function in the pathway which is used for genomic integrity[22-25]. One of these genes is the *PALB2* gene that is a partner of *BRCA2* and also localizer of *BRCA2* in the nucleus during the DNA damage. Genetic investigations have exhibited that *PALB2* is efficient in homologous recombination repair and in tumor suppression. It has also been shown with the studies performed since 2007 to date; mutations of *PALB2* are efficient in breast cancers and double the risk of breast cancer[9].

In this study, we aimed to detect the genetic predisposition by investigating the relationship between three polymorphism identified in the *PALB2* gene and breast cancer. Only a little information is available in the literature regarding impacts of *PALB2* gene polymorphism on the cases of breast cancer[9]. To the best of our knowledge, this study was the first that carried out in Turkey aimed at genotyping and determining the frequency of alleles of *PALB2* gene polymorphism in the Turkish female individuals. In terms of genotype distribution for *PALB2* intron 4 polymorphism differences between the groups was found to be significant; however there was no statistically difference in terms of the frequency of alleles. 1.66 fold increases in the disease prevalence was detected in individuals carrying AG genotype for *PALB2* intron 4 polymorphism. Considering the *PALB2* intron 6 polymorphism, while CC genotype was 100% in patient and control group, CT and TT genotypes were absent in both groups. As for the PALB2 intron 11 polymorphism, distribution of the AA genotype was found to be 100% in both groups. These results provide evidence that there is no significant connection between the intron 6 and 11 polymorphisms and breast cancer. The performed studies associated with *PALB2* gene are mostly in the form of truncating type mutation and only two studies are available with respect to single nucleotide polymorphisms which were conducted in Chinese population. Chen et al.[26] reported that rs249954 and rs16940342 polymorphisms, and Cao et al.[16] reported those rs249935 polymorphisms are connected with breast cancer.

Advanced menopausal age is a factor increasing the risk of breast cancer in women. The breast cancer incidence in postmenopausal women is twice as much as in the premenopausal women[21,22]. However, there was no statistically significant difference between genotype and allelic frequencies of *PALB2* intron 4 polymorphism in premenopausal and postmenopausal women. In familial breast cancer cases, the risk increases more than twofold in women whose first degree relative diagnosed with breast cancer. There was no statistically significant difference between genotype and allelic frequencies of *PALB2* intron 4 polymorphism between the patients with positive and negative family story. Since most of the women participated in this study have no familial breast cancer story, it can be mentioned that they are at the low risk level in terms of development of breast cancer.

Estrogen and progesterone receptors are rather commonly used prognostic factors which influence the selection of treatment regime primarily. The positivity of the estrogen and progesterone receptors generally indicates the good response and long survival in hormone replacement treatment; interacts with many other factors, as well. Because of the fact that, progesterone receptor possesses better indication for response to endocrine cure in case of disease recurrence, it is associated with survival[27,28].

In this study, there was no statistically difference between distributions of genotype and allelic frequencies of *PALB2* intron 4 polymorphism between the ER positive and ER negative patients with breast cancer. There was a statistically significant difference between the ER positive and ER negative patients with breast cancer in regard to genotype distributions, but there was no statistically significant different distribution of allele frequency.

Rahman et al.[15] has detected 5 different mono allelic mutations in women diagnosed with familial breast cancer, all of which increase the risk of breast cancer. Erkko et al.[17] has defined the 1592delT variant at the 4th exon of *PALB2* which is the most detrimental mutation observed till now and also it has been reported that this mutation increases the breast cancers risk in Fin population by six fold[17]. Two protein-truncating *PALB2* mutations, 751C<T and 1050_1051delAAinsTCT were first defined in Chinese populations and it was observed that they are

efficient in early-onset breast cancer[16]. Single protein truncating in *PALB2*, 196C>T (Q66X), was detected in Australian population[12]. E545X and Q921X truncating mutations located in the exon 4 of *PALB2* gene has been identified in the German population, as well[15]. It was reported that 2386G>T, 298insT, 3113G>A, 3116delA and 3549C>G mutations, detected first time in English population, increase the risk of familial breast cancer by twofold[29]. The reason of obtaining different prevalence of variants in the performed investigations focused on *PALB2* gene results from geographical and ethnical variations[30].

According to our literature survey, we encountered a study examining *PALB2* polymorphism and breast cancer in Turkish population. This study bears particular significance for being the first screening with intent to reveal the *PALB2* polymorphism and breast cancer. It can be concluded from the obtained results in this study that among the three polymorphism in intron domain of *PALB2* gene, the intron 4 polymorphism is a good indicator for breast cancer. We think that number of patients should be increased to report an extensive conclusion concerning genotype structure of our population.

As breast cancer is a multifactorial disease, studies in different populations with larger sample volume including also gene-environment interactions by considering environmental factors with the gene-gene interactions need to be performed for providing significant contributions to clarification the pathogenesis of breast cancer[21]. Determining the location of breast cancer in heredity and whether *PALB2* and breast cancer relationship exhibits a variation in different populations would be important for contributing to pharmacogenetics by directing the treatment of breast cancer and for providing genetic consultancy to the breast cancer cases.

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