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**RESEARCH ARTICLE**

# Low-penetrance susceptibility variants and postmenopausal oestrogen receptor positive breast cancer

ASUMAN ÖZGÖZ[1]*, FADİME MUTLU İÇDUYGU[2], AYŞEGÜL YÜKSELTÜRK[3], HALE ŞAMLI[4], KUYAŞ HEKİMLER ÖZTÜRK[5] and ZUHAL BAŞKAN[6]

[1]*Kastamonu School of Medicine, Department of Medical Genetics, Kastamonu University, Kastamonu 37200, Turkey*
[2]*School of Medicine, Department of Medical Genetics, Giresun University, Giresun 28200, Turkey*
[3]*Fazıl Boyner Faculty of Health Sciences, Department of Nutrition and Dietetics, Kastamonu University, Kastamonu 37200, Turkey*
[4]*School of Veterinary Medicine, Department of Genetics, Uludağ University, 16059 Bursa, Turkey*
[5]*School of Medicine, Department of Medical Genetics, Süleyman Demirel University, Isparta 32260, Turkey*
[6]*Department of Medical Oncology, Acibadem Bursa Hospital, Bursa 16110, Turkey*
*For correspondence. E-mail: biologistasu@gmail.com.

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**Abstract.** The risk of breast cancer (BC) in women is high and many factors including genetic factors increase the risk for the disease. It is revealed that the variations of low-penetrance susceptibility genes are important for carcinogenesis as they interact with the environmental and hereditary factors. Recently, the list of BC-associated common single nucleotide polymorphisms (SNPs) and chromosomal loci in low-penetrance susceptibility genes have been expanded in genomewide association studies. FGFR2, LSP1, MAP3K1, TGFB1, TOX3, 2q35 and 8q loci variations are some examples for these common SNPs. These SNPs and their association with BC risk was investigated in many different populations. Therefore in this study, we aimed to evaluate low-penetrance susceptibility SNPs; namely FGFR2 rs1219648, rs2981579, rs2981582; MAP3K1 rs889312; TOX3 rs3803662; LSP1 rs909116, rs3817198 and SLC4A7 rs4973768 together, for the first time in Turkish postmenopausal oestrogen receptor positive BC cases. Following the DNA isolation, multiplex PCR and matrix-assisted laser desorption/ionization mass spectrometry with time of flight measurement (MALDI-TOF) based SNP analysis were performed. MAP3K1 rs889312 SNP demonstrated the strongest association with BC risk among the other low penetrant SNPs, it was also associated with BC risk in a dominant model. Only in a ressesive model, TOX3 rs3803662 was associated with BC risk. In addition, rs4973768 CC and rs909116 CC genotypes are correlated with higher tumour size which is not reported in the literature as yet; on the other hand there are no associations between any of the other SNP genotypes and clinopathological parameters. In our opinion, MAP3K1 rs889312 may be a good BC susceptibility biomarker candidate for Turkish population.

**Keywords.** low penetrance; susceptibility; polymorphism; breast cancer.

## Introduction

According to the 2018 Global Cancer Statistics, female breast cancer (BC) is the second most common cancer with an estimated frequency of 11.6% and also a leading cause of death due to cancer (Khazaei *et al.* 2019). BC aetiology is known to be rather complicated, so the factors underlying the disease could not be totally clarified. It comprises many genetic, endocrinal and environmental factors (Shan *et al.* 2012).

Many BC susceptibility variants have been identified by the genomewide association studies (GWASs), so far. Single-nucleotide polymorphisms (SNPs) in FGFR2, LSP1, MAP3K1, TOX3, MRPS30, COX 11, SLC4A7, and in regions at chromosomes 8p24 and 2q35 have been reported (Easton *et al.* 2007; Hunter *et al.* 2007; Stacey *et al.* 2007, 2008; Ahmed *et al.* 2009).

Some risk factors including age at menarche, parity, age at the first delivery and body mass index (BMI) reported to be associated with these SNPs in BC (Milne *et al.* 2010). It is sugggested that detection of SNPs may help to understand the biological mechanisms underlying BC aetiology. Thus, SNPs in low-penetrance genes detected by GWAS, together

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with the risk factors, demonstrated altered association with oestrogen receptor (ER) (+) and ER (–) BC (Althuis *et al.* 2004; Stacey *et al.* 2007, 2008; Garcia-Closas *et al.* 2008; Dunning *et al.* 2009; Ahmed *et al.* 2009).

*FGFR2* gene polymorphisms were determined to be associated with BC in many GWASs and thus have attracted interest (Easton *et al.* 2007; Hunter *et al.* 2007; Stacey *et al.* 2008). FGFR2 is encoded as a receptor tyrosine kinase that has duties in growing and invasion of cells, forming of new blood vessels (Turner and Grose 2010). One of the pioneers GWAS in this area by Easton *et al.* (2007) demonstrated that some FGFR2 polymorphisms have association with BC risk, where the rs2981582, rs78g5676 and rs15100g7 are the most frequent. Hunter *et al.* (2007) demonstrated that some FGFR2 polymorphisms such as rs1219648, rs2420946, rs2981579 and rs11200014 have association with postmenapausal BC risk; Stacey *et al.* (2007) demonstrated that FGFR2 rs1219648 has association with ER (+) BC risk. Besides GWASs, association of these FGFR2 polymorphisms were verified in meta-analyses in different populations (Zhou *et al.* 2012; Cui *et al.* 2016).

FGFR2 rs2981582 AA genotype was reported to be associated with a higher risk of nonfunctioning pituitary adenoma (Zhu *et al.* 2018); whereas an inverse association was detected between rs1219648, rs2981582 SNPs and endometrial cancer risk (McGrath *et al.* 2008). rs2981582 TT genotype was reported to be significantly associated with shorter progression-free survival (PFS) of renal cancer patients (Beuselinck *et al.* 2013); rs1219648 and rs2981582 were reported to be associated with better overall survival (OS) of primary prostate cancer patients (Miles *et al.* 2015) and rs2981582 was reported to be significantly associated with PFS, OS and response to the treatment in nonsmall cell lung carcinoma (NSCLC) patients (Camidge *et al.* 2014). FGFR2 rs1219648, rs2981582 was not verified to be associated with ovarian cancer (Gates *et al.* 2009) and rs11200014, rs2981579, rs1219648, rs2420946 polymorphisms were not reported to be associated with skin cancer (Nan *et al.* 2009).

MAPK pathways have a pivotal duty during cell growth, differentiation, metastasis and apoptosis (Slattery *et al.* 2012). One of the MAPK pathway component MAP3K1 was proposed to be a potential BC susceptibility gene in a GWAS by Easton *et al.* (2007). Hormone dependent association of MAP3K1 rs8893120 and rs889312 genotypes were investigated by Rebbeck *et al.* (2009) and these SNPs were demonstrated to be associated with ER (+), PR (+) or HER2 (–) tumours. In another study, BC cells were demonstrated to express MAP3K1, 1.8 times more than breast cells without cancer, suggesting a probable relation of MAP3K1 and BC (Hu *et al.* 2014).

MAP3K1 rs889312 was suggested to be an independent predictor candidate of diffuse-type gastric cancer in Chinese population (Wei *et al.* 2014); whereas it was not verified to be associated with ovarian cancer (Gates *et al.* 2009).

Besides, the two most associated BC susceptibility genes, FGFR2 and MAP3K1; TOX3, LSP1, SLC4A7 gene polymorphisms were also reported to be BC risk variants in GWASs and in individual studies from different populations (Easton *et al.* 2007; Ahmed *et al.* 2009; Antoniou *et al.* 2010; Milne *et al.* 2010; Chen *et al.* 2011; Zhang and Long 2015). There were some studies with controversy, reporting no association between some polymorphisms of these genes and BC risk (Zhang and Long 2015; Huijts *et al.* 2007; Chen *et al.* 2016).

TOX3 rs3803662 was reported not to be associated with ovarian cancer in two different studies (Song *et al.* 2009; Gates *et al.* 2009). LSP1 rs3817198 was reported to be associated with invasive epithelial ovarian cancer (Quaye *et al.* 2009); increased risk of lung cancer (Park *et al.* 2014) and non-Hodgkin lymphoma (Lim *et al.* 2014). SLC4A7 rs4973768 SNP was investigated only in breast cancer and in the literature, it was not found to be studied in other types of cancers.

There is no study evaluating low-penetrance susceptibility variants of FGFR2, MAP3K1, TOX3, LSP1 and SLC4A7 determined in GWASs that were verified to be associated with BC in Turkish population. Therefore, our study is the first one to evaluate low-penetrance BC risk variants (FGFR2 rs1219648, rs2981579, rs2981582; MAP3K1 rs889312; TOX3 rs3803662; LSP1 rs909116, rs3817198 and SLC4A7 rs4973768) together in a Turkish population.

## Materials and methods

### *Study population*

This study was approved by the Acibadem Mehmet Ali Aydınlar University, Committee of Medical Research Assessment. The research consisted 101 postmenopausal ER (+) BC patients applied to Acibadem Bursa Hospital, Department of Medical Oncology (mean age: 62 ± 7.8 years) and 100 postmenopausal non-BC healthy control individuals (mean age: 52.6 ± 3.7 years).

An informed consent form was signed by the patients and control individuals. Medical history, demographic properties, age of menarche, age at the first delivery, number of children, age of menopause, receiving hormone replacement therapy, smoking and alcohol consumption history, family history details were filled in the information forms for all cases. In addition, age of diagnosis, tumour grade, tumour histology, tumour metastasis, tumour size, lymph node metastasis status, oestrogen receptor status, progesterone receptor status, and Her2/neu status informations were obtained from medical records of the patient group.

### *Genotyping*

After isolating DNA samples by a High Pure PCR Template Preparation kit (Roche, Diagnostics GmbH, Mannheim,

Germany) following the manufacturer's instructions; multiplex PCR and matrix-assisted laser desorption/ionization mass spectrometry with time of flight measurement (MALDI-TOF) was performed for genotyping. A plate containing 384 wells was used for multiplex PCR and two wells were needed for each of the cases. PCR reaction mixture, 4 $\mu$L and DNA (10 ng) sample were added in each well. PCR conditions were 15 min at 95°C; 44 repeats of 94°C for 20 s, 56°C for 30 s, and 72°C for 60 s; 3 min at 72°C; 5 min at 4°C and infinite at 15°C. After PCR, SAP and iPLEX reactions were performed, spectro chip sample transferring and sample ionization were carried out on Sequenom MassARRAY 4 analyser and MassARRAY TYPER 4.0 software (Agena Bioscience, San Diego, USA) was used for mass spectra analysing.

#### *Statistical analysis*

All statistical analyses were evaluated using SPSS 18.0 software (SPSS 2009, PASW Statistics for Windows, v18.0. Chicago) Hardy–Weinberg equilibrium (HWE) was evaluated by chi-square test. Pearson's chi-square and Fisher exact tests were performed to compare genotype and allele frequencies of BC patients and the controls. To estimate the BC risk, odds ratio (OR) was calculated with 95% confidence intervals (CIs) from logistic regression analyses. Student *t*-test and Mann–Whitney U tests were performed to compare the demographic and clinical data; the level of significance was defined as $P < 0.05$.

## Results

#### *Clinical characteristics of the study subjects*

The factors that are known to be related to the progression of BC are age, BMI, smoking, alcohol consumption, menarche age, age at the first delivery and receiving hormone replacement therapy (HRT) are demonstrated in the demographic profile table (table 1). There was only statistically significant difference in terms of age, age at the first delivery, family history between the BC case and control groups (respectively, $P = 0.000$, $P = 0.000$ and $P = 0.006$).

**Table 1.** Demographic and clinical characteristics of the BC patient and control group individuals.

| Characteristics | Controls *n* (%) *N* = 100 | Cases *n* (%) *N* = 101 | *P* value |
|---|---|---|---|
| Age, years (mean ± SD) | 52.6 ± 3.7 | 62 ± 7.8 | 0.000* |
| BMI (mean ± SD) | 28.8 ± 5.4 | 29.2 ± 5.8 | 0.206 |
| Age of first birth, years (mean ± SD) | 24.3 ± 4.9 | 21.6 ± 4.2 | 0.000* |
| Smoking | | | 0.067 |
| No | 91 (91) | 83 (82.2) | |
| Yes | 9 (9) | 18 (17.8) | |
| Alcohol consumption | | | 0.621 |
| No | 99 (99) | 99 (97.1) | |
| Yes | 1 (1) | 3 (2.9) | |
| Age at menarche | | | 0.856 |
| < 13 | 18 (18) | 19 (19) | |
| ≥ 13 | 82 (82) | 81 (81) | |
| Number of childbirth, *n* (%) | | | 1.000 |
| 0 | 3 (3) | 4 (4) | |
| ≥ 1 | 97 (97) | 97 (96) | |
| Family history of breast cancer in first-degree relatives | | | 0.006* |
| No | 92 (92) | 78 (78) | |
| Yes | 8 (8) | 22 (22) | |
| HRT | | | 0.539 |
| No | 89 (89) | 87 (86.1) | |
| Yes | 11 (11) | 14 (13.9) | |
| ER status | | | |
| No | | 0 (0) | |
| Yes | | 100 (100) | |
| PR status | | | |
| No | | 19 (18.8) | |
| Yes | | 82 (81.2) | |
| Her2/neu status | | | |
| No | | 76 (75.2) | |
| Yes | | 25 (24.8) | |
| Tumour grade | | | |
| I, II | | 62 (61.4) | |
| III | | 28 (27.7) | |
| Tumour size | | | |
| ≤ 5 cm | | 88 (87.1) | |
| > 5 cm | | 9 (8.9) | |
| Node involvement | | | |
| No | | 45 (44.6) | |
| Yes | | 54 (53.5) | |
| Metastasis | | | |
| No | | 88 (87.1) | |
| Yes | | 12 (11.9) | |

*$P < 0.05$. BMI, body mass index; HRT, hormone replacement therapy; ER, oestrogen receptor; PR, progesterone receptor; HER2/neu human epidermal growth factor receptor.

#### *Genotype and allele distribution of SNPs*

Distributions of the genotypes and allele frequencies of FGFR2, MAP3K1, TOX3, LSP1, SLC4A7 SNPs between the groups were demonstrated in table 2. MAP3K1 rs889312 C allele was higher in the BC case group than the control group ($P = 0.016$), the rest of the allele frequency differences were not statistically significant.

In terms of genotype frequencies, among all polymorphisms, the only statistically significant difference was observed in MAP3K1 rs889312 polymorphism ($P = 0.042$). The genotype frequencies of CA (CA vs AA: OR 1.87, 95% CI 1.02–3.43, $P = 0.041$), CC (CC vs AA: OR 2.73, 95% CI 1.07–6.96, $P = 0.039$) and CA+CC (CA+CC vs AA: OR 2.02, 95% CI 1.13–3.60, $P = 0.017$) were higher in the BC group than the controls.

**Table 2.** Genotype and allele distribution of SNPs in BC patients and control group individuals.

| Genotypes | Controls *n* (%) *N* = 100 | Cases *n* (%) *N* = 101 | $\chi^2$ *P*-value | OR (%95 CI) | *P* value |
|---|---|---|---|---|---|
| rs1219648 (FGFR2) | | | 0.326 | | |
| AA | 32 (32) | 24 (23.8) | | 1[a] | |
| GA | 41 (41) | 51 (50.5) | | 1.7 (0.85–3.24) | 0.138 |
| GG | 27 (27) | 26 (25.7) | | 1.28 (0.60–2.73) | 0.567 |
| AA/GA+GG | 68 (68) | 77 (76.2) | | 1.51 (0.81–2.81) | 0.193 |
| GG/GA+AA | | 75 (74.3) | | | 0.840 |
| | 73 (73) | 75 (74.3) | | 0.94 (0.50–1.76) | |
| Alleles | | | 0.484 | | |
| A | 105 (52.5) | 99 (49) | | 1[a] | |
| G | 95 (47.5) | 103 (51) | | 1.15 (0.78–1.70) | 0.484 |
| | HWE: 0.075 | HWE: 0.918 | | | |
| rs2981579 (FGFR2) | | | 0.529 | | |
| CC | 27 (27) | 21 (20.8) | | 1[a] | |
| TC | 43 (43) | 50 (49.5) | | 1.50 (0.74–3.01) | 0.290 |
| TT | 30 (30) | 30 (29.7) | | 1.29 (0.60–2.76) | 0.564 |
| CC/TC+TT | 73 (73) | 80 (79.2) | | 1.41 (0.73–2.71) | 0.325 |
| TT/TC+CC | 70 (70) | 71 (70.3) | | 0.99 (0.54–1.80) | 0.963 |
| Alleles | | | 0.553 | | |
| C | 97 (48.5) | 92 (45.5) | | 1[a] | |
| T | 103 (51.5) | 110 (54.5) | | 1.13 (0.76–1.67) | 0.553 |
| | HWE: 0.164 | HWE: 0.984 | | | |
| rs2981582 (FGFR2) | | | 0.387 | | |
| CC | 35 (35) | 27 (26.7) | | 1[a] | |
| CT | 42 (42) | 51 (50.5) | | 1.57 (0.82–3.00) | 0.168 |
| TT | 23 (23) | 23 (22.8) | | 1.30 (0.60–2.79) | 0.561 |
| CC/CT+TT | 65 (65) | 74 (73.3) | | 1.48 (0.81–2.70) | 0.204 |
| TT/CT+CC | 77 (77) | 78 (77.2) | | 0.99 (0.51–1.91) | 1.000 |
| Alleles | | | 0.419 | | |
| C | 112 (56) | 105 (52) | | 1[a] | |
| T | 88 (44) | 97 (48) | | 1.18 (0.79–1.74) | 0.419 |
| | HWE: 0.140 | HWE: 0.908 | | | |
| rs3803662 (TOX3) | | | 0.099 | | |
| CC | 48 (48) | 44 (43.6) | | 1[a] | |
| CT | 45 (45) | 40 (39.6) | | 0.97 (0.54–1.75) | 0.919 |
| TT | 7 (7) | 17 (16.8) | | 2.65 (1.00–6.99) | 0.065 |
| CC/CT+TT | 52 (52) | 57 (56.4) | | 1.20 (0.69–2.08) | 0.528 |
| TT/CT+CC | 93 (93) | 84 (83.2) | | 2.69 (1.06–6.80) | 0.049* |
| Alleles | | | 0.129 | | |
| C | 141 (70.5) | 128 (63.4) | | 1[a] | |
| T | 59 (29.5) | 74 (36.6) | | 1.38 (0.91–2.10) | 0.129 |
| | HWE: 0.413 | HWE: 0.140 | | | |
| rs3817198 (LSP1) | | | 0.201 | | |
| TT | 45 (45) | 35 (34.7) | | 1[a] | |
| TC | 40 (40) | 53 (52.5) | | 1.70 (0.93–3.11) | 0.082 |
| CC | 15 (15) | 13 (12.9) | | 1.11 (0.47–2.64) | 0.828 |
| TT/TC+CC | 55 (55) | 66 (65.4) | | 1.54 (0.87–2.72) | 0.134 |
| CC/TC+TT | 85 (85) | 88 (87.2) | | 0.84 (0.38–1.86) | 0.689 |
| Alleles | | | 0.394 | | |
| T | 130 (65) | 123 (60.9) | | 1[a] | |
| C | 70 (35) | 79 (39.1) | | 1.19 (0.80–1.79) | 0.394 |
| | HWE: 0.227 | HWE: 0.306 | | | |
| rs4973768 (SLCA7) | | | 0.725 | | |
| CC | 18 (18) | 14 (13.9) | | 1[a] | |
| TC | 48 (48) | 51 (50.5) | | 1.37 (0.61–3.05) | 0.543 |
| TT | 34 (34) | 36 (35.6) | | 1.36 (0.59–3.16) | 0.526 |
| CC/TC+TT | 82 (82) | 87 (86.1) | | 1.36 (0.64–2.92) | 0.447 |
| TT/TC+CC | 66 (66) | 65 (64.4) | | 1.08 (0.60–1.92) | 0.807 |
| Alleles | | | 0.555 | | |
| C | 84 (42) | 79 (39.1) | | 1[a] | |
| T | 116 (58) | 123 (60.9) | | 1.13 (0.76–1.68) | 0.555 |
| | HWE: 0.883 | HWE: 0.545 | | | |

**Table 2** (*contd*)

| Genotypes | Controls *n* (%) *N* = 100 | Cases *n* (%) *N* = 101 | $\chi^2$ *P*-value | OR (%95 CI) | *P* value |
|---|---|---|---|---|---|
| rs889312 (MAP3K1) | | | 0.042* | | |
| AA | 46 (46) | 30 (29.7) | | 1[a] | |
| CA | 45 (45) | 55 (54.5) | | 1.87 (1.02–3.43) | 0.041* |
| CC | 9 (9) | 16 (15.8) | | 2.73 (1.07–6.96) | 0.039* |
| AA/CA+CC | 54 (54) | 71 (70.3) | | 2.02 (1.13–3.60) | 0.017* |
| CC/CA+AA | 91 (91) | 85 (84.2) | | 1.90 (0.80–4.54) | 0.199 |
| Alleles | | | | | |
| A | 137 (68.5) | 115 (56.9) | | 1[a] | |
| C | 63 (31.5) | 87 (43.1) | | 1.65 (1.09–2.47) | 0.016* |
| | HWE: 0.669 | HWE: 0.267 | | | |
| rs909116 (LSP1) | | | 0.138 | | |
| TT | 39 (39) | 29 (28.7) | | 1[a] | |
| TC | 49 (49) | 51 (50.5) | | 1.4 (0.75–2.60) | 0.287 |
| CC | 12 (12) | 21 (20.8) | | 2.35 (1.00–5.54) | 0.058 |
| TT/TC+CC | 61 (61) | 72 (71.3) | | 1.59 (0.88–2.86) | 0.123 |
| CC/TC+TT | 88 (88) | 80 (79.2) | | 1.93 (0.89–4.16) | 0.127 |
| Alleles | | | 0.052 | | |
| T | 127 (63.5) | 109 (54) | | 1[a] | |
| C | 73 (36.5) | 93 (46) | | 1.48 (1.00–2.21) | 0.052 |
| | HWE: 0.568 | HWE: 0.870 | | | |

*$P < 0.05$. OR, odds ratio; CI, confidence interval; 1[a] reference genotype/allele.

TOX3 rs3803662 polymorphism was associated with BC risk only in a ressesive model as the frequency of TT genotype was higher in the cases than the controls (TT vs CT+CC: OR 2.69, 95% CI 1.06–6.80, $P = 0.049$). All of the studied SNPs were in HWE for both of the groups.

#### *SNPs and histopathological characteristics of breast tumours*

There was no relation between BMI, PR status, Her2/neu status, tumour grade, metastasis status, lymph node status, family history and the studied SNPs. SLCA7 rs4973768 CC genotype and LSP1 rs909116 CC genotype frequencies were found to be significantly increased in tumours greater than 5 cm ($P = 0.027$ and $P = 0.028$, respectively) (table 3).

## Discussion

According to the cancer data of Turkey which was released in 2018, BC is the most frequent cancer among women (43.8/100,000 people in 2015) (Türkyılmaz *et al.* 2018), it is also the leading cause of cancer deaths, as in other populations. The frequency of BC in Turkey was rather accelerated in the last two decades as its incidense in 1993 was reported to be 24.1/100,000 (Özmen 2014).

In our study, MAP3K1, and *TOX3* gene SNPs were found to be associated with BC risk in a Turkish population; as low-penetrance susceptibility variant association may vary according to ethnicity differences, it is very important to reveal their association in different populations. Clinically, SNPs are suggested to be potential markers in cancers that may help in diagnosis and developing therapeutic approaches. Localization of SNPs differs, they take place in promoter, exon, intron, 5′-UTR and 3′-UTR regions. Due to this, according to the localization place, SNPs affect expression of genes and susceptibility of cancer. For example, intronic SNPs create transcript splice variants; affect binding regions of long-noncoding RNAs and their functions (Deng *et al.* 2017). Sequences belonging to intronic regions may consist *cis*-acting gene expression regulators such as, insulter, silencer, enhancer and DNA recognition motif for transcription factor that are common important risk variant regions (Zhang *et al.* 2014).

MAP3K1 rs889312 polymorphism was suggested to regulate expression of MAP3K1, without altering its structure or the biochemical function. It is suggested that, this SNP might affect MAPK signal transduction. MAP3K1 rs889312 association is seen in both ER (+), ER (–) BC cases (Zheng *et al.* 2014). MAP3K1 SNPs were considered as BC susceptibility polymorphisms in an important GWAS conducted in a three stage population group including European and Asian originated populations (Easton *et al.* 2007). Rs889312 polymorphism is associated with ER (+), PR (+) or HER2 (–) BC risk in African Americans (Rebbeck *et al.* 2009). MAP3K1 rs889312 is significantly associated with BC risk in Indian (also associated with ER (+), PR (+) BC cancer), Korean populations (Han *et al.* 2011) but is not associated with Polish, African, Vietnamese populations (Ledwoń *et al.* 2013; Zheng *et al.* 2014; Thanh *et al.* 2018). In this study, MAP3K1 rs889312 SNP demonstrated the strongest association with BC risk, among the other low-penetrant SNPs, it was associated with BC risk in both additive and dominant models. There was no association between rs889312 SNP genotypes and clinopathological parameters in the current study.

*FGFR2* and *TOX3* gene polymorphisms which were reported to be associated with BC risk are important

**Table 3.** SNPs and histopathological parameters of the tumours of BC patients.

| Genotype frequency (%) | BMI | | | Progesteron receptor status | | Her2/neu status | | Tumour size | | Node involvement | | Tumour grade | | Metastases | | Family history | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | < 25 | 25–29.9 | ≥ 30 | Negative | Positive | Negative | Positive | ≤ 5 cm | > 5cm | No | Yes | I, II | III | No | Yes | No | Yes |
| rs1219648 (FGFR2) | | | | | | | | | | | | | | | | | |
| AA | 4 (28.6) | 7 (18.9) | 13 (26) | 4 (21.1) | 20 (24.4) | 18 (23.7) | 6 (24) | 22 (25) | 1 (11.1) | 9 (20) | 15 (27.8) | 19 (30.6) | 4 (14.3) | 23 (26.1) | 1 (8.3) | 19 (24.4) | 5 (22.7) |
| GA | 7 (50) | 17 (45.9) | 27 (54) | 10 (52.6) | 41 (50) | 37 (48.7) | 14 (56) | 44 (50) | 6 (66.7) | 26 (57.8) | 24 (44.4) | 26 (41.9) | 17 (60.7) | 42 (47.7) | 9 (75) | 41 (52.6) | 10 (45.5) |
| GG | 3 (21.4) | 13 (35.1) | 10 (20) | 5 (26.3) | 21 (25.6) | 21 (27.6) | 5 (20) | 22 (25) | 2 (22.2) | 10 (22.2) | 15 (27.8) | 17 (27.4) | 7 (25) | 23 (26.1) | 2 (16.7) | 18 (23.1) | 7 (31.8) |
| *P* value | 0.576 | | | 1.000 | | 0.731 | | 0.666 | | 0.411 | | 0.175 | | 0.198 | | 0.700 | |
| rs2981579 (FGFR2) | | | | | | | | | | | | | | | | | |
| CC | 4 (28.6) | 6 (16.2) | 11 (22) | 4 (21.1) | 17 (20.7) | 16 (21.1) | 5 (20) | 19 (21.6) | 1 (11.1) | 7 (15.6) | 14 (25.9) | 16 (25.8) | 4 (14.3) | 20 (22.7) | 1 (8.3) | 16 (20.5) | 5 (22.7) |
| TC | 6 (42.9) | 18 (48.6) | 26 (52) | 10 (52.6) | 40 (48.8) | 36 (47.4) | 14 (56) | 45 (51.1) | 4 (44.4) | 24 (53.3) | 25 (46.3) | 27 (43.5) | 16 (57.1) | 43 (48.9) | 7 (58.3) | 40 (51.3) | 10 (45.5) |
| TT | 4 (28.6) | 13 (35.1) | 13 (26) | 5 (26.3) | 25 (30.5) | 24 (31.6) | 6 (24) | 24 (27.3) | 4 (44.4) | 14 (31.1) | 15 (27.8) | 19 (30.6) | 8 (28.6) | 25 (28.4) | 4 (33.3) | 22 (28.2) | 7 (31.8) |
| *P* value | 0.806 | | | 0.934 | | 0.720 | | 0.587 | | 0.453 | | 0.382 | | 0.569 | | 0.890 | |
| rs2981582 (FGFR2) | | | | | | | | | | | | | | | | | |
| CC | 5 (35.7) | 9 (24.3) | 13 (26) | 5 (26.3) | 22 (26.8) | 19 (25) | 8 (32) | 22 (25) | 3 (33.3) | 10 (22.2) | 16 (29.6) | 19 (30.6) | 6 (21.4) | 24 (27.3) | 3 (25) | 22 (28.2) | 5 (22.7) |
| CT | 7 (50) | 17 (45.9) | 27 (54) | 10 (52.6) | 41 (50) | 39 (51.3) | 12 (48) | 46 (52.3) | 5 (55.6) | 28 (62.2) | 23 (42.6) | 29 (46.8) | 15 (53.6) | 44 (50) | 7 (58.3) | 39 (50) | 11 (50) |
| TT | 2 (14.3) | 11 (29.7) | 10 (20) | 4 (21.1) | 19 (23.2) | 18 (23.7) | 5 (20) | 20 (22.7) | 1 (11.1) | 7 (15.6) | 15 (27.8) | 14 (22.6) | 7 (25) | 20 (22.7) | 2 (16.7) | 17 (21.8) | 6 (27.3) |
| *P* value | 0.702 | | | 0.974 | | 0.780 | | 0.812 | | 0.135 | | 0.663 | | 0.923 | | 0.813 | |
| rs3803662 (TOX3) | | | | | | | | | | | | | | | | | |
| CC | 6 (42.9) | 12 (32.4) | 26 (52) | 12 (63.2) | 32 (39) | 30 (39.5) | 14 (56) | 37 (42) | 4 (44.4) | 20 (44.4) | 23 (42.6) | 29 (46.8) | 12 (42.9) | 37 (42) | 7 (58.3) | 32 (41) | 12 (54.5) |
| CT | 8 (57.1) | 16 (43.2) | 16 (32) | 6 (31.6) | 34 (41.5) | 33 (43.4) | 7 (28) | 37 (42) | 2 (22.2) | 17 (37.8) | 22 (40.7) | 25 (40.3) | 9 (32.1) | 35 (39.8) | 4 (33.3) | 31 (39.7) | 8 (36.4) |
| TT | 0 (0) | 9 (24.3) | 8 (16) | 1 (5.3) | 16 (19.5) | 13 (17.1) | 4 (16) | 14 (16) | 3 (33.3) | 8 (17.8) | 9 (16.7) | 8 (12.9) | 7 (25) | 16 (18.2) | 1 (8.3) | 15 (19.2) | 2 (9.1) |
| *P* value | 0.115 | | | 0.116 | | 0.313 | | 0.388 | | 0.955 | | 0.350 | | 0.468 | | 0.406 | |
| rs3817198 (LSP1) | | | | | | | | | | | | | | | | | |
| TT | 5 (35.7) | 13 (35.1) | 17 (34) | 5 (26.3) | 30 (36.6) | 26 (34.2) | 9 (36) | 28 (31.8) | 6 (66.7) | 16 (35.6) | 19 (35.2) | 21 (33.9) | 10 (35.7) | 30 (34.1) | 5 (41.7) | 27 (34.6) | 8 (36.4) |
| TC | 8 (57.1) | 17 (45.9) | 28 (56) | 11 (57.9) | 42 (51.2) | 41 (53.9) | 12 (48) | 49 (55.7) | 2 (22.2) | 23 (51.1) | 29 (53.7) | 35 (56.5) | 14 (50) | 47 (53.4) | 5 (41.7) | 41 (52.6) | 11 (50) |
| CC | 1 (7.1) | 7 (18.9) | 5 (10) | 3 (15.8) | 10 (12.2) | 9 (11.8) | 4 (16) | 11 (12.5) | 1 (11.1) | 6 (13.3) | 6 (11.1) | 6 (9.7) | 4 (14.3) | 11 (12.5) | 2 (16.7) | 10 (12.8) | 3 (13.6) |
| *P* value | 0.713 | | | 0.685 | | 0.820 | | 0.112 | | 0.936 | | 0.765 | | 0.752 | | 0.978 | |
| rs4973768 (SLCA7) | | | | | | | | | | | | | | | | | |
| CC | 1 (7.1) | 6 (16.2) | 7 (14) | 3 (15.8) | 11 (13.4) | 13 (17.1) | 1 (4) | 10 (11.4) | 4 (44.4) | 6 (13.3) | 8 (14.8) | 9 (14.5) | 5 (17.9) | 13 (14.8) | 1 (8.3) | 10 (12.8) | 4 (18.2) |
| TC | 6 (42.9) | 19 (51.4) | 26 (52) | 6 (31.6) | 45 (54.9) | 38 (50) | 13 (52) | 46 (52.3) | 2 (22.2) | 27 (60) | 23 (42.6) | 29 (46.8) | 13 (46.4) | 45 (51.1) | 6 (50) | 41 (52.6) | 9 (40.9) |
| TT | 7 (50) | 12 (32.4) | 17 (34) | 10 (52.6) | 26 (31.7) | 25 (32.9) | 11 (44) | 32 (36.4) | 3 (33.3) | 12 (26.7) | 23 (42.6) | 24 (38.7) | 10 (35.7) | 30 (34.1) | 5 (41.7) | 27 (34.6) | 9 (40.9) |
| *P* value | 0.782 | | | 0.164 | | 0.224 | | 0.027* | | 0.195 | | 0.912 | | 0.771 | | 0.604 | |
| rs889312 (MAP3K1) | | | | | | | | | | | | | | | | | |
| AA | 5 (35.7) | 12 (32.4) | 13 (26) | 7 (36.8) | 23 (28) | 22 (28.9) | 8 (32) | 25 (28.4) | 5 (55.6) | 18 (40) | 12 (22.2) | 16 (25.8) | 9 (32.1) | 27 (30.7) | 3 (25) | 24 (30.8) | 6 (27.3) |
| CA | 7 (50) | 19 (51.4) | 29 (58) | 9 (47.4) | 46 (56.1) | 42 (55.3) | 13 (52) | 47 (53.4) | 4 (44.4) | 20 (44.4) | 33 (61.1) | 33 (53.2) | 16 (57.1) | 46 (52.3) | 8 (66.7) | 43 (55.1) | 11 (50) |
| CC | 2 (14.3) | 6 (16.2) | 8 (16) | 3 (15.8) | 13 (15.9) | 12 (15.8) | 4 (16) | 16 (18.2) | 0 (0) | 7 (15.6) | 9 (16.7) | 13 (21) | 3 (10.7) | 15 (17) | 1 (8.3) | 11 (14.1) | 5 (22.7) |
| *P* value | 0.945 | | | 0.734 | | 0.953 | | 0.158 | | 0.146 | | 0.479 | | 0.656 | | 0.621 | |
| rs909116 (LSP1) | | | | | | | | | | | | | | | | | |
| TT | 4 (28.6) | 11 (29.7) | 14 (28) | 6 (31.6) | 23 (28) | 21 (27.6) | 8 (32) | 27 (30.7) | 1 (11.1) | 10 (22.2) | 18 (33.3) | 18 (29) | 8 (28.6) | 26 (29.5) | 3 (25) | 20 (25.6) | 9 (40.9) |
| TC | 7 (50) | 16 (43.2) | 28 (56) | 9 (47.4) | 42 (51.2) | 41 (53.9) | 10 (40) | 46 (52.3) | 3 (33.3) | 23 (51.1) | 27 (50) | 31 (50) | 15 (53.6) | 44 (50) | 6 (50) | 41 (52.6) | 9 (40.9) |
| CC | 3 (21.4) | 10 (27) | 8 (16) | 4 (21.1) | 17 (20.7) | 14 (18.4) | 7 (28) | 15 (17) | 5 (55.6) | 12 (26.7) | 9 (16.7) | 13 (21) | 5 (17.9) | 18 (20.5) | 3 (25) | 17 (21.8) | 4 (18.2) |
| *P* value | 0.744 | | | 0.945 | | 0.432 | | 0.028* | | 0.327 | | 0.931 | | 1.000 | | 0.377 | |

*$P < 0.05$. BMI, body mass ındex; PR, progesterone receptor; HER2/neu, human epidermal growth factor receptor.

examples for the intronic region SNPs. It was hypothesized that FGFR2 intron two polymorphisms cause alterations in binding of *cis*-regulatory elements like transcription factors (Robbez-Masson *et al.* 2013). It is suggested that 16q12.1 rs4784227 SNP T allele that is localized on a regulator enhancer affects TOX3 rs2193094 intronic SNP causes an allele specific expression and consequently decreased *TOX3* gene expression (Cowper-Sal lari *et al.* 2012). *FGFR2* gene rs2981578, rs35054928 and rs45631563 polymorphisms were mapped to the transcription silencer regions and caused reduced expression of the gene, which led to an increase in oestrogen response and risk of BC (Campbell *et al.* 2016). FGFR2 rs2981582, rs1219648 polymorphisms were suggested to interact with some transcription factors. Oct-1/Runx2 complex is an example for such transcription factors which increase FGFR2 expression. rs2981582 was reported to be associated with all kinds of BC except the one with ER (–)/PR (–) tumours (Lei and Deng 2017). An increased association of FGFR2 polymorphisms and BC risk was reported by GWASs (Easton *et al.* 2007; Hunter *et al.* 2007; Stacey *et al.* 2008), but also this association was suggested to differ according to the studied polulations (Lei and Deng 2017). In a comprehensive meta-analysis performed recently including 121,740 BC cases and 198,549 control individuals from 53 different studies, 10 mostly studied intron 2 polymorphisms of FGFR2 (rs1078806, rs11200014, rs1219648, rs2420946, rs2981578, rs2981579, rs2981582, rs3135718, rs10736303 and rs3750817) were recruited. This meta-analysis comprised many ethnically diverse populations including a previous study of ours in a Turkish population (Özgöz *et al.* 2013; Cui *et al.* 2016). In this meta-analysis, asociation of the FGFR2 SNPs with BC risk was determined to be higher in some ethnically different populations such as Caucasian, Asian but not in Africans (Cui *et al.* 2016). As being a member of Caucasian origin, in our previous study, despite FGFR2 rs2981582 CT genotype and T allele; rs 1219648 AG genotype and G allele frequencies were higher in BC group, the results were not statistically significant ($P < 0.05$). We have suggested that, this statistically insignificance may be due to the low case number. In the current study, we increased the number of participants and included one more polymorphism (rs2981579), but still we did not find a statistically significant association between FGFR2 polymorphisms and BC risk in Turkish ER (+) postmenapausal BC cases. There was also no association with FGFR2 SNPs and clinopathological parameters (all $P < 0.05$) (table 2).

In TOX3 rs3803662 polymorphism, the T allele was reported to be associated with increased TOX3 expression. It was also found to be related with poor survival of BC patients, besides being associated with increased BC risk (Barrdahl *et al.* 2015; Han *et al.* 2016). rs3803662 polymorphism was also reported to be associated with node positive BC (Kuchenbaecker *et al.* 2014).

*TOX3* gene rs3803662 was reported to be associated with BC risk in GWASs (Easton *et al.* 2007; Stacey *et al.* 2007; Turnbull *et al.* 2010) performed in European populations. Whereas some studies further performed in different populations, such as Chinese, Tunisian and Vietnamese, rs3803662 demonstrated association with BC risk (Zheng *et al.* 2010; Shan *et al.* 2012; Thanh *et al.* 2018); it failed to associate with BC risk in African American, Hispanic, Indian populations (Zheng *et al.* 2009; Barnholtz-Sloan *et al.* 2010; Udler *et al.* 2010; Ruiz-Narváez *et al.* 2010; Nagrani *et al.* 2017). In our study, rs3803662 was associated with BC risk only in a ressesive model (TT vs CT+CC: OR 2.69, 95% CI 1.06–6.80, $P = 0.049$). Being not in line with our study; in a meta-analysis by Deng *et al.* (2016) consisting 13 different case–control studies from different populations belonging to Caucasian and Asian origin, rs3803662 was reported to be significantly associated with BC risk in Caucasians in allele, dominant and additive models but not in a ressesive model ($P = 0.003$, $P = 0.011$, $P = 0.018$, $P = 0.103$, respectively) (Deng *et al.* 2016). In our study, there was no association between rs3803662 SNP genotypes and clinopathological parameters (all $P < 0.05$), as well.

Although LSP1 rs3817198 polymorphism C allele was estimated to increase CDKN1C tumour supressor gene expression (Barrdahl *et al.* 2015), no study could be found about the putative functional effects of *SLC4A7* gene SNPs in the literature. LSP1 rs3817198 and SLC4A7 rs4973768 SNPs were reported to be associated with an increased BC risk in GWAS by Easton *et al.* (2007), association was verified in many of the further studied populations, but not in some. SLC4A7 rs4973768 was reported to be associated with BC risk in a comprehensive meta-analysis consisting 108,632 cases and 135,818 control individiuals of which 15 study from European population; seven from Asian population; two from African-American population (Chen *et al.* 2012); but was not associated in a study from Indian population (Nagrani *et al.* 2017). In our study, rs4973768 was not associated with postmenopausal ER (+) BC risk ($P = 0.725$), in line with a study conducted in a Japanese population (Guo *et al.* 2017). Interestingly, in our study, rs4973768 CC genotype was correlated with higher tumour size ($P = 0.027$) which is not reported in the literature so far. There was no association between rs4973768 SNP genotypes and other clinopathological parameters (all $P < 0.05$). In a study by Barrdahl *et al.* (2015) performed in a large number of study group, namely BPC3; *LSP1* gene rs3817198 C allele was associated with improved survival in 10,255 mostly postmenapausal and all Caucasian women with BC of Europen, Australian and American origin (Barrdahl *et al.* 2015). 12,760 control individuals from the same study group (BPC3) was also studied by Joshi *et al.* (2014) together with 10,146 non-Hispanic White, new BC cases. Joshi *et al.* (2014) found no association between *LSP1* gene rs909116 and BC risk ($P = 0.133$) among the 23 BC susceptibility SNPs determined by GWASes; LSP rs3817198 polymorphism was not investigated in their study. In a meta-analysis, including 30,204 cases and 35,282 control individiauls from 14 different studies, *LSP1* gene rs3817198

polymorphism was significantly associated with BC risk in European, American and African populations, but not in Asian populations (Moghaddam *et al.* 2017). Also in a study from Indian population, rs3817198 failed to demonstrate association with postmenopausal BC risk (Nagrani *et al.* 2017). In our study, LSP1 rs909116 and rs3817198 polymorphisms were not associated with BC risk ($P = 0.138$, $P = 0.201$, respectively). In our study, rs909116 CC genotype was also correlated with higher tumor size ($P = 0.028$) likewise rs4973768 CC genotype, which is again not reported in the literature so far. In addition, no association was observed between rs909116 and rs3817198 SNP genotypes and other clinopathological parameters (all $P < 0.05$).

Genetic reasons are known to have important roles in BC. As being one of the most common genetic variations, SNPs contributing to the BC susceptibility attracted attention and therefore many GWASs, which mostly focussed on people from European ancestry detected many susceptibility SNPs associated with BC risk. SNP minor allele frequencies and patterns of linkage disequilibrium are affected through ethnicities of populations. Therefore SNPs detected in GWASs are needed to be studied and verified in different populations (Han *et al.* 2011). To our knowledge, there is no study in Turkish population evaluating low-penetrance BC susceptibility SNPs together (FGFR2 rs1219648, rs2981579, rs2981582; MAP3K1 rs889312; TOX3 rs3803662; LSP1 rs909116, rs3817198 and SLC4A7 rs4973768), which were detected in GWASs. Our study is the first one conducted in a Turkish polulation, evaluating low-penetrance BC susceptibility SNPs.

In conclusion, this study conducted in a total of 201 Turkish postmenopausal ER (+) BC cases and control group individuals, MAP3K1 rs889312; one of the most frequent BC associated low-penetrance susceptibility SNP demonstrated significant association with BC risk ($P = 0.042$). As our study is the first one revealing this, further studies should be performed in Turkish population to evaluate this potantial BC susceptibility biomarker. Another finding of our comprehensive but relatively size limited study was association of TOX3 rs3803662 polymorphism with BC risk, only in a ressesive model (OR (%95 CI, $P = 0.049$), again for the first time in a Turkish population. SLC4A7 rs4973768 CC and LSP1 rs909116 CC genotypes were correlated with higher tumour size ($P = 0.027$ and $P = 0.028$, respectively), which were not reported in the literature so far. As polymorphisms may have functional effects on BC risk and may have ethnically diverse effects; SNP panels exclusively constructed for different populations may be useful for evaluating BC risk. In BC, rs889312 CC genotype might affect MAPK signal transduction, as mentioned in the literature. We suggest that, together with evaluating new BC risk SNPs detected in GWASes, MAP3K1 rs889312 SNP should take place in a BC risk panel constructed for Turkish population.

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