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RESEARCH

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Prevalence of *TP53* gene Pro72Arg (rs1042522) single nucleotide polymorphism among Egyptian breast cancer patients

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Abstract

Background The P53 protein has an essential role in several cellular processes, including DNA repair, apoptosis, and cell cycle arrest. The pathophysiology of many cancer types has frequently been linked to polymorphisms in the *TP53* locus. Over 200 single nucleotide polymorphisms (SNPs) have been identified in TP53. However, Pro72Arg (rs1042522) at codon 72, shows contradictory results in terms of cancer risk. In this study, we aimed to determine if the Pro72Arg (rs1042522) SNP in the *TP53* gene would be linked to breast cancer (BC) risk among Egyptian patients.

Materials and Methods Genomic DNA was extracted from blood samples of 100 healthy volunteers and 100 breast cancer patients (50 familial and 50 non-familial). *TP53* Genotyping was performed using tetra-primer amplification refractory mutation (Tetra-ARMS) PCR. Data were analyzed using SNPstat software.

Results The prevalence of *TP53* (Pro72Arg) rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] were significantly higher in BC patients compared to healthy volunteers and were associated with BC susceptibility (OR 0.2; [95% CI 0.11–0.38]; $P = 0.0001$). However, there was no statistical significant difference in the prevalence of *TP53* (Pro72Arg) rs1042522 genotypes carrying the high-risk allele between familial and non-familial BC patients. In addition, there was no association between the prevalence of *TP53* (Pro72Arg) rs1042522 genotypes carrying the high-risk allele and BC patients' clinical and pathological characteristics including tumor size, tumor grade, lymph node status, presence of lymphovascular invasion, expression of ER, PR and Her-2 in both of familial and non-familial BC patients.

Conclusions *TP53* (Pro72Arg) rs1042522 is more prevalent among BC patients but not associated with disease progression.

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Introduction

The incidence of Breast Cancer (BC) in the Middle east has substantially increased, especially among young women, and is characterized by late diagnosis [1]. The women diagnosed with BC at earlier stages have a high survival rate, when compared to later stages women [2]. BC mortality rates are increasing in developing countries including Egypt which represents 32% of cancer cases [3] it is ranked fifth as a cause of death in women in less developed regions (324,000 deaths, 14.3% of total) it is now the second leading cause of cancer death in

more developed regions (198,000 deaths, 15.4% of total) [3, 4]. Like other cancers, genetic variations have been shown to have a crucial role in BC development [5, 6]. Most BC predisposing genes are tumor suppressor genes such as; Breast Cancer gene 1 and 2 (*BRCA1*/*BRCA2)*, Tumor Protein 53 (*TP53)*, Phosphatase and TENsin homolog *(PTEN*) and Checkpoint Kinase 2 (*CHK2*) that are involved in DNA damage repair pathways and cell cycle control are reported to be associated with the progression of BC [7]. *TP53* is the most frequently mutated tumor-suppressor gene in BC and previous epidemiological studies have revealed that mutations in *TP53* occur in approximately 30% of BC cases [8, 9]. The role of *TP53* mutations in BC survival is confounded by different studies that revealed that *TP53* mutations are associated with negative or positive disease outcomes [10–13].

TP53 gene is located on chromosome 17p13.1 with a 20 kb gene size [14, 15] constituting 13 exons and 11 introns [16]. *TP53* codes for the transcription factor P53 [17], which is responsible for initiating the transcription process of several genes involved in cellular processes, such as cell cycle arrest, apoptosis, metabolism, and DNA repair [14, 18]. More than 90% of mutations occur in the *TP53* gene encode for a missense mutant protein that extends along 190 different codons localized in the DNA binding domain of the gene [19]. About 10% of the previously stated mutations were reported to have a loss of protein function either through deletion or frameshift mutations [19]. Al Qasem and colleagues indicated that *TP53* mutation prevalence in Arab BC patients is found to be the highest in the world representing more than 40% of all BC cases [20]. More than 200 genetic polymorphisms have been detected in *TP53* [21]. Three single nucleotide polymorphisms (SNPs) in *TP53* gene were associated with tumorigenesis [22]. The first SNP (rs1042522 C > G; CGC-CCC) located at codon 72 of exon 4 of *TP53*, which results in substitution of proline (Pro) to arginine (Arg) which have the capability to alter the P53 function and has been reported to be associated with BC progression [23, 24]. The second polymorphism is a 16-bp insertion repeat in the third intron region of *TP53* gene [25, 26] and the third polymorphism occurs at the MSP I restriction site of *TP53* gene in the sixth intron [27]. *TP53* rs1042522 is most important and extensively studied polymorphism among these three polymorphisms [28]. Many previous studies have shown an association between these three polymorphisms and the genetic susceptibility of many tumors [26, 29, 30]. In particular, the *TP53* rs1042522 SNP is associated with susceptibility to several malignancies including breast, lung, and cervical cancers [28, 31–33], suggesting an important role of this part of the *TP53* gene in the development of cancer. In addition, the rs1042522 has an important role in the P53-mediated apoptosis [34].

Previous study on Egyptian BC women found this variant to be repeatedly found among their patients and was concluded as well to be associated with drug responsiveness [35]. Since codon 72 in *TP53* gene influence the ability of P53 to bind to P73 that has a role to influence the BC patient responsiveness to chemotherapy through modulation of its apoptosis dependent pathway. Their findings were also validated by another study which was done by Cheng and colleagues [36]. According to both studies the mutations in *TP53* may influence the BC patient's response to chemotherapy. Additional studies have reported that patients with these hot spot mutations are associated with poor prognosis where they have also suggested that R72 is associated with resistance to chemotherapy and thereof; can be used as a chemotherapy predictive marker in BC patients [37, 38]. The clinical studies showed controversial results about the predictive and prognostic values of *TP53* mutation in codon 72, where none of them was conclusive up to date [24, 39]. Therefore, herein we aimed to explore the prevalence of *TP53* rs1042522 among familial and non-familial breast cancer patients and its possible association with pathogenesis of BC.

Patients and methods

Patients' samples

The present study was approved by the Institutional Review Board (IRB) of the Ministry of Health (IORG0005704/IRB0000687). A total of 100 Egyptian BC patients (50 familial and 50 non-familial) and 100 healthy volunteers were enrolled in this study. All BC patients were fully subjected to clinical investigations such as the hormonal status (estrogen (ER), progestrogen (PR) and human epidermal receptor-2 (Her-2)), lymph node involvement, menopausal status, tumor size, and tumor grade as well as did not receive neoadjuvant chemotherapy treatment before surgery nor diagnosed with ovarian cancer. Blood samples were recruited from out-patient clinics and Radiodiagnosis Department at El-Demerdash Hospital, National Cancer Institute, and El Matarya Hospital. All enrolled participants signed a consent form for acceptance of the publication of anonymous data.

Genomic DNA isolation and purification

Genomic DNA was isolated from collected blood samples using GeneJET™ genomic DNA purification Kit (Thermo Scientific, MA, USA). The concentration and quality of the genomic DNA were determined using Nanodrop ND2000 Spectrophotometer (Nanodrop Technologies, DE, USA).

Tetra-amplification refractory mutation system PCR

Tetra-amplification refractory mutation system–polymerase chain reaction (T-ARMS-PCR), which is considered a rapid, accurate and simple genotyping technique [40], was conducted for detection of *TP53* rs1042522 genotypes as described before [41]. Sequences of all primers are described in Table 1. T-ARMS-PCR reaction was conducted in 25μL total volume containing 1μL of each upstream and downstream primers (10 pmol/μL), 5μL of the DNA containing a maximum 40 ng DNA, 12.5μL of EmeraldAmp® MAX PCR green master mix, and 5.5μL of free RNase water. The thermal profile (AriaMX real-time PCR system, Agilent,USA) included an initial denaturation at 95 °C for 5 min, followed by 35 cycles of 95 °C for 30 s, 56 °C for 1 min, and 72 °C for 1 min, followed by terminal extension at 72 °C for 10 min as described by [41].

Agarose gel electrophoresis

Amplified PCR products were visualized on 2% agarose gels (BioBasic Inc., Canada), stained with ethidium bromide, and photographed by the Gel Doc XR + Gel documentation system (Bio-Rad Laboratories, CA, USA).

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical difference between groups was assessed by Student's t-test and chi square test. *P*-value < 0.05 were considered to be statistically significant. Hardy–Weinberg equilibrium was used to compare the genotypes prevalence of *TP53* rs1042522 among BC patients and healthy volunteers. Logistic regression was used to calculate the odds ratios (OR) and 95% CI to estimate the relative association between BC progression and a particular allele and genotype using SNPstat software [42]. Correlation was assessed by Pearson correlation coefficient using SPSS 22.0 software [41].

Results

Clinical and pathological characterization of familial and non-familial BC patients

Clinical and pathological characterization of familial ($n = 50$) and non-familial BC patients ($n = 50$) are described in Table 2. Statistical analysis revealed that there were no significant differences in age, tumor size, tumor grade, lymph node involvement, lymphovascular invasion and status of hormonal receptors among familial and non-familial BC patients.

Prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] was higher in BC patients compared to healthy volunteers

The genotypes and alleles distributions for the *TP53* rs1042522 polymorphism are presented in Table 3. The genotype distribution of both studied groups' fits the Hardy–Weinberg equilibrium ($P > 0.05$). The prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] was significantly higher in BC patients in comparison with seemingly healthy volunteers (81% and 46% respectively) and were also associated with BC susceptibility (OR 0.2; [95% CI 0.11–0.38]; $P = 0.0001$). Moreover, Presence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] was not significant between familial and non-familial BC patients (50% and 66% respectively) $P = 0.14$.

A Prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] with no association for BC disease progression

There was no observed association between the prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] and BC patients with regards to clinical and pathological characters including tumor size, tumor grade, lymph node status, presence of lymphovascular invasion, expression of ER, PR and Her-2 in each of familial and non-familial BC patient groups as shown in Table 4 and 5.

Discussion

TP53, also referred to as the guardian of the genome, is one of the most studied tumor suppressor genes, with key roles in the inhibition of angiogenesis, invasion as well as cell cycle control and apoptosis as a key transcription factor [18, 35]. According to Mutations in Cancer

Table 1 Sequences of the tetra primers used in T-ARMS PCR

Primer type	Sequence	Amplicon size (bp)
Forward inner primer (G allele)	5′-GCTGCTGGTGCAGGGGCCAGGG-3′	200
Reverse inner primer (C allele)	5′-CCAGAATGCCAGAGGCTGCTCCGCG-3′	247
Forward outer primer	5′-TGCAGGGGGATACGGCCAGGCATTGAAGTC-3′	493
Reverse outer primer	5′-TGGGGGGCTGAGGACCTGGTCCTCT-3′	

Table 2 Clinical and pathological characterization of familial versus non-familial BC patients

Characteristic	Familial BC ($N=50$)	Non-familial BC ($N=50$)	*P* value
Age [year]			
Range	27–78	29–72	0.223[a]
Mean ± SD	51.98 ± 10.969	49.34 ± 11.994	
NA	1	0	
Tumor size [cm]			
Mean ± SD	2.8 ± 1.5	2.9 ± 1.71	0.813[a]
Pathology			
Ductal Carcinoma In Situ	10 (20%)	7 (14%)	0.769[b]
Invasive Ductal Carcinoma	33 (66%)	34 (68%)	
Invasive Lobular Carcinoma	7 (14%)	9 (18%)	
Tumor grade			
G1	5 (10%)	6 (12%)	0.364[b]
G2	41 (82%)	35 (70%)	
G3	4 (8%)	9 (18%)	
Axillary lymph node metastasis			
Negative	24 (48%)	28 (56%)	0.462[b]
Positive	26 (52%)	22 (44%)	
Lymphovascular invasion			
Negative	31 (62%)	38 (76%)	0.171[b]
Positive	19 (38%)	12 (24%)	
ER			
Negative	20 (40%)	22 (44%)	0.668[b]
Positive	25 (50%)	24 (48%)	
NA	5 (10%)	4 (8%)	
PR			
Negative	19 (38%)	16 (32%)	0.913[b]
Positive	26 (52%)	30 (60%)	
NA	5 (10%)	4 (8%)	
Her-2			
Negative	31 (62%)	27 (54%)	0.915[b]
Positive	14 (28%)	19 (38%)	
NA	5 (10%)	4 (8%)	

Data are reported as means ± SD

ER Estrogen, *PR* Progestogen, *Her-2* Human Epidermal Receptor 2, *NA* not available

[a] Student's *t* test

[b] Chi square test

(COSMIC) database it was found to be the second most frequent mutated gene representing about 40–60% of all breast cancer patients [17, 20, 43]. Prevalence of *TP53* mutation among Arab patients showed to be the highest in the world (40%) [20].

Previous studies have proposed that the *TP53* gene Pro72Arg polymorphism consequently produces a differently functioning protein as a result of transition from CGC to CCC which may be associated with different types of cancer types such as colorectal [41], lung and breast cancer[44], yet the results among different populations are conflicting.

Herein, we evaluated the role of *TP53* gene Pro72Arg (rs1042522) polymorphism in BC among familial and non-familial Egyptian patients, where, we have found that the prevalence of *TP53* rs1042522 heterogenous genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)] were significantly higher in BC patients in comparison with healthy volunteers and were also associated with BC susceptibility which goes in accordance with study among Iranian population who were found to have this heterogenous population among BC patients and control with 75.55% and 62%, respectively. Other studies as well have supported the evidence for the Pro72Arg (rs1042522) polymorphism to be of significant risk for lung and breast cancer among different populations [45, 46] which goes in accordance with our results, where we have found that Pro72Arg (rs1042522) polymorphism was more prevalent in BC patients than healthy women.

Yet, our results contradicts with a study by Al Qasem et al., in Saudi Arabia who reported that this heterogenous genotypes was found higher among the healthy women more than those with BC (60.19% and 25% respectively) [47]. Moreover, our results contradict with the meta-analysis reported by GonÇalves et al., as well as Habyarimana et al., who suggested that the *TP53* gene Pro72Arg polymorphism among Rwandese population could not be assessed as a risk factor for BC. Since Pro/Arg (CG) and Arg/Arg (GG) heterogenous genotype predominated in both; healthy and BC patients with no significant association [24, 45].

Additionally, our results did not show significant difference among the familial and non-familial BC patients nor with clinical and pathological data which goes in accordance with Habyarimana et al., [24] and contradicts with study by Tommiska et al., in Finland where they have found that BC patients with *TP53* gene Pro72Arg (rs1042522) polymorphism were characterize with grade I tumors [48].

In conclusion, this is the first report designed among the Egyptian BC population which assessed the risk of *TP53* gene Pro72Arg polymorphism among familial and non-familial BC patients. Our preliminary results suggest that there is no association between *TP53* gene Pro72Arg (rs1042522) and breast cancer and thereof this polymorphism cannot be considered as a risk factor for the predisposition of BC in Egypt. However, further studies to investigate other genetic mutations affecting the activity of *TP53* in Egyptian BC patients using larger sample size are needed in order to investigate its association with disease development.

Table 3 Genotype and allele prevalence of *TP53* (rs1042522) polymorphism among studied groups using SNPstat software

***TP53* (rs1042522)**	**Healthy (*n* = 100) No (%)**	**BC (*n* = 100) No (%)**	**Odds ratio (95% CI)**	***P*-value**	**Familial BC (*n* = 50) No (%)**	**Non-familial BC (*n* = 50) No (%)**	**Odds ratio (95% CI)**	***P*-value**
CC (Pro/Pro)	54 (54%)	19 (19%)	1.00		25 (50%)	17 (34%)	1.00	
CG (Pro/Arg)	38 (38%)	39 (39%)	0.34 (0.17–0.68)	< 0.0001*	17 (34%)	22 (44%)	1.9 (0.79–4.6)	0.27
GG (Arg/Arg)	8 (8%)	42 (42%)	0.07 (0.03–0.17)	< 0.0001*	8 (16%)	11 (22%)	2.02 (0.67–6.07)	0.27
CG (Pro/Arg) + GG (Arg/Arg)	46 (46%)	81 (81%)	0.2 (0.11–0.38)	< 0.0001*	25 (50%)	33 (66%)	1.48 (0.54–4.06)	0.14
TP53 alleles								
C	146 (73%)	77 (38%)		0.01*	33 (33%)	44 (44%)		0.16
G	54 (27%)	123 (62%)			67 (67%)	56 (56%)		

Table 4 Clinical and pathological characterization of familial BC patients with prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)]

Characteristic	**Familial BC [Pro/Pro (CC)] (*N* = 25)**	**Familial BC [Pro/Arg (CG) and Arg/Arg (GG)] (*N* = 25)**	***P* value**
Tumor size [cm]			
Mean ± SD	2.3 ± 1.7	2.6 ± 1.2	0.153[a]
Tumor grade			
G1	3 (%)	2 (%)	0.674[b]
G2	19 (%)	22 (%)	
G3	3 (%)	1 (%)	
Axillary lymph node metastasis			
Negative	11 (%)	13 (%)	0.576[b]
Positive	14 (%)	12 (%)	
Lymphovascular invasion			
Negative	15 (%)	16 (%)	0.347[b]
Positive	10 (%)	9 (%)	
ER			
Negative	8 (%)	12 (%)	0.539[b]
Positive	15 (%)	10 (%)	
NA	2 (%)	3 (%)	
PR			
Negative	9 (%)	10 (%)	0.196[b]
Positive	14 (%)	12 (%)	
NA	2 (%)	3 (%)	
Her-2			
Negative	9 (%)	14 (%)	0.139[b]
Positive	14 (%)	8 (%)	
NA	2 (%)	3 (%)	

Data are reported as means ± SD

ER Estrogen, *PR* Progestogen, *Her-2* Human Epidermal Receptor 2, *NA* not available

[a] Student's *t* test

[b] Chi square test

Table 5 Clinical and pathological characterization of non-familial BC patients with prevalence of *TP53* rs1042522 genotypes carrying the high-risk allele [Pro/Arg (CG) and Arg/Arg (GG)]

Characteristic	Non-Familial BC [Pro/Pro (CC)] (N = 17)	Non-Familial BC [Pro/Arg (CG) and Arg/Arg (GG)] (N = 33)	*P* value
Tumor size [cm]			
Mean ± SD	2.3 ± 1.7	2.6 ± 1.2	0.156[a]
Tumor grade			
G1	2 (%)	4 (%)	0.783[b]
G2	10 (%)	25 (%)	
G3	5 (%)	4 (%)	
Axillary lymph node metastasis			
Negative	10 (%)	18 (%)	0.475[b]
Positive	7 (%)	15 (%)	
Lymphovascular invasion			
Negative	12 (%)	26 (%)	0.277[b]
Positive	5 (%)	7 (%)	
ER			
Negative	8 (%)	14 (%)	0.629[b]
Positive	8 (%)	16 (%)	
NA	1 (%)	3 (%)	
PR			
Negative	7 (%)	9 (%)	0.236[b]
Positive	9 (%)	21 (%)	
NA	1 (%)	3 (%)	
Her-2			
Negative	6 (%)	21 (%)	0.349[b]
Positive	10 (%)	9 (%)	
NA	1 (%)	3 (%)	

Data are reported as means ± SD

ER Estrogen, *PR* Progestogen, *Her-2* Human Epidermal Receptor 2, *NA* not available

[a] Student's *t* test

[b] Chi square test

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Author contributions
SA and SAL suggested the idea and designed the research strategy and experimental protocols. Surgeon MMM was responsible for enrolling patients. SA collected patients' clinical and pathological data. SA conducted all practical experiments of the study. SA and SAL analyzed the data using SNPSTATS online tools and Statistical Package of the Social Sciences and biomedical informatics software. SA and SAL drafted and wrote the manuscript with the input of all co-authors. SAL, AEG, AAE, and GS revised and edited the final draft.

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Availability of data and materials
There are no restrictions on the availability of the presented materials, data, and associated protocols.

Declarations

Ethics approval and consent to participate
The present study was approved by the Institutional Review Board (IRB) of the Ministry of Health (IORG0005704/IRB0000687). Before participation, all patients signed consent forms.

Consent for publication
Written informed consent for publication of the study results was obtained from all patients before participation.

Competing interests
The authors declare that they have no competing interests.

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