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ORIGINAL ARTICLE

Association of ABCB1 and ABCG2 single nucleotide polymorphisms with clinical findings and response to chemotherapy treatments in Kurdish patients with breast cancer

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Abstract The possible interaction between gene polymorphisms and risk of cancer progression is very interesting. Polymorphisms in multi-drug resistance genes have an important role in response to anti-cancer drugs. The present study was aimed to evaluate the possible effects of ABCB1 C3435T and ABCG2 C421A single nucleotide polymorphisms on clinical and pathological outcomes of Kurdish patients with breast cancer. One hundred breast cancer patients and 200 healthy controls were enrolled in this case–control study. Clinical and pathological findings of all individuals were reported, and immunohistochemistry staining was used to assess the tissue expression of specific breast cancer proteins. The ABCB1 C3435T and ABCG2 C421 genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP). The distribution of different genotypes between patient and control groups was only significant for ABCG2 C421A. A allele of ABCG2 C421A polymorphisms were significantly higher in patients than in controls. Patients with AA genotype of ABCG2 C421A were at higher risk of progressing breast cancer. Patients with A allele of ABCG2 had complete response to chemotherapeutic agents. There was no statistically significant association between ABCB1 C3435T and ABCG2 C421A polymorphisms and tissue expression of ER, PR, Her2/neu, and Ki67. The ABCB1 C3435T has no correlation with clinical findings and treatment with chemotherapy drugs. The A allele of ABCG2 C421A may be a risk factor for progression of breast cancer in Kurdish patients. In addition, breast cancer patients with C allele of this polymorphism have weaker response to treatments with anthracyclines and Paclitaxol.

Keywords ABCB1 · ABCG2 · Breast cancer · Single nucleotide polymorphism

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Introduction

Breast cancer (BC) is the most common cancer among women worldwide, and its incidence is increasing [1]. BC is a multifactorial disease, which results from complex interactions between environmental and genetic factors [2]. Recently, an increasing number of studies have been conducted to evaluate the relationship between the genetic factors and cancer risk. On the other side, individual genetic differences, especially genetic variations in drug-metabolizing enzymes play an important role on the metabolism and dispensation of the drugs [3–5].

The ATP-binding cassette subfamily B member 1 or multidrug resistance protein 1 (ABCB1 or MDR1,) and ATP-binding cassette subfamily G member 2 or breast cancer resistance protein (ABCG2/BCRP) are involved in multidrug resistance, and they can actively eliminate different kinds of anticancer drugs from tumor cells [6, 7].

MDR1 gene produces permeability glycoprotein (P-gp)—a membrane glycoprotein carrier—that outflows xenobiotics and toxic substances from cells [8]. On the other hand, in patients treated with chemotherapeutics, the protein is involved in the development of drug resistance by preventing cell uptake of anticancer agents. Therefore, P-gp is one of the most important reasons of ineffective treatment by chemotherapy drugs in cancer management [9].

P-gp is widely distributed in various human tissues mainly in the apical border of intestinal epithelial cells, brain capillary endothelial cells, biliary canalicular cells, renal proximal tubular epithelial cells, placenta, and testes [10].

Another important member of the ATP-binding cassette (ABC) transporters is ABCG2 that also has an essential impact on host detoxification of various xenobiotic substrates [11]. The human ABCG2 gene contains 19 exons and is located on chromosome 4q2 and encodes a 655-amino acid polypeptide [12].

Our previous studies clearly showed that single nucleotide polymorphisms (SNPs) in ABCB1 and ABCG2 genes might positively be correlated to risk of cancer and play an important role in response to chemotherapy agents [13, 14].

ABCB1 3435C>T (rs1045642) SNP occurs in exon 26; this polymorphism is a silence and attractive genetic variation in ABCB1 gene and has been found to be correlated with the progression of chronic lymphoblastic leukemia [14], colorectal cancer [15], acute lymphoblastic leukemia [16], prostate [17], and CML [13].

Regarding ABCG2, polymorphism in exon 5 (C421A or Q141K, rs2231142) is one of the most important genetic variations and has an important effect on BCRP activity [18–20]. Previous studies in different races found that the frequencies of A or C allele of C421A vary between different populations [21, 22].

Despite many studies that have been conducted in this issue, previous epidemiological studies have evaluated the association between the ABCB1 polymorphism and the risk of breast cancer with conflicting results [23]. Furthermore, although the associations between ABCB1 and ABCG2 SNPs with risk of breast cancer as well as response to anticancer agents have separately been shown; there is a paucity of information on the concurrent effects of ABCB1 and ABCG2 and the risk of breast cancer. Therefore, the present study attempts to assess the potential role of ABCB1 C3435T and ABCG2 A421C on risk of cancer and clinical outcomes in a Kurdish population with breast cancer.

Materials and methods

Subjects: During January 2012 to May 2015, a total of 100 women who were admitted to Tohid hospital in Sanandaj (Kurdistan, Iran) with an average age of 47.13 ± 8.4 years were diagnosed with breast cancer, according to the histopathology of the breast tissue. The control group consisted of 200 healthy individuals with a mean age of 46.8 ± 7.3 years, with normal mammography result. Both control and cancer groups were drawn from the same geographical area, which were from Kurdistan, a province in western Iran with a population that is Kurds. Written informed consent was obtained from all patients, and the study has been approved by the ethics committee of Kurdistan University of Medical Sciences. Patients with a history of other organ cancers were excluded from the study. All the tumors were graded using the criteria of Scarf–Bloom–Richardson [24], and the clinical staging of patients was evaluated according to TNM staging system for breast cancer [25]. Data on morphologic characteristics, grade, and stage of the tumor and adjuvant treatment were obtained from the medical records. The median follow-up was 24 months (range, 6–48 months), and the chemotherapy treatment consisted of anthracyclines (doxorubicin and cyclophosphamide) and Paclitaxol.

Immunohistochemistry: Hematoxylin/eosin staining was used for histological evaluation under light microscope. Sequential sections were used for estrogen receptor (ER), progesterone receptor (PR), and Ki67 and Her2/neu staining. Protein expression assessment was performed by scoring based on the percentage of stained cells and the intensity of nuclear stain, according to the method described previously [26–28].

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis: DNA was extracted from whole blood samples according to our previous studies [13, 14]. The C3435T ABCB1 and C421A ABCG2 SNPs were identified using PCR-RFLP. The PCR-RFLP for the C3435T ABCB1 C421A and ABCG2 SNPs was carried out according to our previous studies [13, 14]: Master Mix kit (CinnaGen Inc, Tehran, Iran), 10 pmol of each primer with a final concentration of 400 nM, and 100-ng DNA. A fragment of 184 bp of exon 5 ABCG2 gene was amplified by forward 5′-ATGTTGTGATGGGCACTCTG-3′ and reverse primers 5′-TGCTGATCATGATGCTTTCAG-3′. In addition, two primers were used to amplify a fragment of 196 bp of the exon 26-ABCB1 gene. The ABCB1-exon 26 forward primer was 5′-TGTTTTCAGCTG CTTGATGG-3′, and the ABCB1-exon 26 reverse primer was 5′-GAGGCCAA

CATACATGCCTT-3′. The PCR-RFLP conditions for above genes were according to our previous study.

Statistical analysis: Data were analyzed by SPSS 16 (SPSS Inc., Chicago, IL, USA), and one-sample Kolmogorov–Smirnov test was applied to determine the normal distribution of data. Results were presented as mean ± SD, and independent samples t-test was used to compare mean differences. One-way ANOVA followed by post hoc, Tukey, and Dunnett tests were used to analyze differences between groups, and a P value less than 0.05 was considered significant. Chi-square test was employed to evaluate whether the alleles or genotype frequencies differ between cases and controls. For 2 × 2 contingency tables, the odds ratio and its confidence interval were calculated to determine if the association was statistically significant at nominal 5 % level.

Results

There were no statistically significant association between studied SNPs and age of individuals. The frequencies of BC types in patient group were invasive ductal carcinoma (IDC) (88 patients) and invasive lobular carcinoma (ILC) (12 subjects). Histological grading was evaluated for all patients. The frequencies of low, intermediate, and high grades in BC group were 12, 60, and 28, respectively. Furthermore, 15 patients had stage I, 30 with stage II, 38 with stage III, and 17 patients had stage IV cancer. Positive results for ER, PR, Her2/neu, and Ki67 tissue expression were seen in 83, 76, 48, and 54 breast cancer patients, respectively. Modalities of treatment were surgery (60 patients), chemotherapy regimen (88 patients), and radiotherapy (59 patients), as needed.

We evaluated all patients and control individuals for ABCB1 C3435T and ABCG2 C421A gene polymorphisms (Table 1). The distribution of ABCB1 C3435T genotype in patients ($p = 0.0037$) but not for controls ($p = 0.339$) showed significant deviation from a Hardy–Weinberg equilibrium. The frequency of CC genotype of ABCB1 C3435T SNP was higher in patients than in controls group; however, it was not statically significant. Furthermore, the C allele was higher in patients, but we could not find any significant difference between the two studied groups for this allele. On the other hand, there was a significant correlation between ABCB1 C3435T SNP and clinical grades of breast cancer patients ($p = 0.027$) (Table 2). However, we could not find any significant correlation between this SNP with clinical stages and types of breast cancer ($p > 0.05$). We also assessed the possible association between C3435T SNP and response to chemotherapy agents ($p = 0.412$). There was not a significant correlation between C3435T SNP and response to chemotherapy regimen. Finally, the possible association between ER, PR, and Her2/neu and Ki67 protein expression and the ABCB1 C3435T genotypes were analyzed. Furthermore, there was not a significant correlation between C3435T SNP with protein expression in breast tumor tissues (Table 3).

Table 1 Genotypes frequency in patient and control groups

		BC patients ($N = 100$)	Controls ($N = 200$)	p value
ABCB1	CC	75 (75 %)	141 (70.5 %)	0.36
	CT	16 (16 %)	50 (25 %)	0.07
	TT	9 (9 %)	9 (4.5 %)	0.08
ABCG2	CC	28 (28 %)	95 (47.5 %)	0.016
	CA	5 (5 %)	13 (6.5 %)	0.6
	AA	67 (67 %)	92 (46 %)	0.04

Data is presented as number (%)

With regard to ABCG2 C421A, the most frequent genotype in the patients groups was AA genotype and its frequency had a significant difference compared to control subjects (67 vs. 46 %, $p = 0.04$). Our results showed that people who are carriers for A at position 421 of the ABCG2 gene (carriers of 421 AA and 421 CA genotype) were significantly increased in patient subjects as compared to controls (70 vs. 30 %, $p < 0.05$). In addition, the 421 A allele was associated with BC (OR = 2.2782, 95 %CI = (1. 57–4.9104), Z statistic = 2.102, $p = 0.0356$). A summary of the genotyping results is shown in Table 1. Furthermore, based on our results, A allele of ABCG2 C421A polymorphism was associated with the IDC ($p < 0.05$), and there was a significant correlation between A allele and clinical staging of breast cancer patients ($p < 0.05$) (Table 2). We also assessed the possible association between C421A SNP and response to chemotherapy agent. According to our results, there was a significant correlation between AA genotype (and A allele) and response to chemotherapy regimen ($p < 0.05$). However, we could not find any significant difference between this SNP and protein expression in tumor tissues (Table 3).

Discussion

Resistance to anticancer agents is one of the most important problems in chemotherapy treatment of cancerous patients. Although breast cancer is one of the most sensitive solid tumors to anticancer agents, after a successful course of treatment, most patients show different degrees of drug resistance [29]. Despite various treatment regimens used for breast cancer, the complete response to treatment is between 17–80 % [30]. One of the most important resistant to anticancer drug mechanisms is to pump drugs out of cells by increasing the activity of efflux pumps, such as ATP-binding cassettes transporters [31]. In the present study, we evaluated the possible effects of ABCB1 C3435T and ABCG2 C421A SNPs on risk of cancer and clinical outcomes in breast cancer patients

Table 2 Correlation of ABCB1 C3435T and ABCG2 C421A genotypes with clinical outcomes of breast cancer patients

Genotypes		Type of BC		Grade			Clinical stage			
		IDC	ILC	Low	Intermediate	High	I	II	III	IV
ABCB1[a, b, c]	CC	65 (73.86)	9 (75)	9 (75)	46 (76.67)	24 (85.72)	12 (80)	21 (70)	32 (84)	15 (88)
	CT	15 (17.05)	2 (16.67)	3 (15)	12 (20)	2 (7.14)	0 (0)	9 (30)	0 (0)	2 (12)
	TT	8 (9.09)	1 (8.33)	0 (0)	2 (3.33)	2 (7.14)	3 (20)	0 (0)	6 (16)	0 (0)
ABCG2[d, e, f]	CC	27 (30.68)	10 (83.34)	4 (33.33)	24 (40)	2 (7)	6 (40)	9 (30)	6 (20)	2 (12)
	CA	4 (4.55)	1 (8.33)	0 (0)	7 (11.67)	0 (0)	0 (0)	0 (0)	3 (8)	0 (0)
	AA	57 (64.77)	1 (8.33)	9 (66.67)	29 (48.33)	26 (93)	9 (60)	21 (70)	29 (72)	15 (88)

Data is presented as number (%)

According to the table, ABCB1 C3435T SNP has no correlation with type of BC and clinical stage; however, it seems that patients with higher grade of cancer have CC genotype. The AA genotype of ABCG2 C421A has direct correlation with IDC type of breast cancer and stage of cancer. Patients with higher stage have higher frequency of AA genotype

[a] Correlation between ABCB1 C3435T SNP with type of BC: $p = 0.705$

[b] Correlation between ABCB1 C3435T SNP with grade of BC: $p = 0.027$

[c] Correlation between ABCB1 C3435T SNP clinical stage of BC: $p = 0.321$

[d] Correlation between ABCG2 C421A SNP with type of BC: $p = 0.04$

[e] Correlation between ABCG2 C421A SNP with grade of BC: $p = 0.38$

[f] Correlation between ABCG2 C421A SNP with clinical stage of BC: $p = 0.033$

treated with anthracyclines (doxorubicin and cyclophosphamide) and Paclitaxol regimen.

There are many studies that reject the relationship between ABCB1 C3435T polymorphism with the risk of breast cancer. The results of our study are similar to previous investigations. Macías-Gómez et al. [32] showed that there is no significant difference between patients and control groups for this SNP. So, it was proposed that the ABCB1 C3435T SNP is not a risk factor for development of BC. Similarly, in another study, Rodrigues et al. [30] evaluated 41 breast cancer patients and found that there is no correlation between C3435T SNP and clinical response to anticancer drugs. But, they showed that patients with pathologic complete response had only T allele (TT and CT genotypes). In addition, although Chang et al. [33] found that there is no correlation between C3435T SNP and response to chemotherapy; however, they showed that patients with CT genotype had shorter disease period. According to these studies, it seems that T allele may be a better factor in chemotherapy. On the other side, there are several studies that reject these reports [34]. In a recent study by Wang et al. [34], it has been suggested that the MDR1 C3435T polymorphism may contribute to individual susceptibility to breast cancer. Besides, in our recent studies, we showed positive effect of C3435T SNP on susceptibility to CML and CLL [13, 14]. Generally, with regard to ABCB1 C3435T SNP, as it was shown by Lu PH et al. [23] in a meta-analysis, there are not enough evidences that could name this SNP as a risk factor for progression of breast cancer. In line with previous data, we could not find any statistically significant relationship for C3435T SNP between cancerous and healthy groups. Besides, we did not find any correlation between C3435T SNP and clinical and pathological features of breast cancer patients. Furthermore, there was no correlation between ABCB1 C3435T and response to chemotherapeutic agents.

We also assessed the possible association between ABCG2 C421T SNP with risk of cancer and clinical outcomes in breast cancer patients. ABCG2 has an important role in xenobiotic transport, and hence, it may be involved in anticancer resistance mechanisms. It has been previously shown that various chemotherapeutic agents including anthracyclines, mitoxantrone, and camptothecin analogs void out from tumor cells by ABCG2 [35]. On the other side, the A allele of ABCG2 C421A polymorphism is a protective factor for developing cancer [36]. Furthermore, it seems that patients with A allele of C421A SNP had better response to anticancer drugs [37]. Conversely, Hu et al. [38] and Korenaga et al.

Table 3 Association of ABCB1 C3435T and ABCG2 C421A single nucleotide polymorphisms with protein expression in breast tumors

Protein	*p* value for ABCB1 C3435T	*P* value for ABCG2 C421A
ER	0.22	0.92
PR	0.09	0.88
Her2/neu	0.33	0.23
Ki67	0.34	0.78

As it is shown in this table, neither ABCB1 C3435T nor ABCG2 C421A SNPs do not have relation with specific protein expression in tumor cells

ER Estrogen receptor, *PR* Progesterone receptor, *Her2/neu* human epidermal growth factor receptor 2

[39] found that carriers of the A allele of ABCG2 C421A had an increased risk of cancer. In our study, we found that the A allele has a higher rate in patients compared to controls. In line with previous studies, our results showed a significant correlation between A allele of ABCG2 C421A polymorphism and response to chemotherapeutic regimen.

In summary, we found that ABCG2 C421A polymorphism has an important role in development of breast cancer in Kurdish patients. Besides, AA421 ABCG2 increased the risk of BC. We showed that A allele of ABCG2 C421A correlated with complete response to anticancer drugs in BC patients. In addition, we could not find a significant correlation between ABCB1 C3434T SNP and clinical and pathological findings of breast cancer patients.

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Compliance with ethical standards

Conflicts of interest None

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