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REVIEW

The effect of *ABCB1* polymorphisms on the outcome of breast cancer treatment

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Sonam Tulsyan[1]
Rama Devi Mittal[2]
Balraj Mittal[1]

[1]Department of Genetics, [2]Department of Urology and Renal Transplant, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Abstract: The *ABCB1* gene encodes a permeability glycoprotein, which is one of the most extensively studied human adenosine-triphosphate (ATP)-dependent efflux transporters. Permeability glycoprotein is expressed in the apical membranes of tissues such as intestine, liver, blood–brain barrier, kidney, placenta, and testis and contributes to intracellular drug disposition. It is also highly expressed in tumor cells conferring drug resistance, which is one of the major problems in the efficacy of cancer chemotherapy treatment. *ABCB1* is highly polymorphic, and three well-known single-nucleotide polymorphisms such as 1236C>T, 2677G>T/A, and 3435C>T have been found to be associated with altered messenger RNA levels, protein folding, and drug pharmacokinetics. Many association studies and meta-analyses have demonstrated the clinical impact of *ABCB1* polymorphisms in breast cancer treatment outcomes with respect to therapeutic response, chemotoxicity, and overall survival. Therefore, the aim of this review was to evaluate the effects of *ABCB1* polymorphisms on the outcome of breast cancer treatment which, in future, would be important for tailoring individualized anticancer therapy.

Keywords: *ABCB1*, P-glycoprotein, polymorphisms, breast cancer treatment, chemotherapy, response, drug resistance

Introduction

Breast cancer is the most common cancer in women worldwide. It involves multimodal treatment that includes drugs such as anthracyclines (epirubicin/doxorubicin, adriamycin), cytotoxics (cyclophosphamide, paclitaxel, docetaxel), antiestrogens (tamoxifen), and aromatase inhibitors (exemestane, anastrozole, letrozole). Cytotoxic agents are the backbone of systemic treatment in chemotherapies. Patients with early-staged breast cancer (stages I and II) are treated primarily with surgery followed by adjuvant chemotherapy, while patients with later-staged (stages III and IV) disease are treated with neo-adjuvant chemotherapy (NACT). However, such treatment is accompanied by various side effects, ranging from nausea to hair loss to myelotoxicity. The severity of these side effects varies from one patient to another, and it is an important problem in breast cancer therapy.[1] Pharmacokinetic processes of absorption, distribution, metabolism, and excretion (ADME) play an important role in deciphering the drug treatment outcomes.[2] Furthermore, genetic differences in various drug metabolizing and transporter enzymes may be responsible for interindividual variation in drug treatment outcomes[3,4] and could be one of the factors for pharmacokinetic alterations.

Adenosine triphosphate (ATP)-binding cassette (ABC) subfamily B member 1 (*ABCB1*) belongs to a large superfamily of primary active transporters that are present

Correspondence: Balraj Mittal
Department of Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow 226014, Uttar Pradesh, India
Tel +91 522 249 4322
Fax +91 522 266 8973
Email bml_pgi@yahoo.com

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in all kingdoms of life. This gene is also known as multidrug resistance gene 1 (MDR1) or cluster of differentiation 243. *ABCB1* gene encodes a protein known as permeability glycoprotein (P-gp), which is responsible for energy (ATP)-dependent efflux of drugs. It has broad substrate specificity.[5] Literature on breast cancer has shown that the expression as well as genetic variations in *ABCB1* is associated with altered therapeutic response.[6–11] Several studies have also evaluated the effect of *ABCB1* polymorphisms with chemotherapy-dependent toxicity and overall survival (OS) on patients with breast cancer.[9–17] An expression study on P-gp has shown that the upregulation of this protein is a cause of multidrug resistance phenotype in anticancer therapy.[18] Therefore, in order to promote effective therapeutic response, lower drug toxicity, and increased OSs, it is essential to understand the critical role of polymorphisms in *ABCB1* drug transporters on the outcome of breast cancer treatments.

In this review, we have focused on the structure, function, genetic variations present in *ABCB1*, and their effects on breast cancer treatment outcomes in terms of therapeutic response, survival, and drug toxicity.

ABCB1 structure, function, and mode of action

P-gp, a transmembrane-associated protein, is responsible for the exchange of molecules across the membranes by using energy from the hydrolysis of ATP.[19] It belongs to one of the largest superfamilies of proteins, that is, ABC transporters.[20] ABC genes are classified into seven different subfamilies – ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, and White (http://nutrigene.4t.com/humanabc.htm). In humans, P-gp is a member of the MDR/TAP subfamily and is encoded by the *ABCB1* gene located on chromosome 7q21.12 (UCSC Genome Browser, March 2006 Assembly [hg18]).[21,22]

The complete molecular structure of the gene is well known. *ABCB1* was first cloned in the year 1985.[23] The gene contains 28 exons and 28 introns in a genomic region of 209.6 kb (GenBank accession number NT_007933).[24] Transcriptional start region consists of a proximal and distal promoter. Proximal promoter responsible for constitutive expression is present in exon 1 and intron 1, while distal promoter is active in patients with cancer for overexpression of the protein product. However, two 5′ exons are not translated.

Protein-coding sequence consists of two similar halves with approximately the same number of exons. However, two intron pairs within the nucleotide-binding domains (NBDs) are located at conserved positions in the two halves of the protein. Out of 28 introns, 26 that left disrupt the protein-coding sequence relative to the open reading frame, thereby suggesting that the P-gp arose by fusion of genes.[25]

The first structure of a mammalian P-gp was derived from the mouse *Mdr3* gene product heterologously expressed in *Pichia pastoris* yeast in the year 2009.[26] The structure of mouse P-gp is almost similar to the bacterial ABC transporter MsbA (3B5W and 3B5X).[27] *ABCB1* gene is expressed as 4,872 bp-long messenger RNA (mRNA),[24,25] which encodes P-gp, a single polypeptide chain of 1,280 amino acids. It has a molecular weight of 170 kDa and spans ~100 kb. Both the N and C termini of the polypeptide chain are cytoplasmic and contain three N-linked glycosylation sites (N91, N94, and N99) of 10–15 kDa in the first extracellular loop.[28,29] P-gp consists of two similar halves with >65% amino acid similarity.[30] The two halves are separated by a flexible linker region.[30] Each half is made up of six transmembrane domains and a cytoplasmic NBD. All these 12 domains are located in plasma membrane.[30] NBD aids in ATP-dependent efflux of substrates or ions across the cell membrane[31–33] (Figure 1). Several motifs have also been identified in each of the ATP-binding domains, including the Walker-A, Walker-B, A-loop, H-loop, D-loop, Q-loop, and the signature motif "LSSGQ" consensus sequences.[30] All these motifs play an important role in the translocation process, which occurs via ATP binding, hydrolysis, and nucleotide release.[34,35] Each ATP-binding site is formed from the Walker A and B motifs of one NBD subunit and the "LSSGQ" signature C motif of the other NBD subunit. The P-gp drug-binding pocket is formed by the transmembrane helices of the protein and is located in the cytoplasmic inner membrane leaflet.[36] The substrate interacts with P-gp, forming an opening within the inner leaflet of the membrane through Van der Waal's forces, hydrophobic and hydrogen bonding. Then, two molecules of ATP bind at the NBD dimer surface.[37] After ATP binding, ATP hydrolysis transfers the substrate into a position to be effluxed from the cell. At the time of release of the phosphate from ATP, substrate excretion occurs and ADP is released. Hydrolysis and the release of ADP and a phosphate molecule reset the protein, so that the process can start again.[38,39] A study has shown that a glycosylation-defective mutant does not show altered drug transport.[40]

P-gp is widely expressed in the tissues essential in drug disposition such as the intestinal epithelium, adrenal glands, canalicular membrane of the hepatocytes of the liver, kidney proximal tubules, and blood–brain barrier.[37,41–44] Major functions of P-gp proteins include the transport of drugs such as colchicine, tacrolimus, and quinidine; chemotherapeutic agents such as etoposide, doxorubicin, taxol, and vinblastine;

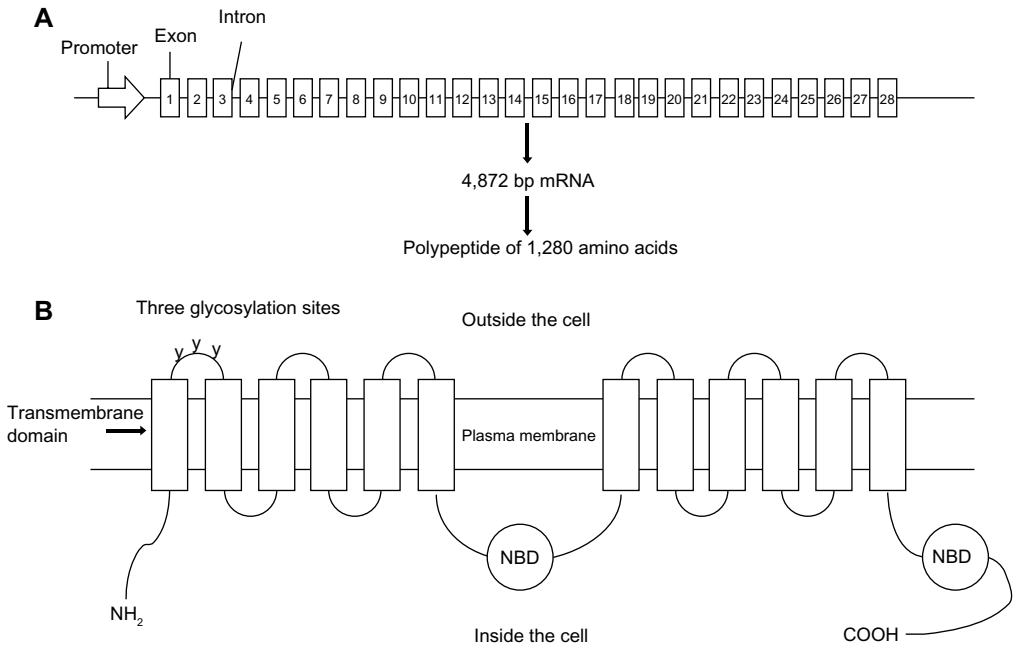

Figure 1 A. Molecular structure of ABCB1 gene: Containing 28 exons and 28 introns; encoding P-gp of 1280 amino acids. B. Secondary structure of P-gp protein: This has a single polypeptide chain with both the N and C termini located inside the cytoplasmic region while the 12 trans-membrane domains are located inside the plasma membrane. It also consists of two nucleotide binding domains (NBD), which act as ATP binding sites. The first extracellular loop contains three glycosylation sites.
Abbreviations: mRNA, messenger RNA; NBD, nucleotide-binding domain.

and various lipids, bile salts, toxic compounds, and peptides for antigen presentation across the membranes. Due to its ability to transport substrates out of the cell, it helps in the removal of xenobiotics and other drug metabolites from the cell. It also functions as a transporter in the blood–brain barrier.[37,45] It is overexpressed in cancer cells, resulting into faster efflux of drugs out of the cells.[46] This causes a lower concentration of the drugs within the cell, subsequently reducing the efficacy of the drugs in destroying cancer cells. Therefore, P-gp is involved in the process of resistance to anticancer drugs. It was reported that the P-gp is the first ABC transporter implicated in MDR. In breast cancer treatment, chemotherapeutic drugs such as anthracyclines (doxorubicin and v) and the microtubule-stabilizing taxol are affected by MDR.

Genetic variations in *ABCB1* gene

The *ABCB1* gene encoding P-gp is highly polymorphic. Till date, ~66 coding single-nucleotide polymorphisms (SNPs) in *ABCB1* gene have been identified. Out of these, 22 are synonymous and 44 nonsynonymous.[47] Several studies have shown that these polymorphisms alter the functional expression of the *ABCB1* gene.[48,50] The expression, efflux, substrate specificity, and mRNA stability of P-gp are influenced by various SNPs present in *ABCB1* gene.[51] Some studies have also shown that genetic variations affecting the function and expression of *ABCB1* are responsible for resistance to many anticancer drugs and therapeutic failure.[2,6,46] Therefore, *ABCB1* genetic variations affect the pharmacokinetic profiles of various drugs, leading to changes in drug efficacy and side effects. Out of 66 SNPs, three of them in the coding region of *ABCB1* gene such as 2677G>T/A (exon 21, rs2032582), 3435C>T (exon 26, rs1045642), and 1236C>T (exon 12, rs1128503) are extensively studied and characterized. Studies have shown these polymorphisms to be associated with altered mRNA levels,[52] protein folding,[53] and drug pharmacokinetics.[54]

The 2677G>T/A polymorphism is a triallelic variant, and it is found in the wild-type sequence with G at nucleotide 2677 and in the variant sequence with A or T. It is located on the intracellular side of P-gp after transmembrane region 10. It contains a nonsynonymous amino acid change from Ala at codon 893 to Ser/Thr (Ala893Ser/Thr; *ABCB1**10).

The other two polymorphisms – 3435C>T (Ile1145Ile; *ABCB1**6) and 1236C>T (Gly412Gly; *ABCB1**8) – are synonymous SNPs. The 3435C>T is present in exon 26 of the *ABCB1* gene, involves a C-to-T transformation, and does not alter the amino acid isoleucine. The variant allele frequency of 3435C>T in Asian population differed significantly from the African and Caucasian population.[55,56] The frequency

distribution of this polymorphism in Chinese and Malay population was found to be similar to the Caucasians, whereas it was different among Indians. Among the Thai-Indians, variant allele frequency was found to be 33%.[57] Although the 3435C>T is a silent mutation, it has been shown to affect the expression and function of the P-gp in many ways.[50] Studies have reported conflicting functional effects of this polymorphism with higher[58–61] and lower expression levels of P-gp protein.[50,62–64]

The synonymous 1236C>T SNP is located on exon 12 and encodes for the TM6 region of the P-gp. This region is necessary for substrate binding.[30] The polymorphism does not involve an amino acid change at position 412 (Gly). It has been shown to affect protein folding due to the use of a rare codon when combined with the 3435C>T polymorphism.[51,65]

These three SNPs are found to be in strong linkage disequilibrium (LD). Higher LD value was found between *ABCB1* 1236C>T and 2677G>T/A polymorphisms (r^2=0.89; D'=0.98), whereas *ABCB1* 2677G>T/A and 3435C>T (r^2=0.65; D'=0.87) and *ABCB1* 1236C>T and 3435C>T (r^2=0.62; D'=0.83) showed lower values.[66] Polymorphisms 2677G>T/A and 3435C>T are in strong LD with >90% of Japanese,[67] 60% of European American,[68] and 80% of Germans[69] having both of these genetic variants. There is a considerable large interethnic difference in the combination of all the three polymorphisms present (also designated as *ABCB1**2).[59] In Africans, the combination of 1236C–G2677G–C3435T alleles is rare, while 1236T–G2677G–C3435C haplotype is frequent.[70] However, the results that have been reported so far are inconsistent and the real functional impact of these three SNPs remains controversial.[71] Thus, haplotype-dependent analysis has been taken into consideration in various association studies.

Recently, the 1199G>A (rs2229109) polymorphism in P-gp has also been studied. It is a nonsynonymous polymorphism, involving an amino acid change from serine to asparagine at position 400 (Ser400Asn) in the cytoplasmic domain of P-gp. It has a reported allelic frequency of ~5.5% in Caucasians.[50,59,72] This polymorphism alters the efflux and transepithelial permeability of rhodamine-123. Cells with the G1199A variants were more sensitive to vinblastine and vincristine therapies, but no difference in resistance was found for doxorubicin.[73]

ABCB1 polymorphisms in breast cancer treatment outcome

Large interindividual variation exists in breast cancer therapeutic outcomes. These outcomes are measured in terms of pathological response to NACT, chemotoxicity, and OS. Adverse drug reactions are due to variations in ADME profile of therapeutic drugs. As polymorphisms in gene encoding for metabolizing enzymes and drug transporters can affect drug efficacy, toxicity, and survival rate, pharmacogenetics helps in the assessment of individuals predisposed to poor response to NACT, higher risk of chemotherapy-induced toxicity, and OS.[1,9–11,14,74–77]

As we know, *ABCB1* gene is highly polymorphic, and these polymorphisms are found to be correlated with phenotypic variation in P-gp expression levels of various tissues. Polymorphisms in *ABCB1* gene also contribute substantially to MDR, thus accounting for a wide variation in treatment outcomes of patients with breast cancer to standard doses of drug therapy. This review focuses on the clinical significance of polymorphisms in *ABCB1* gene with respect to breast cancer treatment outcomes.

Anthracycline-based treatment outcomes

Response

Various studies have demonstrated the influence of *ABCB1* polymorphism in breast cancer therapeutic response, but the studies are mainly limited to the three SNPs (1236C>T, 2677G>T/A, and 3435C>T) in *ABCB1* gene. Among them, 3435C>T is the most studied *ABCB1* polymorphism. Table 1 depicts the list of association studies based on anthracycline-based breast cancer response to NACT.

Many studies report that 3435C>T plays a role in response to chemotherapy in patients with locally advanced breast cancer.[75] A Chinese study found TT genotype of 3435C>T polymorphism to be associated with worse clinical response when compared with CC genotype (P=0.001). In the same study, haplotype analysis also revealed significant association with clinical response.[15] Another Chinese study on 148 patients treated with anthracycline-based NACT also observed a significantly enhanced therapeutic response in CT, TT, and CT + TT genotypes of *ABCB1* 3435C>T polymorphism (P=0.039, P=0.018, and P=0.020, respectively).[17] The same Chinese study also found haplotype 3435T–1236T–2677T to be significantly associated with response (P=0.041).[17] In addition, they reported that patients with CC genotype had a poor prognosis than those with CT and TT genotypes in *ABCB1* 3435C>T polymorphism (P=0.043).[17]

Furthermore, a study on 19 patients treated with preoperative anthracycline-based chemotherapy reported that patients with TT genotype of *ABCB1* 3435C>T polymorphism showed clinical response, while patients with CT

Table 1 Association studies of *ABCB1* polymorphisms with anthracycline-based breast cancer response to neo-adjuvant chemotherapy

ABCB1 polymorphisms studied	Sample size	Ethnicity	Association	References
3435C>T	41	Brazil	No	Rodrigues et al[1]
3435C>T	96	India	No	George et al[8]
1236C>T, 3435C>T	120	China	No	Zhang et al[9]
1236C>T, 2677G>T/A, 3435C>T	100	India	No	Chaturvedi et al[10]
1236C>T, 2677G>T/A, 3435C>T	153	China	Association with TT genotype of 3435C>T polymorphism	Ji et al[15]
3435C>T	38	Slovakia	Association with CC genotype of 3435C>T polymorphism	Cizmarikova et al[16]
1236C>T, 2677G>T/A, 3435C>T	148	China	Association with CT, TT, CT + TT genotypes of 3435C>T polymorphism and haplotype 3435T–1236T–2677T	Wu et al[17]
3435C>T	68	Germany	Association with TT genotype of 3435C>T polymorphism	Kafka et al[75]
3435C>T	19	Asia	Association with TT genotype of 3435C>T polymorphism	Ashariati[78]

genotype did not show any clinical response.[78] Similarly, Cizmarikova et al indicated that the CC genotype in *ABCB1* 3435C>T polymorphism significantly increased the response rate (P=0.021) in 38 subjects, who were administered with anthracycline-based NACT.[16] In addition, a study on 68 patients with advanced breast cancer demonstrated the same association (P=0.029).[75] It suggests that *ABCB1* polymorphisms, especially *ABCB1* 3435C>T, have a role in predicting response to NACT.

However, other studies did not find any role of the polymorphism in treatment response.[9,10,16] George et al[8] evaluated the effect of 3435C>T polymorphism in 96 patients with locally advanced breast carcinoma but did not find any significant association with response to chemotherapy. Another study on 120 patients with stage II or III invasive breast cancer found no correlation of *ABCB1* 1236C>T and 3435C>T polymorphisms with good response.[9] Furthermore, Rodrigues et al[1] did not find any association between 3435C>T polymorphisms and response to chemotherapy. In another study on 100 patients undergoing 5-flurouracil, epirubicin/adriamycin, cyclophosphamide chemotherapy, investigators observed no association with therapeutic response.[10] One more study also showed no association of 2677G>T/A SNP with treatment response in patients with breast cancer.[15]

Contradictory reports in the literature regarding the effects of *ABCB1* polymorphisms on treatment response in patients with breast cancer can be due to small sample sizes and interethnic variations. Therefore, meta-analyses were performed to draw overall conclusions. We found three meta-analyses studies related to therapeutic response. In one study involving subgroup meta-analysis, significant association of *ABCB1* 1236C>T polymorphism with therapeutic response in Asian patients with breast cancer under dominant model was seen.[79] However, meta-analysis performed on *ABCBI* 1236C>T (three studies), 2677G>T/A (three studies), and 3435C>T (seven studies) polymorphisms with breast cancer response to NACT found no associations.[10] Another meta-analysis including a total of seven studies of 464 patients with advanced breast cancer also revealed lack of association between the *ABCB1* 3435C>T polymorphisms to the response of chemotherapy. The subgroup analysis by ethnicity yielded the same results.

Toxicity

Many studies and clinical trials have evaluated the impact of genetic variants in *ABCB1* with respect to breast cancer treatment side effects. These side effects are recorded in terms of edema, fever, diarrhea, and hematological and gastrointestinal toxicities. Most of the studies have focused their research on chemotherapy-induced hematological toxicity, such as anemia, leukopenia, neutropenia, and thrombocytopenia.

In one study, 59 Taiwanese women treated with docetaxel, epirubicin, and cyclophosphamide therapy were genotyped for *ABCB1* –41A>G, –145C>G, 1236C>T, 2677G>T/A, and 3435C>T SNPs. Side effects in terms of neutropenia, febrile neutropenia, leukopenia, febrile leukopenia, pleural effusion, diarrhea, fever, and edema were recorded in the same study. The authors have shown significant association of *ABCBI* 2677G/G genotype with fever (P=0.024) and febrile neutropenia (P=0.027), while 3435C/C genotype with leukopenia (P=0.057).[14] On the contrary, Cizmarikova et al[16] found no association of 3435C>T with hematologic toxicities in patients with breast cancer, which were measured in terms of grades 2–4 anemia, leukopenia, neutropenia, and thrombocytopenia.

For 1236C>T, few reports are available which correlate genotype with breast cancer chemotoxicity. Two studies have demonstrated that variant genotype of *ABCBI* 1236C>T polymorphism were not associated with drug-induced severe toxicity (grade 3 or 4).[9,14] However, a study on 207 North Indian patients with breast cancer reported significant association of 1236C>T with grades 2–4 toxicity and anemia (P=0.049 and P=0.046).[10] The same study also evaluated the effect of *ABCBI* 2677G>T/A and 3435C>T polymorphisms with hematological toxicity but could not find any association.[10]

Another study evaluated the impact of 2677G>T/A, 3435C>T, and 1236C>T polymorphisms with hematologic toxicity in 153 Chinese Han patients with breast cancer and reported no association of any of the *ABCB1* polymorphisms with grades 3–4 neutropenia.[15] Similarly, a recent study determined the influence of pharmacogenetics of *ABCB1* (1236C>T, 2677G>T/A, 3435C>T) polymorphisms on toxicity in 230 patients with breast cancer treated with doxorubicin and cyclophosphamide but found no impact on toxicity.[12] Only meta-analysis reported till date with chemotoxicity also did not show any association.[10]

In addition to hematological toxicities, gastrointestinal toxicities are common side effects among patients with breast cancer treated with cyclophosphamide and doxorubicin. A clinical trial analyzed 78 SNPs in ABCB1, ABCC1, and ALDH1A1 in 882 patients with breast cancer enrolled in the SWOG Phase III trial S0221 and found none of the *ABCB1* polymorphisms to be significantly associated with grades 3–4 hematological as well as gastrointestinal toxicity.[80] Table 2 illustrates the studies related to anthracycline-dependent chemotoxicity.

Survival

Treatment outcomes in terms of disease-free survival (DFS), progression-free survival (PFS), and recurrence rate are also followed up by few studies, and the influence of *ABCB1* polymorphisms with these outcomes has been observed. Table 3 lists various studies in context with anthracycline-dependent survival outcomes.

In a study, Kaplan–Meier survival analysis showed that clinical response and TT genotype of 3435C>T polymorphism were related to DFS (P=0.002 and P=0.049). However, this association was weakened after adjustment for potential confounding factors such as the tumor node metastasis (TNM) stage, chemotherapy regimens, and clinical response.[15] Recently, a report also found *ABCB1* 3435C>T polymorphism to be significantly associated with longer OS in 216 patients with breast cancer treated with docetaxel and doxorubicin NACT.[76]

Table 2 Association studies of *ABCB1* polymorphisms with anthracycline-based chemotoxicity in breast cancer

Study endpoints	*ABCB1* polymorphisms studied	Sample size	Ethnicity	Association	References
Grades 3–4 hematological toxicity	1236C>T, 3435C>T	120	China	No	Zhang et al[9]
Grades 2–4 anemia, leukopenia, overall toxicity	1236C>T, 2677G>T/A, 3435C>T	207	India	Association of 1236C>T with grades 2–4 toxicity and anemia	Chaturvedi et al[10]
Dose delay, dose reduction, and inability to complete planned course due to leukopenia/neutropenia	1236C>T, 2677G>T/A, 3435C>T	229	UK	No	Bray et al[12]
Fever, pleural effusion, leukopenia, febrile leukopenia, neutropenia, febrile neutropenia, edema, diarrhea	–41A>G, –145C>G, 1236C>T, 2677G>T/A, 3435C>T	59	Taiwan	Association of GG genotype of *ABCB1* 2677G>T/A with fever and febrile neutropenia; association of CC genotype of *ABCB1* 3435C> T with leukopenia	Tsai et al[14]
Grades 3–4 neutropenia	1236C>T, 2677G>T/A, 3435C>T	153	China	No	Ji et al[15]
Grades 2–4 anemia, leukopenia, neutropenia, thrombocytopenia	3435C>T	111	Slovakia	No	Cizmarikova et al[16]
Grades 3–4 hematological toxicities and grade 3 gastrointestinal toxicities	1236C>T, 2677G>T/A, 3435C>T	882	North American Breast Cancer Intergroup clinical trial	No	Yao et al[80]

Table 3 Association studies of *ABCB1* polymorphisms with anthracycline-based breast cancer survival outcomes

Polymorphisms studied in *ABCB1* gene	Sample size	Ethnicity	Association	References
1236C>T, 2677G>T/A, 3435C>T	230	UK	Association of variant A of 2677G>T/A with shorter TTP and OS	Bray et al[12]
−1 A>G, 1236C>T, 2677G>T/A, 3435C>T, 2685+49T>C	103	Czech Republic	Association of GG genotype of −1 A>G with worse PFS	Vaclavikova et al[13]
1236C>T, 2677G>T/A, 3435C>T	153	China	Association of TT genotype of 3435C>T polymorphism with DFS	Ji et al[15]
3435C>T	102	Slovakia	Association of CT + TT genotype of 3435C>T with longer TTP	Cizmarikova et al[16]
1236C>T, 2677G>T/A, 3435C>T	148	China	Association of 3435C>T variants with prolonged PFS and OS in patients with triple-negative status; association of 2677G>T/A variants with longer OS in patients with HER2-negative status	Wu et al[17]
2677G>T/A	991	Belgium	Association of GT genotype of 2677G>T/A with BCSS	Vulsteke et al[81]

Abbreviations: BCSS, breast-cancer-specific survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

A study found *ABCB1* C3435T variants to have a significant prolonged PFS and OS in patients with triple-negative (estrogen receptor−/progesterone receptor−/human epidermal growth factor receptor 2 [HER2]−) status (P=0.001 and P=0.016, respectively). Furthermore, a significant association of *ABCB1* 2677G>T/A variants was seen with longer OS in patients with HER2-negative status in the same study (P=0.036).[17] Similarly, a study on 991 patients found GT genotype of the *ABCB1* 2677G>T/A to be significantly associated with better breast-cancer-specific survival (hazard ratio: 0.5; P=0.021).[81] Another study also found variant A of *ABCB1* 2677G>T/A to be associated with shorter time to progression and OS in 230 patients with breast cancer treated with doxorubicin and cyclophosphamide.[12] Similarly, CC genotype in *ABCB1* 3435C>T significantly increased the longer time to progression (P=0.049) in 38 subjects.[16] In addition, a study on five SNPs in *ABCB1* (rs2214102, rs1128503, rs2032582, rs2032583, and rs1045642) gene found significant association of −1 A>G (rs2214102) SNP with PFS in 103 patients with breast cancer (P=0.005).[13]

Taxane-based treatment outcomes

Taxanes are important cytotoxic drugs administered to patients with breast cancer along with anthracycline-based chemotherapy. Paclitaxel and docetaxel are two taxane drugs. Docetaxel is associated with peripheral neuropathy. Therefore, variations in genes encoding drug metabolizing and transportation enzymes might be responsible for the differences in docetaxel-dependent peripheral neuropathy. Table 4 summarizes the association studies reported till date, based on taxane-based chemotherapy in breast cancer treatment outcomes.

Chang et al[74] evaluated the influence of *ABCB1* 2677G>T/A and 3435C>T polymorphisms in 113 patients with metastatic breast cancer administered with paclitaxel monotherapy. Clinical outcomes in terms of response to chemotherapy, toxicity, OS, and chemoresistance were noticed. The authors found that none of the genotype or haplotype was correlated with response to chemotherapy or toxicity. However, on applying Cox regression analysis, *ABCB1* 3435 CT genotype was found to be significantly correlated with shorter OS (P=0.026).[74] Furthermore, they showed significant association of *ABCB1* 2677 GG genotype with chemoresistance to paclitaxel and anthracycline (P=0.04 and P=0.04, respectively).[74] A report also found *ABCB1* 3435C>T polymorphism to be significantly associated with longer OS in 216 patients with breast cancer treated with docetaxel and doxorubicin NACT.[76]

In a study involving 150 patients with early-staged breast cancer, no association of variant genotypes as well as haplotypes of *ABCB1* 2677G>T/A, 1236C>T, and 3435C>T polymorphisms was seen with neurotoxicity.[82] However, in a study on 218 lymph-node-positive Korean patients with breast cancer, TT genotype of *ABCB1* 3435C>T SNP showed significantly higher risks of neutropenia when compared with its wild-type genotype (P=0.015).[83] In the same study, no association of *ABCB1* 2677G>T/A and 1236C>T polymorphisms was found.[83]

However, Tran et al demonstrated that *ABCB1* TT genotype of *ABCB1* 3435C>T polymorphism had an increased incidence of grade 3 neutropenia when compared with

Table 4 Association studies of *ABCB1* polymorphisms with taxane-based breast cancer treatment outcomes

Polymorphisms studied in *ABCB1* gene	Sample size	Ethnicity	Association	Study endpoints	Type of taxane	References
1236C>T, 2677G>T/A, 3435C>T	58 (response); 132 (toxicity)	India	Association of variant T of 2677G>T/A with "grade 1 or no leukopenia"	Response to chemotherapy, grades 2–4 anemia, leukopenia, overall toxicity	Docetaxel and paclitaxel	Tulsyan et al[11]
2677G>T/A, 3435C>T	113	Korea	Association of CT genotype of 3435C>T with shorter OS; association of GG genotype of 2677G>T/A with chemoresistance	Response to chemotherapy, grades 3–4 toxicity, OS, chemoresistance	Paclitaxel	Chang et al[74]
1236C>T, 2677G>T/A, 3435C>T	216	Korea	Association of TT genotype of 3435C>T with higher risks of diarrhea and neutropenia; association of TT genotype of 3435C>T polymorphism with OS	Diarrhea, nausea, vomiting, stomatitis, neutropenia, febrile neutropenia, thrombocytopenia	Docetaxel	Kim et al[76]
−129T>C, 61A>G, 1236C>T, 2677G>T/A, 3435C>T	101	France	Association of CT + CC genotype of 3435C>T with pathological good response to chemotherapy	Response to chemotherapy	Docetaxel	Levy et al[77]
1236C>T, 2677G>T/A, 3435C>T	150	Denmark	No	Peripheral neuropathy	Docetaxel	Eckhoff et al[82]
1236C>T, 2677G>T/A, 3435C>T	218	Korea	Association of TT genotype of 3435C>T with increased toxicities of neutropenia	Myalgia, nail changes, edema, hand–foot skin changes, neutropenia	Docetaxel	Kim et al[83]
3435C>T	58	France	Association of TT genotype of 3435C>T with grade 3 neutropenia	Grade 3 neutropenia, febrile neutropenia	Docetaxel	Tran et al[84]
1236C>T, 2677G>T/A, 3435C>T	26	Germany	*ABCB1* 2677G>T/A and 3435C>T polymorphisms with paclitaxel-dependent neutropenia	Neuropathy, neutropenia	Paclitaxel	Sissung et al[85]
−129T>C, 61A>G, 1236C>T, 2677G>T/A, 3435C>T	1,303	Europe	Association of CC genotype of −129T>C with taxane-related sensory neuropathy	Sensory neuropathy	Paclitaxel	Abraham et al[86]

Abbreviation: OS, overall survival.

CC genotype.[84] Another study showed positive correlation of variant genotypes of *ABCB1* 2677G>T/A and 3435C>T polymorphisms with paclitaxel-dependent neutropenia.[85]

A recent study analyzed the effect of genetic variants in *ABCB1* −129T>C, 61A>G, 1236C>T, 2677G>T/A, and 3435C>T polymorphisms with pathological response in 101 patients with breast cancer receiving NACT with doxorubicin and docetaxel. The authors found *ABCB1* 3435C>T polymorphism to be associated with pathological good response to chemotherapy (P=0.015).[77]

A replication study on 1,303 European patients showed significant association of rs3213619 (*ABCB1* −129T>C) with taxane-related sensory neuropathy.[86] Recently, a report found *ABCB1* 3435C>T polymorphism to be significantly associated with increased toxicities of neutropenia and diarrhea in 216 patients with breast cancer treated with docetaxel and doxorubicin NACT.[74]

Similarly, another study evaluated the role of these three polymorphisms of *ABCB1* in taxane-dependent response to NACT in 58 patients and toxicity in 132 patients. The authors performed logistic regression, haplotype, and multidimensional reduction analysis for analyzing the data. On performing logistic regression, no association was seen with therapeutic response. However, in assessing toxicity, significant association of TT genotype and T allele of *ABCB1* 2677G>T/A polymorphism was found with "grade 1 or no leukopenia" (P=0.0465 and P=0.048, respectively).[11] No significant association was reported with response to both NACT and toxicity on haplotype analysis. Higher-order gene–gene interaction was performed

by multidimensional reduction analysis, and these *ABCB1* polymorphisms were present in combination with other genetic variants affecting breast cancer treatment outcomes. *ABCB1* 1236C>T polymorphism along with *CYP3A5*3* was found to be the best interaction model for treatment response (P=0.024) and grades 2–4 anemia (P=0.004).[11] However, *ABCB1* 2677G>T/A, *ABCB1* 3435C>T polymorphisms were present in higher-order gene–gene interaction model for dose delay/reduction due to neutropenia (P=0.026).[11] Thus, we can say that multi-analytical approaches may provide a better evaluation of pharmacogenetic-based treatment outcomes in patients with breast cancer.

Other anticancer therapies

Tamoxifen, an antiestrogen, is given to hormone-receptor-positive premenopausal women with breast cancer. This prodrug requires bioactivation by cytochrome P450 enzymes such as CYP2D6 and 3A4 to generate its active metabolite, endoxifen, which stops cancer cell growth by preventing estrogen from binding to its receptor. However, less information is available regarding the role of *ABCB1* drug transporters in endoxifen disposition and response. We found two studies in context with *ABCB1* polymorphisms and tamoxifen-dependent treatment outcomes in patients with breast cancer. One study investigated the clinical impact of *ABCB1* polymorphisms with recurrence risk and metastasis in 95 patients with breast cancer treated with tamoxifen and observed patients with homozygous CC genotypes of *ABCB1* C3435T with a shorter time to recurrence (P=0.002).[87] Other study on 30 Thai patients with breast cancer also showed similar results. In patients treated with tamoxifen adjuvant therapy, CT genotype of *ABCB1* 3435C>T polymorphism was significantly associated with shorter DFS and five times higher risk of recurrence (P=0.041 and P=0.043).[57] It shows that *ABCB1* 3435C>T might have an impact on recurrence risk.

Trastuzumab is a monoclonal antibody that interferes with the HER2/neu receptor. It treats patients with breast cancer with HER2/neu-positive status. A study reported that *ABCB1* polymorphisms were associated with PFS after first-line trastuzumab chemotherapy in 57 patients with HER2-positive metastatic breast cancer. They found T allele carriers in *ABCB1* 2677G>T/A polymorphism to be associated with longer PFS (P=0.037) and OS (P=0.057). However, in patients with *ABCB1* 3435CC genotype, association with shorter PFS (P=0.039) and OS (P=0.093) was found. In combined analysis, PFS was significantly longer in *ABCB1* 1236CC and/or 2677TT carriers compared with the others (P=0.006).[88]

Conclusion

P-gp, encoded by *ABCB1* gene being a drug transporter, plays an important role in ADME profile of chemotherapeutic drugs, which are administered in the treatment of breast cancer. There are large interindividual variations in therapeutic response and toxicity in breast cancer treatment outcomes. Many studies have shown the association of genetic variants in *ABCB1* gene with breast cancer treatment outcomes in terms of response to NACT, hematological toxicity, and OS. Therefore, *ABCB1* gene may be potential candidate in pharmacogenetic evaluation of breast cancer treatment outcomes and optimizing individualized therapy. However, the results so far are contrasting, and this inconsistency can be due to small sample-sized studies or interethnic variations. Most of the previous studies had evaluated the role of several *ABCB1* variants; however, a tagger SNP-based approach that covers most of the common variants in a particular population could be more fruitful. In addition, the outcome of breast cancer treatment is determined by not only the *ABCB1* polymorphisms but also many other polymorphisms belonging to various metabolizing enzyme pathways.

Future perspective multicenter studies comprising large number of samples along with adjustments for various prognostic factors for pharmacogenetic assessment of *ABCB1* polymorphisms are required for evaluating their clinical utility in breast cancer therapy protocols. Such type of approach would definitely aid in individualized therapy for breast cancer.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Rodrigues FF, Santos RE, Melo MB, et al. Correlation of polymorphism C3435T of the MDR-1 gene and the response of primary chemotherapy in women with locally advanced breast cancer. *Genet Mol Res*. 2008;7(1):177–183.
2. Mizuno N, Sugiyama Y. Drug transporters: their role and importance in the selection and development of new drugs. *Drug Metab Pharmacokinet*. 2002;17(2):93–108.
3. Evans WE, McLeod HL. Pharmacogenomics – drug disposition, drug targets, and side effects. *N Engl J Med*. 2003;348(6):538–549.
4. Stearns V, Davidson NE, Flockhart DA. Pharmacogenetics in the treatment of breast cancer. *Pharmacogenomics J*. 2004;4(3):143–153.

5. Zinzi L, Capparelli E, Cantore M, Contino M, Leopoldo M, Colabufo NA. Small and innovative molecules as new strategy to revert MDR. *Front Oncol*. 2014;4:2.
6. Burger H, Foekens JA, Look MP, et al. RNA expression of breast cancer resistance protein, lung resistance-related protein, multidrug resistance-associated proteins 1 and 2, and multidrug resistance gene 1 in breast cancer: correlation with chemotherapeutic response. *Clin Cancer Res*. 2003;9(2):827–836.
7. Mutoh K, Tsukahara S, Mitsuhashi J, Katayama K, Sugimoto Y. Estrogen-mediated post transcriptional down-regulation of P-glycoprotein in MDR1-transduced human breast cancer cells. *Cancer Sci*. 2006;97(11):1198–1204.
8. George J, Dharanipragada K, Krishnamachari S, Chandrasekaran A, Sam SS, Sunder E. A single-nucleotide polymorphism in the MDR1 gene as a predictor of response to neoadjuvant chemotherapy in breast cancer. *Clin Breast Cancer*. 2009;9(3):161–165.
9. Zhang BL, Sun T, Zhang BN, et al. Polymorphisms of GSTP1 is associated with differences of chemotherapy response and toxicity in breast cancer. *Chin Med J (Engl)*. 2011;124(2):199–204.
10. Chaturvedi P, Tulsyan S, Agarwal G, et al. Influence of ABCB1 genetic variants in breast cancer treatment outcomes. *Cancer Epidemiol*. 2013;37(5):754–761.
11. Tulsyan S, Chaturvedi P, Singh AK, et al. Assessment of clinical outcomes in breast cancer patients treated with taxanes: multi-analytical approach. *Gene*. 2014;543(1):69–75.
12. Bray J, Sludden J, Griffin MJ, et al. Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. *Br J Cancer*. 2010;102(6):1003–1009.
13. Vaclavikova R, Ehrlichova M, Hlavata I, et al. Detection of frequent ABCB1 polymorphisms by high-resolution melting curve analysis and their effect on breast carcinoma prognosis. *Clin Chem Lab Med*. 2012;50(11):1999–2007.
14. Tsai SM, Lin CY, Wu SH, et al. Side effects after docetaxel treatment in Taiwanese breast cancer patients with CYP3A4, CYP3A5, and ABCB1 gene polymorphisms. *Clin Chim Acta*. 2009;404(2):160–165.
15. Ji M, Tang J, Zhao J, Xu B, Qin J, Lu J. Polymorphisms in genes involved in drug detoxification and clinical outcomes of anthracycline-based neoadjuvant chemotherapy in Chinese Han breast cancer patients. *Cancer Biol Ther*. 2012;13(5):264–271.
16. Cizmarikova M, Wagnerova M, Schonova L, et al. MDR1 (C3435T) polymorphism: relation to the risk of breast cancer and therapeutic outcome. *Pharmacogenomics J*. 2010;10(1):62–69.
17. Wu H, Kang H, Liu Y, et al. Roles of ABCB1 gene polymorphisms and haplotype in susceptibility to breast carcinoma risk and clinical outcomes. *J Cancer Res Clin Oncol*. 2012;138(9):1449–1462.
18. Ling V. Multidrug resistance: molecular mechanisms and clinical relevance. *Cancer Chemother Pharmacol*. 1997;40(suppl):S3–S8.
19. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. *Adv Drug Deliv Rev*. 2003;55(1):3–29.
20. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochim Biophys Acta*. 1976;455(1):152–162.
21. Ueda K, Clark DP, Chen CJ, Roninson IB, Gottesman MM, Pastan I. The human multidrug resistance (mdr1) gene. cDNA cloning and transcription initiation. *J Biol Chem*. 1987;262(2):505–508.
22. Fojo A, Lebo R, Shimizu N, et al. Localization of multidrug resistance-associated DNA sequences to human chromosome 7. *Somat Cell Mol Genet*. 1986;12(4):415–420.
23. Riordan JR, Deuchars K, Kartner N, Alon N, Trent J, Ling V. Amplification of P-glycoprotein genes in multidrug-resistant mammalian cell lines. *Nature*. 1985;316(6031):817–819.
24. Bodor M, Kelly EJ, Ho RJ. Characterization of the human MDR1 gene. *AAPS J*. 2005;7(1):E1–E5.
25. Chen CJ, Clark D, Ueda K, Pastan I, Gottesman MM, Roninson IB. Genomic organization of the human multidrug resistance (MDR1) gene and origin of P-glycoproteins. *J Biol Chem*. 1990;265(1):506–514.
26. Aller SG, Yu J, Ward A, et al. Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science*. 2009;323(5922):1718–1722.
27. Ward A, Reyes CL, Yu J, Roth CB, Chang G. Flexibility in the ABC transporter MsbA: alternating access with a twist. *Proc Natl Acad Sci USA*. 2007;104(48):19005–19010.
28. Gribar JJ, Ramachandra M, Hrycyna CA, Dey S, Ambudkar SV. Functional characterization of glycosylation-deficient human P-glycoprotein using a vaccinia virus expression system. *J Membr Biol*. 2000;173(3):203–214.
29. Zhang JT, Ling V. Study of membrane orientation and glycosylated extracellular loops of mouse P-glycoprotein by in vitro translation. *J Biol Chem*. 1991;266(27):18224–18232.
30. Fung KL, Gottesman MM. A synonymous polymorphism in a common MDR1 (ABCB1) haplotype shapes protein function. *Biochim Biophys Acta*. 2009;1794(5):860–871.
31. Jones PM, George AM. The ABC transporter structure and mechanism: perspectives on recent research. *Cell Mol Life Sci*. 2004;61(6):682–699.
32. Borst P, Elferink RO. Mammalian ABC transporters in health and disease. *Annu Rev Biochem*. 2002;71:537–592.
33. Ambudkar SV, Dey S, Hrycyna CA, Ramachandra M, Pastan I, Gottesman MM. Biochemical, cellular, and pharmacological aspects of the multidrug transporter. *Annu Rev Pharmacol Toxicol*. 1999;39:361–398.
34. Krishnamurthy P, Ross DD, Nakanishi T, et al. The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J Biol Chem*. 2004;279(23):24218–24225.
35. Frelet A, Klein M. Insight in eukaryotic ABC transporter function by mutation analysis. *FEBS Lett*. 2006;580(4):1064–1084.
36. Loo TW, Clarke DM. Recent progress in understanding the mechanism of P-glycoprotein-mediated drug efflux. *J Membr Biol*. 2005;206(3):173–185.
37. Sharom FJ. ABC multidrug transporters: structure, function and role in chemoresistance. *Pharmacogenomics*. 2008;9(1):105–127.
38. Callaghan R, Ford RC, Kerr ID. The translocation mechanism of P-glycoprotein. *FEBS Lett*. 2006;580(4):1056–1063.
39. Higgins CF. Multiple molecular mechanisms for multidrug resistance transporters. *Nature*. 2007;446(7137):749–757.
40. Schinkel AH, Kemp S, Dolle M, Rudenko G, Wagenaar E. N-glycosylation and deletion mutants of the human MDR1 P-glycoprotein. *J Biol Chem*. 1993;268(10):7474–7481.
41. Borst P, Schinkel AH, Smit JJ, et al. Classical and novel forms of multidrug resistance and the physiological functions of P-glycoproteins in mammals. *Pharmacol Ther*. 1993;60(2):289–299.
42. Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR. Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. *J Histochem Cytochem*. 1990;38(9):1277–1287.
43. Fojo AT, Ueda K, Slamon DJ, Poplack DG, Gottesman MM, Pastan I. Expression of a multidrug-resistance gene in human tumors and tissues. *Proc Natl Acad Sci U S A*. 1987;84(1):265–269.
44. Sugawara I, Kataoka I, Morishita Y, et al. Tissue distribution of P-glycoprotein encoded by a multidrug-resistant gene as revealed by a monoclonal antibody, MRK 16. *Cancer Res*. 1988;48(7):1926–1929.
45. Kwan P, Brodie MJ. Potential role of drug transporters in the pathogenesis of medically intractable epilepsy. *Epilepsia*. 2005;46(2):224–235.
46. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer*. 2002;2(1):48–58.
47. Wolf SJ, Bachtiar M, Wang J, Sim TS, Chong SS, Lee CG. An update on ABCB1 pharmacogenetics: insights from a 3D model into the location and evolutionary conservation of residues corresponding to SNPs associated with drug pharmacokinetics. *Pharmacogenomics J*. 2011;11(5):315–325.

48. Ieiri I, Takane H, Hirota T, Otsubo K, Higuchi S. Genetic polymorphisms of drug transporters: pharmacokinetic and pharmacodynamic consequences in pharmacotherapy. *Expert Opin Drug Metab Toxicol*. 2006;2(5):651–674.
49. Human ATP-Binding Cassette Transporters [database on the Internet]. Nutrition, Metabolism and Genomics Group, Wageningen University, The Netherlands. Available from: http://nutrigene.4t.com/humanabc.htm. Accessed February 25, 2016.
50. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci USA*. 2000;97(7):3473–3478.
51. Kimchi-Sarfaty C, Oh JM, Kim IW, et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science*. 2007;315(5811):525–528.
52. Cascorbi I. Role of pharmacogenetics of ATP-binding cassette transporters in the pharmacokinetics of drugs. *Pharmacol Ther*. 2006;112(2):457–473.
53. Sauna ZE, Kimchi-Sarfaty C, Ambudkar SV, Gottesman MM. Silent polymorphisms speak: how they affect pharmacogenomics and the treatment of cancer. *Cancer Res*. 2007;67(20):9609–9612.
54. Longo R, D'Andrea M, Sarmiento R, Gasparini G. Pharmacogenetics in breast cancer: focus on hormone therapy, taxanes, trastuzumab and bevacizumab. *Expert Opin Investig Drugs*. 2010;19(suppl 1):S41–S50.
55. Balram C, Sharma A, Sivathasan C, Lee EJ. Frequency of C3435T single nucleotide MDR1 genetic polymorphism in an Asian population: phenotypic-genotypic correlates. *Br J Clin Pharmacol*. 2003;56(1):78–83.
56. Tang K, Ngoi SM, Gwee PC, et al. Distinct haplotype profiles and strong linkage disequilibrium at the MDR1 multidrug transporter gene locus in three ethnic Asian populations. *Pharmacogenetics*. 2002;12(6):437–450.
57. Sensorn I, Sirachainan E, Chamnanphon M, et al. Association of CYP3A4/5, ABCB1 and ABCC2 polymorphisms and clinical outcomes of Thai breast cancer patients treated with tamoxifen. *Pharmgenomics Pers Med*. 2013;6:93–98.
58. Illmer T, Schuler US, Thiede C, et al. MDR1 gene polymorphisms affect therapy outcome in acute myeloid leukemia patients. *Cancer Res*. 2002;62(17):4955–4962.
59. Kim RB, Leake BF, Choo EF, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. *Clin Pharmacol Ther*. 2001;70(2):189–199.
60. Nakamura T, Sakaeda T, Horinouchi M, et al. Effect of the mutation (C3435T) at exon 26 of the MDR1 gene on expression level of MDR1 messenger ribonucleic acid in duodenal enterocytes of healthy Japanese subjects. *Clin Pharmacol Ther*. 2002;71(4):297–303.
61. Brinkmann U, Roots I, Eichelbaum M. Pharmacogenetics of the human drug-transporter gene MDR1: impact of polymorphisms on pharmacotherapy. *Drug Discov Today*. 2001;6(16):835–839.
62. Siegsmund M, Brinkmann U, Schaffeler E, et al. Association of the P-glycoprotein transporter MDR1(C3435T) polymorphism with the susceptibility to renal epithelial tumors. *J Am Soc Nephrol*. 2002;13(7):1847–1854.
63. Wang D, Johnson AD, Papp AC, Kroetz DL, Sadée W. Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C>T affects mRNA stability. *Pharmacogenet Genomics*. 2005;15(10):693–704.
64. Hitzl M, Drescher S, van der Kuip H, et al. The C3435T mutation in the human MDR1 gene is associated with altered efflux of the P-glycoprotein substrate rhodamine 123 from CD56+ natural killer cells. *Pharmacogenetics*. 2001;11(4):293–298.
65. Hung CC, Chen CC, Lin CJ, Liou HH. Functional evaluation of polymorphisms in the human ABCB1 gene and the impact on clinical responses of antiepileptic drugs. *Pharmacogenet Genomics*. 2008;18(5):390–402.
66. Levran O, O'Hara K, Peles E, et al. ABCB1 (MDR1) genetic variants are associated with methadone doses required for effective treatment of heroin dependence. *Hum Mol Genet*. 2008;17(14):2219–2227.
67. Tanabe M, Ieiri I, Nagata N, et al. Expression of P-glycoprotein in human placenta: relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther*. 2001;297(3):1137–1143.
68. Yamashita M, Nakamura T, Cho DY, Lee JD, Soh WY. [Rotational motion of flowering stalk in Spiranthes sinensis and its machinery]. *Biol Sci Space*. 2001;15(3):254–255.
69. Siegmund W, Ludwig K, Giessmann T, et al. The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. *Clin Pharmacol Ther*. 2002;72(5):572–583.
70. Ozawa S, Soyama A, Saeki M, et al. Ethnic differences in genetic polymorphisms of CYP2D6, CYP2C19, CYP3As and MDR1/ABCB1. *Drug Metab Pharmacokinet*. 2004;19(2):83–95.
71. Haufroid V. Genetic polymorphisms of ATP-binding cassette transporters ABCB1 and ABCC2 and their impact on drug disposition. *Curr Drug Targets*. 2011;12(5):631–646.
72. Cascorbi I, Gerloff T, Johne A, et al. Frequency of single nucleotide polymorphisms in the P-glycoprotein drug transporter MDR1 gene in white subjects. *Clin Pharmacol Ther*. 2001;69(3):169–174.
73. Woodahl EL, Yang Z, Bui T, Shen DD, Ho RJ. Multidrug resistance gene G1199A polymorphism alters efflux transport activity of P-glycoprotein. *J Pharmacol Exp Ther*. 2004;310(3):1199–1207.
74. Chang H, Rha SY, Jeung HC, et al. Association of the ABCB1 gene polymorphisms 2677G>T/A and 3435C>T with clinical outcomes of paclitaxel monotherapy in metastatic breast cancer patients. *Ann Oncol*. 2009;20(2):272–277.
75. Kafka A, Sauer G, Jaeger C, et al. Polymorphism C3435T of the MDR-1 gene predicts response to preoperative chemotherapy in locally advanced breast cancer. *Int J Oncol*. 2003;22(5):1117–1121.
76. Kim HJ, Im SA, Keam B, et al. ABCB1 polymorphism as prognostic factor in breast cancer patients treated with docetaxel and doxorubicin neoadjuvant chemotherapy. *Cancer Sci*. 2015;106(1):86–93.
77. Levy P, Gligorov J, Antoine M, et al. Influence of ABCB1 polymorphisms and docetaxel pharmacokinetics on pathological response to neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer Res Treat*. 2013;139(2):421–428.
78. Ashariati A. Polymorphism C3435T of the MDR-1 gene predict response to preoperative chemotherapy in locally advanced breast cancer with Her2/neu expression. *Acta Med Indones*. 2008;40(4):187–191.
79. Zhou Z, Chen Q, Zuo D, Wang H, Hua Y, Cai Z. ABCB1 (rs1128503) polymorphism and response to chemotherapy in patients with malignant tumors-evidences from a meta-analysis. *Int J Clin Exp Med*. 2015;8(1):265–272.
80. Yao S, Sucheston LE, Zhao H, et al. Germline genetic variants in ABCB1, ABCC1 and ALDH1A1, and risk of hematological and gastrointestinal toxicities in a SWOG Phase III trial S0221 for breast cancer. *Pharmacogenomics J*. 2014;14(3):241–247.
81. Vulsteke C, Pfeil AM, Schwenkglenks M, et al. Impact of genetic variability and treatment-related factors on outcome in early breast cancer patients receiving (neo-) adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide, and docetaxel. *Breast Cancer Res Treat*. 2014;147(3):557–570.
82. Eckhoff L, Feddersen S, Knoop AS, Ewertz M, Bergmann TK. Docetaxel-induced neuropathy: a pharmacogenetic case-control study of 150 women with early-stage breast cancer. *Acta Oncol*. 2015;54(4):530–537.
83. Kim KP, Ahn JH, Kim SB, et al. Prospective evaluation of the drug-metabolizing enzyme polymorphisms and toxicity profile of docetaxel in Korean patients with operable lymph node-positive breast cancer receiving adjuvant chemotherapy. *Cancer Chemother Pharmacol*. 2012;69(5):1221–1227.
84. Tran A, Jullien V, Alexandre J, et al. Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. *Clin Pharmacol Ther*. 2006;79(6):570–580.

85. Sissung TM, Mross K, Steinberg SM, et al. Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. *Eur J Cancer*. 2006;42(17):2893–2896.
86. Abraham JE, Guo Q, Dorling L, et al. Replication of genetic polymorphisms reported to be associated with taxane-related sensory neuropathy in patients with early breast cancer treated with Paclitaxel. *Clin Cancer Res*. 2014;20(9):2466–2475.
87. Teh LK, Mohamed NI, Salleh MZ, et al. The risk of recurrence in breast cancer patients treated with tamoxifen: polymorphisms of CYP2D6 and ABCB1. *AAPS J*. 2012;14(1):52–59.
88. Kim JW, Kim JH, Im SA, et al. ABCB1, FCGR2A, and FCGR3A polymorphisms in patients with HER2-positive metastatic breast cancer who were treated with first-line taxane plus trastuzumab chemotherapy. *Oncology*. 2012;83(4):218–227.