HHS Public Access

Author manuscript

Pharmacogenet Genomics. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Pharmacogenet Genomics. 2017 November ; 27(11): 420–427. doi:10.1097/FPC.0000000000000305.

PharmGKB summary: very important pharmacogene information for *ABCG2*

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Keywords

ABCG2; BCRP; pharmacogenetics; pharmacogenomics; chemotherapy

Overview

ABC subfamily G, isoform 2 (*ABCG2*) is a gene encoding the Breast Cancer Resistance Protein (BCRP), which is an ATP-binding cassette (ABC) efflux transporter [1]. The transporter has a broad substrate profile, including much overlap with P-glycoprotein (P-gp; encoded by the gene *ABCB1*) and with MRP1 (encoded by the gene *ABCC1*). Together these 3 transporters are among the most studied members of the ABC efflux transporter family [2].

BCRP substrates include endogenous and naturally occurring polar molecules, particularly conjugated organic ions, in addition to chemotherapeutics [1]. These substrates include dietary flavonoids, porphyrins such as heme, estrogen precursors, and the carcinogenic heterocyclic amines (PhIP) found in cooked meat and fish [1,3]. Over-activity and overexpression of the BCRP protein, such as caused by genetic variation, have been associated with resistance to chemotherapy, including tyrosine kinase inhibitors. The International Transporter Consortium has identified *ABCG2* as a pharmacogene with clinically important polymorphisms [4]. Here we describe the role of *ABCG2* in efflux transport and highlight its pharmacogenetic relationships.

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Disclaimers: none

Conflicts of Interest: RBA is a stockholder in Personalis Inc. and a paid advisor for Pfizer and Karius. TEK is a paid scientific advisor to Rxight Pharmacogenetics. Remaining authors have no conflicts of interest.

Molecular and Protein Structure

The *ABCG2* gene was first discovered in 1998 in a breast cancer cell line, MCF-7/AdrVp, which was resistant to chemotherapy, but did not express other efflux transporters that had already been associated with resistance at that time [3]. As a result the protein was named Breast Cancer Resistance Protein (BCRP). Subsequently, the cDNA was cloned, and the gene, *ABCG2*, was identified on chromosome 4q22 [2]. *ABCG2* consists of 16 exons and 15 introns that span 66 kb [5] (Entrez Gene ID: 9429, GenBank reference sequence NG_032067.2). The BCRP protein is 72 kDa in size and contains 655 amino acids, with the translation start site located in exon 2 [6,7]. There have been three distinct upstream promoters identified that affect the size of the 5′ UTR, but all three isoforms retain the ATG start site in exon 2 [8]. The *ABCG2* promoter is TATA-less and contains multiple SP-1 sites downstream of a CpG island [5]. BCRP expression is significantly decreased by methylation of the CpG island and increased upon the inhibition of histone deacetylase (HDAC) [9–11].

Despite much overlap in substrates, the protein orientation is the reverse configuration compared to other ABC transporters, with the ATP-binding domain at the N terminus and the transmembrane domains at the C terminus [7,12]. The consequences of this reversed orientation are unknown. However, transport direction does not seem to be affected, as binding pockets flank the nucleotide binding domain as they do for P-gp [13]. G family transporters like BCRP are considered “half-transporters” because they have only one of each of the nucleotide binding and membrane spanning domains compared to other ABC transporters, which have two [14,15]. A 3-D structure of BCRP, analyzed by electron crystallography from 2-D crystals, revealed that BCRP exists as a symmetric homodimer, but recent studies have suggested the possibility that BCRP may also function as a higher order oligomer such as a tetramer [16,17]. The protein is thought to homodimerize via intermolecular disulfide bridges to create the active transporter [18,19]. This dimerization is mediated by Pim-1 phosphorylation at Thr362 in the endoplasmic reticulum before the protein is transferred to the golgi for post-translational processing, after which it is transported to the apical cell membrane [20,21]. Although BCRP is typically glycosylated at the Arg596 residue, this glycosylation does not appear to be important for expression, trafficking, or function [22].

The *ABCG2* gene is found in all vertebrates that have been sequenced [23]. While fish have 3 or more copies of the *ABCG2* gene, most species have only one copy [23,24].

Tissue Distribution and Physiological Function

The BCRP protein functions as an efflux transporter that protects tissues from xenobiotics and harmful metabolites. Expressed on apical cell membranes of the placenta, brain, prostate, gastrointestinal tract, testes, ovaries, hepatocytes, renal tubules, stem cells, adrenal gland, uterus, bile ducts, gallbladder, central nervous system, and endothelium of veins and capillaries, BCRP mediates absorption, distribution, and elimination of its substrates [1,25–29]. BCRP is most highly expressed in brain tissue, the cervix, the small intestine, and the uterus [30]. Efflux by BCRP requires ATP hydrolysis to shuttle molecules against the

concentration gradient [2,3,31]. Activity is altered by the lipid membrane environment, specifically cholesterol content, and may vary between tissues [3,32,33].

BCRP-mediated efflux protects tissues against mutagens and carcinogens found in the diet, such as polycyclic aromatic hydrocarbons and heterocyclic amines [7]. Mice deficient in BCRP1 were found to have higher area under the plasma concentration-time curve (AUC) exposure to the carcinogen PhIP [7]. BCRP is also highly expressed in a side population of stem cells derived from the bone marrow. These cells have long-term repopulating capacity and BCRP acts as a protective barrier from oxidative stress products that could cause genetic damage. It is also thought that BCRP, along with P-gp, may play an important role in organ regeneration [34].

Efflux via BCRP acts as a protective barrier in tissues central to substrate absorption and elimination. Within the intestine, BCRP expression decreases along the length of the intestine, where it limits absorption of xenobiotics from the gut [35]. BCRP is also highly expressed in the kidney and liver, where it mediates the elimination of its substrates from the blood. A vital part of the blood-brain barrier, BCRP limits the penetration of compounds into the brain. In the kidney, BCRP is a high-capacity transporter for uric acid and actively secretes excess uric acid into the urine [36].

BCRP protein expression is upregulated in the ducts and lobules of lactating breast tissue, and may thereby concentrate vitamins such as ribaflavin and minerals into milk [2,28], while simultaneously concentrating xenobiotics present in the systemic circulation into milk. It is also highly expressed in the placental syncytiotrophoblasts, protecting the fetus from harmful metabolites and compounds [28,37].

Based on studies in humans and mice, reports conflict as to whether women or men might have increased hepatic BCRP expression [6,38,39], though gender-related differences in the pharmacokinetics of the BCRP substrates topotecan [40] and doxorubin [41] suggest that men may have higher BCRP activity [38].

Compounds that Interact with BCRP

Many factors influence BCRP expression and activity. As mentioned previously, epigenetic factors such as methylation and histone deacetylation can affect BCRP expression as well as binding to hypoxia, estrogen, and progesterone response elements within the promoter [23]. As a result, estrogen and progesterone upregulate *ABCG2* expression [42–44], while estradiol and the microRNAs hsa-miR-519c, hsa-miR520h, and hsa-miR328 downregulate *ABCG2* expression [45–47]. Stressors and exogenous compounds can also affect expression via activation of AhR, CAR, PXR, GR, ER-β, PPAR-γand Nrf2 [17,48]. Finally, BCRP expression is mediated via the PI3K-Akt pathway and can be down-regulated using tyrosine kinase inhibitors [49,50].

Although the exact topology of BCRP's binding sites is unknown, kinetic and equilibrium data suggest that there are two symmetric substrate binding sites and multiple allosteric sites allowing for non-competitive inhibition [3,51,52]. The list of compounds that interact with BCRP continues to grow (Table 1). BCRP inhibition is complex because any substrate for

BCRP may also serve as a competitive inhibitor at the right concentration. However, since BCRP has multiple binding sites, a lack of competitive inhibition does not imply that the compound is not a BCRP substrate. Further studies are needed to elucidate the exact properties of these binding sites and the effects of competitive and allosteric inhibition. Some compounds currently listed as inhibitors may later be discovered also to be BCRP substrates. Fumitremorgin C and its more potent derivative Ko143, however, appear to inhibit BCRP transport through an allosteric mechanism and offer an effective way to inhibit BCRP transport no matter the substrate or binding pocket. In fact, Ko143 is one of the most potent yet least toxic BCRP inhibitors known to date [51,53–56].

Many substrates that undergo efflux by BCRP also undergo efflux by P-gp and MRP1 [2]. In addition to compounds listed in Table 1, more comprehensive lists of BCRP substrates can be found in reviews [1,3,7,17,23,57].

Drug Interactions/Multi-drug Resistance

BCRP-mediated drug-drug interactions (DDIs) can severely affect the safety and efficacy of BCRP substrates, particularly those with a narrow therapeutic index. Because of this, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend pre-clinical testing to determine whether a new molecular entity is a BCRP substrate, and thus a potential victim of DDIs, or a BCRP inhibitor, and thus a perpetrator of DDIs. The FDA has published complete guidance on whether a compound should be tested in a clinical DDI study based on potency and ADME characteristics [58–60].

Safety is a consideration for BCRP substrates when dosed with an inhibitor because of increased oral bioavailability and decreased hepatic clearance. Plasma concentrations of BCRP substrates increase when dosed with a BCRP inhibitor, such as the interaction between topotecan and elacridar, and between pitavastatin and cyclosporin A [1,2,7]. Conversely, an increase in BCRP expression has been linked to lower plasma drug levels, although there is little and conflicting data on compounds that might induce BCRP expression [61]. Clinical DDI studies should be designed thoughtfully, because many BCRP substrates and inhibitors interact with other membrane transporters. For example, rosuvastatin is recommended as a probe for identifying BCRP inhibition, but rosuvastatin pharmacokinetics are also highly dependent on OATP1B1 activity [19,62]. BCRP activity can also be inhibited by natural compounds in the diet such as curcumin, so dietary restrictions should also be considered for DDI studies [19].

BCRP overexpression is prevalent in many cancers, especially stomach, colon, and esophageal cancer. It has been shown that cancer cells can induce BCRP expression through gene amplification and chromosomal translocation [63]. Overexpression is typically associated with a worse prognosis, as many chemotherapeutics are BCRP substrates. In clinical studies, patients with higher expression of BCRP responded more poorly to the tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib, and to photosensitizer chemotherapeutics [64–67]. ABC inhibitors, antisense oligonucleotides, siRNA, transcriptional regulation, antibodies, and drug delivery systems have all been examined as potential therapies to resensitize these resistant cancer cells, although few have shown

clinical promise. Many BCRP inhibitors caused serious neurotoxicity, perhaps due to off-target BCRP inhibition at the blood-brain barrier. Although some BCRP inhibitors are still being examined for their efficacy and safety, the field has moved away from developing chemotherapeutics that undergo efflux by ABC transporters [66,68].

ABCG2 variants

Many single nucleotide polymorphisms, resulting in both synonymous and nonsynonymous changes, have been identified in the *ABCG2* gene [69–71]. Additionally, sequence diversity in the *cis*-regulatory regions has been reported to affect BCRP expression, and over 100 non-coding variants of *ABCG2* have been associated with altered mRNA expression [30,72,73]. Both germline and somatic mutations have important implications for chemotherapeutic resistance. Table 2 summarizes the most common germline BCRP missense variants.

The two most common and extensively studied variants are rs2231137 (NM_004827.2: c.34G>A), which results in a V12M replacement (NP_004818.2: p.Val12Met), and rs2231142 (NM_004827.2:c.421C>A), which results in a Q141K substitution (NP_004818.2:p.Gln141Lys) [31,74]. The c.34G>A SNP (rs2231137) variant is located in exon 2 and reportedly does not affect expression, localization, or function of BCRP, or affect the pharmacokinetics of BCRP substrates [1,6,75]. However, in *in vitro* studies in transfected K562 cells, the c.34G>A variant was associated with reduced activity of the BCRP transporter, resulting in decreased resistance to tyrosine kinase inhibitors [76].

The c.421C>A (rs2231142) variant is located in exon 5 and is in the nucleotide binding domain of the transporter. It has been found to decrease the expression of BCRP due to increased degradation of the variant protein in the endoplasmic reticulum [1,6,7,38,77]. Expression of the BCRP protein was reported to be 30-40% that of protein with the reference sequence, and expression in the placenta, specifically, also was reportedly lower [74,75]. The c.421C>A variant has been found to affect pharmacokinetics of, response to, and toxicity of compounds that are BCRP substrates, including chemotherapeutics and endogenous compounds [70,78–81]. This variant was identified by the International Transporter Consortium as a clinically important transporter pharmacogene based on three criteria: 1) genome wide significance of an association between the variant and one or more drugs from genome wide association studies, 2) significant association of the variant and drug outcome from candidate gene studies, and 3) functional changes resulting from the polymorphism found in *in vitro* studies [4]. The *in vivo* intestinal BCRP transport activity in people homozygous for the A allele is reported to be approximately 23% of that in the c.421CC subjects [80]. Furthermore, the AUC of sulfasalazine, a drug used as a BCRP probe *in vivo*, is reportedly 2.5 times greater in patients carrying the A allele compared to patients without it [82]. A study in people of Japanese descent reported a 1.9 - 3.5 times greater AUC of sulfasalazine in patients with the c.421C>A variant, but this finding was not replicated in a study of people of Chinese descent [83]. Other studies found that patients of Japanese descent with the c.421C>A variant who were being treated with sunitinib for advanced renal cell carcinoma were more likely to develop grade 3 or grade 4 thrombocytopenia [81,84,85], and that the variant was significantly associated with increased sunitinib exposure [86]. Furthermore, patients homozygous for the reference allele may have lower plasma

concentrations of atorvastatin, simvastatin, and fluvastatin [1,87,88] and may respond more poorly to FOLFOX/XELOX therapy [89] compared to patients homozygous for the A allele. Additionally, patients with the AA genotype at c.421 may have reduced response to allopurinol when treated for gout as compared to patients with the AC or CC genotypes [90,91], and a greater incidence of adverse events with gefitinib treatment was reported with the c.421C>A variant [2,38]. The A allele is found more commonly in East Asian populations (27-35% in Japanese and Chinese study participants) than in Caucasian populations (6-14%) and African American populations (1-4%) [4,38,75,92]. This difference in allele frequency at c.421 may be responsible for the different recommended initial dosing of rosuvastatin for patients of Asian descent (5 mg/day) compared to patients not of Asian descent (10-20 mg/day) [93]. Compared to Caucasian patients, Asian patients were found to have a 2-fold increase in drug exposure, resulting in increased risk for myopathy due to higher drug concentrations [93].

Besides what is known about c.34 and c.421, there are nonsense and missense variants that have been characterized *in vitro* but are rarely found in germline variation. The variants rs1061018 (NM_004827.2:c.623T>C; NP_004818.2:p.Phe208Ser), rs3116448 (NM_004827.2:c.742T>C; NP_004818.2:p.Ser248Pro), rs3201997 (NM_004827.2:c.1000G>T; NP_004818.2:p.Glu334Stop), rs773828630 (NM_004827.2:c.1321_1331delAGTGTTTCAGC; NP_004818.2:p.Ser441Argfs) and rs192169063 (NM_004827.2:c.1465T>C; NP_004818.2:p.Phe489Leu) are all reported to result in null BCRP protein activity based on the impact on the transport of methotrexate and haematoporphyrin [71]. Furthermore, the variants c.623T>C, and c.1321_1331delAGTGTTTCAGC were reported to have severely reduced protein levels, perhaps due to instability or degradation [71,75]. BCRP variants c.742T>C and c.1465T>C were all reported to have altered protein expression and to affect drug resistance [71]. In addition to what was found in K562 cells transfected with c.34G>A, in vitro studies in K562 cells showed reduced sensitivity to tyrosine kinase inhibitors in cells transfected with c.421C>A, c.623T>C, c.886G>C, or c.1574T>G [76].

Acquired somatic cell variants that have been implicated in chemotherapeutic resistance include protein sequence changes Arg482Gly and Arg482Thr, which are thought to increase BCRP activity [2,94,95]. Due to increased efflux activity, patients with these variants exhibit decreased response to the anthracyclines, doxorubicin, daunorubicin, and to rhodamine 123 [2,94,95]. The Arg482 site is likely involved in substrate recognition, as it is found in a large drug binding pocket at the cytoplasmic interface [1]. On the other hand, the variants Thr402Ala and Thr402Arg reportedly decrease BCRP activity, reducing mitoxantrone and the probes BODIPY-prazosin and Hoechst33342 efflux by 50-90% [1]. The Pro485Ala variant is also thought to decrease BCRP function, and has been found to reduce efflux of the probe BODIPY-prazosin by 70% [96]. However, this variant did not affect the efflux of mitoxantrone or Hoechst33342, suggesting that the variant lies in the drug binding pocket and thereby determines substrate specificity [1].

Fluorescent probes, including BODIPY-prazosin, Hoechst33342, and pheophorbide A, can be used to assess BCRP expression and function [1]. Probes specific for particular variants of the *ABCG2* gene include Rhodamine 123 for R482G and Lyso-Tracker Green for R482T,

as these probes are not substrates of the protein produced from the *ABCG2* reference sequence [97].

Genetic Associations

Variants in *ABCG2* have been associated with a number of phenotypes via genome-wide association studies (GWAS), both as a risk for developing disease and altered drug response. One of the most well-characterized associations is that of the reduced-function BCRP Q141K variant and the risk for developing gout and hyperuricemia [36,98–100]. Since BCRP is a high-capacity urate transporter, reduced-function variants are linked to a decrease in urate excretion and higher uric acid levels. This in turn increases the risk for developing gout. Since the time BCRP Q141K was linked to urate excretion via GWAS, other reduced-function variants have also been linked to uric acid levels, such as Q126X [100,101].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) evaluates the strength of evidence for gene-drug associations and publishes peer-reviewed guidelines for changing drug dose or drug choice based on the genotype of a patient. While most CPIC dosing guidelines have focused on genetic variation in enzymes causing an increase in drug toxicity [102–104], two large GWAS have linked *ABCG2* c.421 variants with altered drug efficacy. The JUPITER trial in over 4,000 patients with cardiovascular disease demonstrated a strong association (at genome-wide level significance) of the C genotype with improved LDL cholesterol response to rosuvastatin [105]. These results were further studied in a cohort of 291 Chinese patients to reveal that this altered efficacy was due to an increased bioavailability in these patients [106]. In a recent GWAS in over 1500 multi-ethnic gout patients, the C genotype was associated at genome-wide level significance with worse uric-acid lowering response to allopurinol [90]. One follow up study in 264 patients confirmed this association, even when controlling for adherence to allopurinol, a prevalent factor of non-response in gout treatment [91].

Conclusion

ABCG2, encoding the efflux pump BCRP, plays an important role in drug response and disposition. It is widely expressed and has a broad substrate specificity to efflux xenobiotics and harmful metabolites from systemic circulation. BCRP is also an important mediator of multi-drug resistance in cancers and protection of vital yet vulnerable tissues such as the brain, stem cells, and placenta.

The regulation of *ABCG2* is complex. To date, studies have shown that BCRP expression and function can be controlled via genetic response elements, post-translational modifications, epigenetics, DDIs, and genetic variation. Variation in BCRP activity affects the pharmacokinetic profiles of many drugs, and has been associated with risks of toxicity and efficacy of therapy. One of the most common reduced-function variants, BCRP p.Q141K, has been implicated in improved response to statins, increased side effects of chemotherapeutics, altered response to allopurinol, and reduced excretion of endogenous substrates such as uric acid. This variant reduces the expression of BCRP on the plasma membrane due to an increased breakdown in the endoplasmic reticulum. In vitro site-

directed mutagenesis studies have helped identify other residues important for BCRP transport, trafficking, and expression, but identification of a BCRP crystal structure is needed to definitively describe the multiple binding pockets and allosteric sites of the efflux protein.

Acknowledgments

Sources of funding: NIH/NIGMS R24 GM61374

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Table 1

A selection of *ABCG2* substrates and inhibitors[a]

Substrates	Inhibitors
5-fluorouracil	atazanavir
abacavir	chromanone derivatives
atorvastatin	curcumin
azidopine	cyclosporin A
ciprofloxacin	delavirdine
daunorubicin	fumitremorgin C (FTC) Ko143
doxorubicin	itraconazole
efavirenz	ketoconazole
epirubicin	lopinavir
erlotinib	nelfinavir
erythromycin	poloxamines
etoposide	reserpine
flavopiridol	ritonavir
fluvastatin	saquinavir
folic acid	sirolimus
ganciclovir	tacrolimus
gefitinib	
glutathione	
glyburide	
homocamptothecins	
imatinib	
irinotecan	
lamivudine	
methotrexate	
mitoxantrone	
nilotinib	
pantoprazole	
pheophorbide A	
PhIP	
pitavastatin	
porphyrins	
pravastatin	
riboflavin	
rosuvastatin	
SN-38	
sorafenib	
sulfasalazine	
sulfated estrogens	
sunitinib	

Substrates	Inhibitors
tamoxifen	
tariquidar	
topotecan	
urate	
vitamin K_3	
zidovudine	

[a]The references used to compile this list are [17, 87, 107–119]

Table 2

ABCG2 variants, including genome location and coding change, the effect on transporter function, and the global variant allele frequency.

Variant rs number	cDNA (NM_004827.2)	Protein coding effect (NP_004818.2)	Protein function effect	Global Minor Allele Frequency[a]
rs2231137	c. 34G>A	p. Val12Met	no function [107, 120, 121]	0.1076
rs2231142	c. 421C>A	p. Gln141Lys	reduced function [107, 120, 121]	0.1180
rs34783571	c. 1858G>A	p. Asp620Asn	reduced function [122]	0.0056
rs138606116	c. 1060G>A	p. Gly354Arg	unknown	0.0026
rs45605536	c. 1582G>A	p. Ala528Thr	unknown	0.0014
rs192169063	c. 1465T>C	p. Phe489Leu	reduced function [121]	0.0009
rs148475733	c. 211A>G	p. Met71Val	unknown	0.0009
rs147547385	c. 1787A>G	p. Asn596Ser	unknown	0.0005
rs72552713	c. 376C>T	p. Gln126Stop	no function [107, 123, 124]	0.0005
rs199473672	c. 335C>A	p. Pro112Gln	unknown	0.0004
rs34264773	c. 1768A>T	p. Asn590Tyr	reduced function [122]	0.0003
rs140207606	c. 706 C>A	p. Arg236Stop	no function[*] [123]	0.0003
rs149106245	c. 383A>T	p. Asp128Val	unknown	0.0002
rs35965584	c. 1624 A>G	p. Thr542Ala	unknown	0.0002
rs547742211	c. 1312T>C	p. Cys438Arg	unknown	0.0002

[a] From the ExAC server, accessed December 15, 2016 [125]

[*] not validated *in vitro*