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Multidrug resistance-associated protein 1 (*MRP1/ABCC1*) polymorphism: from discovery to clinical application

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Abstract

Multidrug resistance-associated protein 1 (*MRP1/ABCC1*) is the first identified member of ABCC subfamily which belongs to ATP-binding cassette (ABC) transporter superfamily. It is ubiquitously expressed in almost all human tissues and transports a wide spectrum of substrates including drugs, heavy metal anions, toxicants, and conjugates of glutathione, glucuronide and sulfate. With the advance of sequence technology, many *MRP1/ABCC1* polymorphisms have been identified. Accumulating evidences show that some polymorphisms are significantly associated with drug resistance and disease susceptibility. *In vitro* reconstitution studies have also unveiled the mechanism for some polymorphisms. In this review, we present recent advances in understanding the role and mechanism of *MRP1/ABCC1* polymorphisms in drug resistance, toxicity, disease susceptibility and severity, prognosis prediction, and methods to select and predict functional polymorphisms.

Keywords

multidrug resistance-associated protein 1; ABCC1; single nucleotide polymorphism; drug resistance; prognosis; disease susceptibility

Multidrug resistance-associated protein 1 (MRP1/ABCC1) is a member of the ATP-binding cassette (ABC) transporter superfamily which contains 49 members in human that are divided into 7 subfamilies, named from ABCA to ABCG (http://nutrigene.4t.com/humanabc.htm)[1-2]. *MRP1/ABCC1* is the first identified gene in the ABCC subfamily and was cloned from a multidrug resistant small cell lung cancer cell line H69AR[3]. Subsequent studies revealed the important role of MRP1/ABCC1 as an exporter of drugs and metabolites in many physiological, pathological and pharmacological processes. Thus, polymorphism is likely an important feature of MRP1/ABCC1 in disease susceptibility, drug response, and treatment outcomes[4]. In this review, we will evaluate recent advances in discovery of *MRP1/ABCC1* polymorphisms and understanding their potential clinical applications.

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1 STRUCTURE AND TISSUE DISTRIBUTION

The *MRP1/ABCC1* gene is located in chromosome 16p13. 1 and spans approximately 200 kb. It contains 31 exons and encodes a protein of 1 531 amino acid residues with an apparent molecular weight of 180-190 kD[3-5]. *MRP1/ABCC1* is an atypical ABC transporter with three membrane-spanning domains (MSD) and two cytosolic nucleotide binding domains (NBD) [6]. While MSD1 and MSD2 each consists of 6 transmembrane (TM) segments, MSD0 has 5 TM segments with a predicted extracellular amino terminus (Fig. 1A). However, recent studies showed that the amino terminus of human MRP1/ABCC1 may have an unusual U-shaped structure which possibly serves as a gate for MRP1/ABCC1 function[7-9].

The sequence of MSD is highly divergent among different members of ABC transporter family, consistent with MSD's possible function in determining substrate specificity[10]. Thus, polymorphisms in this domain may affect the substrate spectrum of MRP1/ABCC1. While a typical ABC transporter has two MSDs, the additional MSD0 of human MRP1/ ABCC1 is peculiar and its function is not yet fully elucidated. However, our recent studies showed that MSD0 contributes to MRP1/ABCC1 homo-dimerization[11-12].

In contrast to MSD, NBD is highly conserved among different ABC transporters. It is responsible for binding and hydrolysis of ATP to provide energy for substrate transport[10]. Similar to other ABC transporters, the NBD of MRP1/ABCC1 has two consensus motifs designated as "Walker A" and "Walker B"[13] and a third consensus motif designated as ABC-signature motif of approximate 13 amino acids between Walker A and Walker B[10]. These highly conserved motifs are critical for MRP1/ABCC1 function and a single mutation may abolish the activity of the whole protein[14-15]. Thus, polymorphisms in NBD may produce inactive MRP1/ABCC1.

MRP1/ABCC1 appears to be ubiquitously expressed in almost all human tissues[16-18]. Its expression level is high in lung, spleen, testis, kidney, placenta, thyroid, bladder and adrenal gland, but low or no expression in some cells of circulatory system, such as eosinophils, helper T-cells and erythrocytes[19]. MRP1/ABCC1 is also expressed in blood-brain, blood-testis and blood-cerebrospinal fluid (CSF) barriers, which was thought to contribute to protection of these organs by keeping out toxic substances[20-21]. Indeed, it has been shown that accumulation of etoposide in CSF increased 10-fold in MRP1/ABCC1 knockout mice[20]. At the cellular level, in contrast to the apical membrane location of other ABC transporters, MRP1/ABCC1 is predominantly located in the basolateral membrane of polarized cells[22-23]. Thus, MRP1/ABCC1 likely pumps its substrate into the interstitial space of body, rather than excreting them into bile, urine or gut.

2 SUBSTRATES

MRP1/ABCC1 can transport a wide spectrum of substrates ranging from anticancer drugs to fluorescent dye (Tab. 1). A wide variety of anticancer drugs including anthracyclines, epipodophyllotoxins, vinca alkaloids, camptothecins, methotrexate and mitoxantrone are known substrates of MRP1/ABCC1 and, thus, MRP1/ABCC1 over-expression leads to multidrug resistance in cancer chemotherapy. In addition to anticancer drugs, MRP1/

ABCC1 also transports many other types of drugs, such as anti-HIV drugs. Therefore, *MRP1/ABCC1* gene polymorphisms may affect patient response to chemotherapy of these diseases. Previously, we have shown that G2168A polymorphism significantly reduced MRP1/ABCC1 activity in resistance to anthracyclines, vinca alkaloids and etoposide[24].

Another important group of substrates of MRP1/ABCC1 is organic anion conjugates including glutathione, glucuronides and sulfate conjugates. Transporting these conjugates helps cells to remove toxins and protect tissues from damage[25-26]. LTC4, a very important mediator of inflammatory response which controls vascular permeability and smooth muscle contraction, is another high affinity substrate of MRP1/ABCC1[19,27]. Thus, *MRP1/ABCC1* polymorphisms may affect therapeutic efficiency of some LTC4 targeting drugs, such as montelukast and zileuton [28-29].

3 POLYMORPHISMS

A large number of naturally occurrmg *MRP1/ABCC1* polymorphisms have been identified with most studies in Asian and Caucasian populations[30-37]. A comprehensive list of naturally occurring *MRP1/ABCC1* polymorphisms in different populations can be found in several publicly accessible databases [Pharmacogenetics Research Network: http://www.pharmgkb.org; National Central for Biotechnology Information (NCBI): http://www.ncbi.nlm.nih.gov/snp; Japanese Single Nucleotide Polymorphisms (JSNP) database: http://snp.ims.u-tokyo.ac.jp/; International HapMap Project: www.hapmap.org/].

Most identified *MRP1/ABCC1* polymorphisms are single nucleotide polymorphisms (SNPs), although repeats, insertions and deletions are also found. There are vast ethnical differences in *MRP1/ABCC1* polymorphism distribution and frequency, especially between Asian and Caucasian. For example, G2168A is a common SNP in the Asian population, but it has not been found in Caucasian[24]. On the contrary, G2012T polymorphism is common in Caucasian, but not found in Asian populations [31]. Most *MRP1/ABCC1* polymorphisms have a very low frequency (< 5%), which indicating that *MRP1/ABCC1* is a highly conserved gene. The majority of identified polymorphisms are located in the untranslational region (UTR) and introns and few polymorphisms are located in the coding region. Polymorphisms in the coding region are more likely to be functional and can be divided into three types: synonymous (no change in amino acid sequence resulting in a wild-type protein), non-synonymous (change in amino acid sequence resulting in a mutant protein), and nonsense (change to a stop codon resulting in a truncated protein). Up to date, only 14 non-synonymous polymorphisms have been identified with very low frequencies and no nonsense polymorphism has been found (Fig. 1). These non-synonymous polymorphisms were intensively studied both *in vitro* and *in vivo* since they could be easily recreated using site-directed mutagenesis and they might affect the expression and function of MRP1/ABCC1[24-39]. Although the polymorphisms in the non-coding region do not affect the sequence of the protein, they are also important and can be used as genetic markers[40-41].

4 ASSOCIATION OF *MRP1/ABCC1* POLYMORPHISMS WITH THERAPEUTIC RESPONSE

As discussed above, many therapeutic drugs are substrates of MRP1/ABCC1. Thus, it is conceivable that some *MRP1/ABCC1* polymorphisms may affect treatment responses and toxicities. Tab. 2 lists *MRP1/ABCC1* polymorphisms that have been studied for their association with therapeutic responses. One of these polymorphisms, G2012T which was first identified by Conrad et al.[34] in Caucasian population, has been extensively studied. It causes mutation of a highly conserved Gly^{671} to Val. Investigation of its potential relationship with response to atorvastatin in treatment of hypercholesterolemia, telatinib in treatment of solid tumors, and induction therapy of leukemia, however, showed no significant correlattion with treatment responses[42-44]. Consistent with these clinical observations, *in vitro* studies also showed that the mutant MRP1/ABCC1 carrying this mutation had no detectable difference in drug transport activity from the wild type MRP1/ABCC1 [34], Thus, the G2012T polymorphism may not have functional impact on chemotherapy.

Another extensively studied polymorphism is G4002A, a synonymous SNP located in exon 28. Several studies exploring the correlation of G4002A polymorphism and responses to anticancer drugs gemcitabine, cisplatin, taxanes and methotrexate showed no significant association in pancreatic cancer patients [45-47]. However, Lee et al. [48] found that this polymorphism was strongly associated with the response of patients with major depressive disorder to antidepressant citalopram. Although patients with the G4002A polymorphism had a 4. 7-fold increase in citalopram response, there is no evidence that G4002A polymorphism of *MRP1/ABCC1* in the blood-brain barrier affects citalopram uptake and if citalopram is a substrate of MRP1/ABCC1. Another non-synonymous polymorphism located in exon 28, A4009G, was found to correlate with methotrexate therapeutic efficacy in a study of 374 chronic plaque psoriasis patients who received methotrexate monotherapy[49]. It was found that the heterozygous A4009G in the responders is significantly higher than that in non-responders, suggesting that the A4009G polymorphism may increase methotrexate responses. However, it has not yet been determined if the A4009G polymorphism affects *MRP1/ABCC1* expression, trafficking, or function. Future studies on the possible effects of the A4009G polymorphism on these aspects of MRP1/ABCC1 are needed.

A well studied polymorphism that has been shown to significantly reduce drug transport activity of MRP1/ABCC1 is G2168A[24]. It has also been shown to increase chemotherapy response in advanced ovarian cancer patients[50]. In the study of advanced ovarian cancer patients, several other polymorphisms of *MRP1/ABCC1* (T825C, T1062C, T1684C, C2007T and G4002A) were also investigated. However, none of these polymorphisms were found to significantly associate with chemotherapy responses. Thus, the G2168A polymorphism may be an indicator of chemotherapy response of advanced ovarian cancers. However, whether this polymorphism also affects chemotherapy responses of other human cancers need to be investigated.

In addition to the polymorphisms in the coding region, some polymorphisms in the non-coding region of MRP1/ABCC1 are also found to associate with drug responses. Two such polymorphisms in the non-coding region are IVS23 G-1960A and IVS9 T-176C located in intron 23 and 9, respectively. They both have been shown to significantly associate with methotrexate response in psoriasis patients and patients carrying these polymorphisms appear to have worse response to methotrexate treatment[49]. Another example of polymorphisms in the non-coding region is IVSI C-14840T which is located in intron 1 and has been found to correlate with significantly higher response to both montelukast and zileuton in asthma patients than wild-type homozygotes [28-29]. Thus, polymorphisms in *MRP1/ABCC1* may affect montelukast and zileuton response and lung function. Interestingly, in another study of two independent cohorts, polymorphisms of *MRP1/ABCC1* in the 3'-UTR (G3361A and A2615G) and IVS14 C-1575T also significantly correlate with lung function[51]. While 3'-UTR G3361A correlates with higher forced expiratory volume at one second (FEV1), 3'-UTR A2615G correlates with lower FEVI. Another polymorphism, IVS14 C-1575T in the intron 14 of MRP1/ABCC1, correlates with highly excessive FEVI decline. However, how these polymorphisms in the non-coding region possibly affect MRP1/ABCC1 is not yet known. It is also unknown if MRP1/ABCC1 plays any role in lung function. While the polymorphisms in the UTR may affect the translation and expression of MRP1/ABCC1, the polymorphisms in the intron may affect RNA processing. Clearly, these hypothetical mechanisms of action and the role of MRP1/ABCC1 in lung function needs to be investigated in the near future.

5 ASSOCIATION OF *MRP1/ABCC1* POLYMORPHISMS WITH PROGNOSIS PREDICTION

Based on the above discussion of association of *MRP1/ABCC1* polymorphisms with therapeutic response, it is tempting to speculate that polymorphisms of *MRP1/ABCC1* may be used as markers to predict prognosis. Indeed, two polymorphisms have been shown to associate with prognosis (Tab. 3). In a study of possible contribution of four non-synonymous polymorphisms of *MRP1/ABCC1* to neuroblastoma outcome in a cohort of 195 Caucasian patients, it was found that the presence of the G2010T polymorphism has significant improvement in outcome[52]. It was also found that the G2010T polymorphism reduces the stability and expression level of *MRP1/ABCC1* mRNA. Hence, it is possible that patients with the G2010T polymorphism may have reduced level of *MRP1/ABCC1*, which would enhance drug response and increase chemotherapy efficacy. In another study of correlating 5'-UTR G-1666A polymorphism with hepatocellular carcinoma (HCC) outcome in 162 Chinese patients, it was found that the mutant genotype carriers had better prognosis with increased 4-year disease free survival[53]. Using *in vitro* electrophoretic mobility shift assay (EMSA), these authors also found that the mutant allele had much less binding affinity to nuclear proteins, suggesting that this promoter polymorphism may cause decreased transcription of *MRP1/ABCC1*. However, whether this promoter polymorphism inhibits MRP1/ABCC1 transcription has not yet been demonstrated. It is also unknown if the nuclear proteins that bind to this region are involved in the transcription of *MRP1/ABCC1*. Nevertheless, these polymorphisms may be used as makers predicting prognosis and survival in neuroblastoma and HCC.

6 ASSOCIATION OF *MRP1/ABCC1* POLYMORPHISMS WITH DRUG TOXICITY

Since some toxicants and drug metabolites are also substrates of MRP1/ABCC1, possible association of *MRP1/ABCC1* polymorphisms and drug toxicity is also of importance and interest to investigate. In this regard, correlation of *MRP1/ABCC1* polymorphisms and drug-induced neuropathy is mostly studied (Tab. 4). In a recent study correlating polymorphisms of *MRP1/ABCC1* (IVS9A8G, IVS11C-48T, T1684C, IVS18C-30G, G4002A and IVS30A18G) with irinotecan-induced neutropenia in cancer patients, it was found that the TT genotype carriers of IVSI1 C-48T had significant lower neutrophil count (ANC) in patients receiving irinotecan monotherapy[54]. Irinotecan-induced neutropenia is thought to be due to production of the cytotoxic irinotecan metabolite, SN-38, which is a substrate of MRP1/ABCC1. Consistent with this study, *MRP1/ABCC1* polymorphism has also been found to correlate with peripheral neuropathy induced by vincristine[55]. In this study of 833 myeloma patients, it was found that the carriers of MRP1/ABCC1 polymorphism IVS16 A1695T were more likely to develop vincristine-induced peripheral neuropathy than the wild type carriers. Similar to SN-38, it is also speculated that this polymorphism may decrease *MRP1/ABCC1*-mediated transport of vincristine and, thus, increases vincrinstine-induced peripheral neuropathy. However, the molecular mechanisms need further investigation.

One interesting polymorphism is G2012T, which shows correlation with doxorubicin toxicity in non-Hodgkin lymphoma patients[56]. The patients with this polymorphism have more anthracycline-induced cardiotoxicity than the wild-type patients. It was thought that the special subcellular localization of *MRP1/ABCC1* in cardiomyocytes, in both plasma and lysosome membranes, permits sequestration of doxorubicin in lysosomes and prevent doxorubicin cardiotoxicity[17-57]. However, it has been demonstrated previously that the G2012T polymorphism of *MRP1/ABCC1* has no effect on its function and substrate transport activity[34]. Thus, it is not clear how this polymorphism affects anthrocycline-induced cardiotoxicity. Furthermore, since multidrug chemotherapy was used for these cohorts of patients, interpretation of these observations should be cautious. Doxorubicin mono-therapy and further investigation of G2012T mutation on MRP1/ABCC1 activity in transporting doxorubicin would help clarify this issue.

Several other polymorphisms of *MRP1/ABCC1* (IVS3 G-3198A, IVS4 G409A, IVS5G413A, IVS5 A-7942G, IVS5G-1641A and IVS23 G-1960A) have been found to significantly correlate with methotrexate toxicity in liver and GI tract of psoriasis patients[49]. All these polymorphisms are located in introns and form a haplotype although it is not yet known if they affect the expression of MRP1/ABCC1 individually or as a haplotype. Based on the above discussion, *MRP1/ABCC1* polymorphisms are likely important genetic indicators in drug toxicity during chemotherapy.

7 ASSOCIATION OF *MRP1/ABCC1* POLYMORPHISMS WITH DISEASE SUSCEPTIBILITY AND SEVERITY

Association of MRP1/ABCC1 with disease susceptibility has also been identified (Tab. 5). In a case control study of 500 lung cancer patients and 517 cancer free control subjects in Chinese population, Wang et al. [58] detected the association of three polymorphisms in the 3'-UTR of *MRP1/ABCC1* (C543T, T866A and T1512C) with lung cancer susceptibility. They found that subjects carrying mutant allele of 3'-UTR T866A had an increased risk of lung cancer. However, the other two polymorphisms had no significant correlation with lung cancer susceptibility. Further investigation showed that these three polymorphisms form a haplotype and the GTA haplotype was associated with increased risk of lung cancer compared with the most prevailing AAA haplotype. Therefore, this polymorphism haplotype may increase lung cancer predisposition in Chinese population. We recently identified association of another non-synonymous polymorphism G2168A with lung cancer susceptibility[59]. In our study of 77 lung cancer patients and 71 control individuals in Chinese population, we showed that the subjects carrying the G2168A allele had 3. 5 fold increased risk (adjusted OR = 3. 42; 95% CI, 1. 29 - 9. 06; *P* =0. 013) of lung cancer compared with wild-type carriers. Further stratified analysis showed that the elderly people (> 50 years) carrying mutant allele of this polymorphisms were more likely to develop lung cancer (adjusted OR, 4. 10; 95% *CI*, 1. 25-13. 48; *P* =0. 020) than younger ones. Taken together, it is possible that *MRP1/ABCC1* polymorphisms may play important roles in lung cancer susceptibility. Although the mechanism of MRP1/ABCC1 action in lung cancer susceptibility is unknown, it is tempting to speculate that *MRP1/ABCC1* may protect lung tissues against carcinogens by preventing them from entering bronchial epithelial cells. Carriers of these *MRP1/ABCC1* polymorphisms are likely more susceptible to carcinogenesis due to reduced protection by MRP1/ABCC1. This possibility is consistent with our observation that the G2168A polymorphism decreases MRP1/ABCC1 function in drug transport activity (unpublished observations). However, further clinical studies are needed to test this possibility.

Possible impact of *MRP1/ABCC1* polymorphisms on disease severity has also been reported in other studies (Tab. 5). In a study of 203 cystic fibrosis (CF) patients, it was found that the G-260C polymorphism in the 5'-UTR of MRP1/ABCC1 significantly increased CF severity[60]. Patients with CC genotype had earlier onset of chronic colonization by *Pseudomonas aeruginosa* (PA). Although *in vitro* study showed no impact of this polymorphism on promoter transcriptional activity, mRNA levels, basal and cAMP-induced anion transport, the possibility that this polymorphism affects translation/synthesis of MRP1/ABCC1 and, thus, its expression level cannot be ruled out.

In another study of five *MRP1/ABCC1* polymorphisms (3'-UTR T866A, 3'-UTR G3361A, 5'-UTR C-435G, IVSl T5977G and IVS14 C-1575T) and their possible effect on chronic obstructive pulmonary disease (COPD) severity, it was found that the 3'-UTR T866A was associated with higher FEV1 level and less airway wall inflammation while the 3'-UTR G3361A was associated with lower FEV1 level and higher inflammation. However, the other three polymorphisms have no significant association with COPD severity[61]. The

mechanism of the 3'-UTR T866A in affecting COPD severity remains unknown. However, it is speculated that 3'-UTR T866A may affect *MRP1/ABCC1* mRNA stability together with another 3'-UTR polymorphism 801 C > GR[51-61] They were found to be in complete linkage disequilibrium[40]. Clearly, *MRP1/ABCC1* polymorphisms are likely associated with lung cancer susceptibility and with COPD and CF disease severity. However, whether and how each polymorphism possibly affects disease susceptibility and severity need to be investigated in the future.

8 CONCLUSIONS SPECTIVES

Since the discovery of MRP1/ABCC1 in 1992, many *MRP1/ABCC1* polymorphisms have been identified. Most of the identified polymorphisms are synonymous and have low frequency, indicating that MRP1/ABCC1 is a highly conserved gene. Some of the *MRP1/ABCC1* polymorphisms have been found to associate with drug response, prognosis, toxicity, disease susceptibility and severity. Some of these polymorphisms have also been shown to affect MRP1/ABCC1 expression or function which may indicate the underling mechanism of association with the observed phenotype. With the advances of next generation sequencing, International HapMap Project and 1 000 Genomes Project[62-63], more *MRP1/ABCC1* polymorphisms are likely to be identified. However, identifying functional *MRP1/ABCC1* polymorphisms and their mechanisms of action will not be easy. Thus, both opportunities and challenges exist.

Because not every polymorphism is functional, selecting potentially functional polymorphisms for further clinical relevance study is important considering the large number of polymorphisms is to be identified. Use of *in silico* and bioinformatics tools such as SIFT, PANTHER and Polyphen algorithms to detect sequence conservation can help identify the likely functional polymorphism since sequences that are highly conserved across different species tend to be functionally important[64-66]. However, this strategy should be used with caution due to both false positive and negative predictions. For example, G689A, G1057A and G3173A polymorphisms of MRP1/ABCC1 are predicted as deleterious polymorphisms using SIFT. However, none of these polymorphisms adversely affects MRP1/ABCC1 function[24-39].

Examination of polymorphism databases shows that most polymorphisms are located in introns and UTRs. In addition, some polymorphisms located in the exons are synonymous polymorphisms. Thus, study of sequence conservation will unlikely be able to predict if these polymorphisms are functional. For these polymorphisms, a genome-wide approach to identify polymorphisms of positive and negative selection is helpful[41-67]. Positive selection is an evolutionary process and the positively selected polymorphisms contribute to the favorable phenotype of species and, thus, these polymorphisms may be of higher frequency in the population and important for the gene function[66-68]. Opposite to positive selection, negative selection is the decline of disadvantage phenotype and harmful and, thus, the negatively selected polymorphisms usually have very low frequency (minor allele frequency < 0. 05) in the population although they may be important for the function and rare drug adverse effects[66]. Both strategies have been used to identify functional *MRP1/ABCC1* polymorphisms[38,41,56,67]. However, it is noteworthy that combination of sequence

conservation and evolutionary features may be more powerful than any approach alone to predict and identify functional polymorphisms.

Another challenge is to understand how each polymorphism affects gene function. While it is easy to study the effect of the non-synonymous polymorphisms on the structure and function of MRP1/ABCC1 by re-creating the mutant protein and analyzing the protein in cell lines[24-39], it is challenging to investigate the synonymous or non-coding region polymorphisms due to complexity of their functional gene effect by different mechanisms such as transcription, splicing, RNA stability, and combined haplotype [40, 49, 53, 69-70].

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Biography

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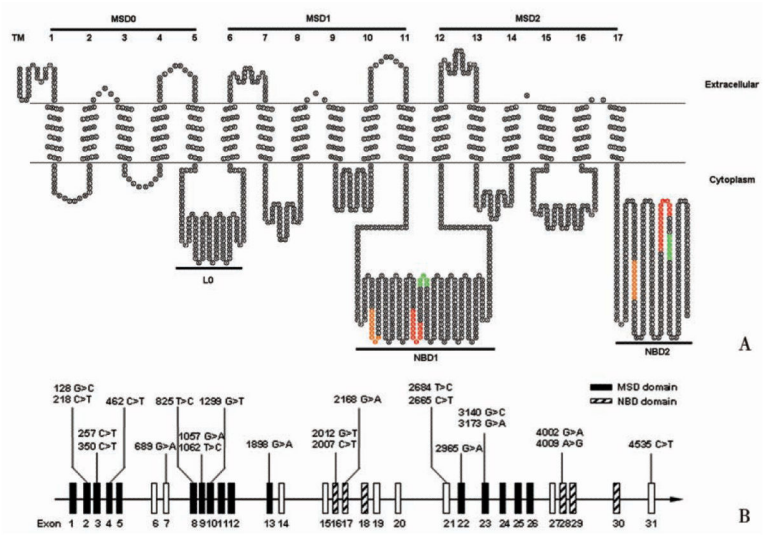

Fig. 1.

A:Schematic representation of the topological structure of MRP1/ABCC1 protein predicted using TOPO2 program with modification (http://www.sacs.ucsf.edu/TOPO-run/wtopo.pl). The consensus sequences of Walker A and B are highlighted in orange and green, respectively. The ABC-signature motif is highlighted in red. TM, transmembrane; MSD, membrane spanning domain; NBD, nucleotide-binding domain. B: Distribution of clinically relevant MRP1/ABCC1 exon polymorphisms.

Tab. 1

Clinically relevant substrates of MRP1/ABCC1 *

Type of substrates	Examples
Drugs	Anticancer drugs
	Vinca alkaloids: vinblastine and vincristine
	Epipodophyllotoxins: etoposide (VP-16) and teniposide
	Camptothecins: topotecan, irinotecan and SN-38
	Methotrexate and mitoxantrone
	Other drugs
	Anti HIV drugs; ritonavir and saquinavir
	Antibiotics: difloxacin and grepafloxicin
	Tyrosine kinase inhibitors: imatinib mesylate and gefitinib
Heavy metal anions	Arsenite
	Arsenate
	Trivalent and pentavalent antimonials
Glutathione conjugates(-GS)	Dinitrophenyl-GS
	Etacrynic acid-GS
	Doxorubicin-GS
	Cyclophosphamide-GS
	Melphalan-GS
	Aflatoxin B_1-epoxide-GS
	Hydroxynonenal-GS
	Prostaglandin A_2-GS
	Glutathione (GSH, GSSG)
Glucuronide conjugates (-G)	Bilirubin-G
	Estradiol 17βD-G
	Hyodeoxycholate-G
	Etoposide (VP-16)-G
	NS-38-G
Sulfate conjugates (-S)	Estrone-3-S
	Taurocholate-3-S
	Dehydroepiandrosterone-3-S
	Sulfatolithocholyl taurine
Folates	Folic acid
	L-leucovorin
Toxicants	Aflatoxin B1
	Methoxychlor
	Fenitrothion
Others	Leukotrienes C4, D4 and E4
	Curcuminoids
	Calcein

* The primary references are available from the following reviews. [1, 10, 19, 71]

Tab. 2

Association of *MRP1/ABCC1* polymorphisms with therapeutic response

Polymorphisms	rs number	Amino acid exchange	Location	Drugs	Disease/Observation	References
G2012T	rs45511401	Gly671Val	Exon 16	Atorvastatin	Hypercholesterolemia/No correlation	[42]
				Telatinib	Solid tumor/No correlation	[44]
				Induction Therapy	Leukemia/No correlation	[43]
G4002A	rs2239330	No change	Exon 28	Gemcitabine, cisplatin, taxane, methotrexate	Pancreatic cancer/No correlation	[45-47]
				Citalopram	Major depressive disorder/Strong correlation	[48]
G2168A	rs4148356	Arg723Gln	Exon 17	Platinum	Ovarian cancer/Correlation	[50]
				Taxane	Ovarian cancer/Correlation	[50]
A4009G	rs28364006	Alal337Thr	Exon 28	Methotrexate	Psoriasis/Correlation	[49]
IVS23 G-1960A	rs2238476	No change	Intron 23	Methotrexate	Psoriasis/Correlation	[49]
IVS9 T-176C	rs35592	No change	Intron 9	Methotrexate	Psoriasis/Correlation	[49]
T2684C		No change	Exon 21		Leukemic/No correlation	[43]
C2007T	rs2301666	No change	Exon 16		Leukemic/No correlation	[43]
G2012T	rs45511401	Gly671Val	Exon 16		Leukemic/No correlation	[43]
C2665T		No change	Exon 21		Leukemic/No correlation	[43]
IVS1 C-14840T	rsll9774	No change	Intron 1	Montelukast	Asthma/Correlation	[28]
				Zileuton	Asthma/Correlation	[29]
GCC repeat		No change	5′UTR	Azithromycin	Cystic fibrosis/No correlation	[72]
IVS18 C -30G	rs2074087	No change	Intron 18	Taxanes	Ovarian cancer/No correlation	[47]

Tab. 3

Association of *MRP1/ABCC1* polymorphisms with prognosis prediction

Polymorphisms	rs number	Amino acid exchange	Location	Disease/Observation	References
G2012T	rs45511401	Gly671Val	Exon 16	Neuroblastoma/Correlation	[52]
5′-UTR G-1666A	rs4148330	No change	5′UTR	Hepatocellular carcinoma/Correlation	[53]

Tab. 4

Association of *MRP1/ABCCl* polymorphisms with drug toxicity

Polymorphisms	rs number	Amino acid exchange	Location	Drugs	Drug toxicity/Disease/Observation	References
G4002A	rs2239330	No change	Exon 28	Irinotecan	Neutropenia/Solid tumor/Correlation	[54]
				Methotrexate	Overall MTX toxicity/Rheumatoid arthritis/No correlation	[46]
IVS11 -48C > T	rs3765129	No change	Intron 11	Irinotecan	Neutropenia/Solid tumor/Correlation	[54]
IVS9 A8G	rs35588	No change	Intron 9	Irinotecan	Neutropenia/Solid tumor/No correlation	[54]
T1684C	rs35605	No change	Exon 13	Irinotecan	Neutropenia/Solid tumor/No correlation	[54]
IVS30 A18G	rs212088	No change	Intron 30	Irinotecan	Neutropenia/Solid tumor/No correlation	[54]
IVS3 G-3198A	rsll075291	No change	Intron 3	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS4 G409A	rsl967120	No change	Intron 4	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS5 G413A	rs3784862	No change	Intron 5	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS5 A-7942G	rs246240	No change	Intron 5	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS5 G-1641A	rs3784864	No change	Intron 5	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS23 G-1960A	rs2238476	No change	Intron 23	Methotrexate	Hepatic and gastrointestinal toxicity/Psoriasis/ Correlation	[49]
IVS14 C115T		No change	Intron 14	Methotrexate	Overall MTX toxicity/Rheumatoid arthritis/No correlation	[46]
IVS18 C-30G	rs2074087	No change	Intron 18	Methotrexate	Overall MTX toxicity/Rheumatoid arthritis/No correlation	[46]
G2012T	rs45511401	Gly671Val	Exon 16	Doxorubicin	Cardiotoxicity/NHL/Correlation	[56]
IVS16 A1695T	rs3887412	No change	Intron 16	Vincristine	Peripheral neuropathy/Multiple myeloma/Correlation	[55]

Tab. 5

Association of *MRP1/ABCC1* polymorpliisms witli disease susceptibility and severity

Polymorphisms	rs number	Amino acid exchange	Location	Diseases	Phenotype/Observation	References
3′-UTRT866A	rs212090	No change	3′-UTR	Lung cancer	Susceptibility/Correlation	[58]
				COPD	Severity/Correlation	[61]
3′-UTR C543T	rs3743527	No change	3′-UTR	Lung cancer	Susceptibility/No correlation	[58]
3′-UTRT1512C	rs212091	No change	3′-UTR	Lung cancer	Susceptibility/No correlation	[58]
T825C	rs246221	No change	Exon 8	Autism	Susceptibility/No correlation	[73]
G2168A	r9tt48356	Arg723Gln	Exon 17	Lung cancer	Susceptibility/Correlation	[59]
5′-UTR G -260C	rs504348	No change	Promoter	Cystic fibrosis	Severity/Correlation	[60]
3′-UTR G3361A	rs4148382	No change	3′-UTR	COPD	Severity/Correlation	[61]
				Lung function	Severity/Correlation	[51]
5′-UTR C435G	rs504348	No change	5′-UTR	COPD	Severity/No correlation	[61]
IVS1 T5977G	rs4781699	No change	Intron 1	COPD	Severity/No correlation	[61]
IVS14 C-1575T	rs35621	No change	Intron 14	COPD	Severity/No correlation	[61]
				Lung function	Severity/Correlation	[51]
3′-UTR A2615G	rs212093	No change	3′-UTR	Lung function	Severity/Correlation	[51]