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Very important pharmacogene summary: *ABCB1* (*MDR1*, P-glycoprotein)

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ABCB1 description

ABCB1 (*MDR1*) is one of many ubiquitous adenosine triphosphate (ATP)-binding cassette (ABC) genes present in all kingdoms of life that is responsible for cellular homeostasis [1–3]. ABC genes encode transporter and channel proteins possessing multiple membrane-spanning domains that form a pore, and intracellular nucleotide-binding domains for ATP-dependent translocation of substrates or ions across the cell membrane [1,4,5]. Although bacterial ABC proteins function as both importers and exporters [6], all eukaryotic ABC proteins are efflux pumps [1,7]. *ABCB1* is one of 49 putative members in the superfamily of human ABC transporters [8,9] within subfamily B (*MDR/TAP*), which is one of seven phylogenetically distinct sub-families [4] with overlapping substrate specificity [10] (see Wageningen University website, www.nutrigene.4t.com/humanabc.htm).

Molecular and protein structure

ABCB1 was first cloned by Riordan *et al*. [11] in 1985. The gene lies less than 25 kb from *ABCB4* on chromosome 7q21.12 [UCSC Genome Browser, March 2006 Assembly (hg18)]. Analysis of human cell lines, liver tissue, and lymphocytes consistently show *ABCB1* to contain 29 exons in a genomic region spanning 209.6 kb [12] (GenBank accession number NT_007933). Two 5′ exons are untranslated. Two primary transcriptional start regions exist: a proximal promoter in exon 1 and intron 1 for constitutive expression, and a cryptic distal promoter active in drug-selected cell lines and cancer patient samples for overexpression of the protein product. The *ABCB1* promoter region contains a few low-frequency polymorphisms and is relatively invariant compared with other genes in the genome [13].

The messenger RNA (mRNA) is 4872 bp in length, including the 5′ untranslated region (RefSeq accession NM_000927.3), which gives rise to a protein that is 1280 amino acids in

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length, named P-glycoprotein (P-gp) [12]. The secondary structure of P-gp reveals two homologous halves to the protein, each containing six transmembrane domains and a nucleotide-binding domain (see image from Fung *et al.* [14]). The existence and number of putative splice variants is undetermined [12]. Alternative transcripts for *ABCB1* have been predicted from sequence alignments with human complementary DNA (search *ABCB1* at www.ncbi.nlm.nih.gov/IEB/Research/Acembly in AceView), protein sequences, and expressed sequence tags [15]. P-gp is posttranslationally modified by phosphorylation and *N*-glycosylation. Differential phosphorylation of P-gp by kinases has been shown to influence P-gp activity [16,17]. A number of mechanistic observations have been made from low-resolution crystal structures for P-gp in bacteria [18] and Chinese hamster ovary cells [2], and from a high-resolution structure of the mouse homolog with 87% sequence identity to humans (see Protein Data Bank accession numbers 3G60, 3G5U, 3G61 at www.rcsb.org) [19]. The 12 transmembrane helices form a toroidal protein with an aqueous pore (see image from Higgins *et al.*) [2,20]. Two nucleotide-binding domains for the protein lie in the cytoplasm. The pore is lined with hydrophobic and aromatic amino acids at the extracellular-facing half of the pore, whereas the cytosolic-facing portion of the pore contains polar, charged residues [19]. Structural analysis reveals two openings in the protein at the lipid bilayer to permit extraction of substrates directly from the membrane upon their passive diffusion into the cell (see image from Aller *et al.*) [2,18,19]. Several highly conserved residues within the pore are able to recognize a diverse range of substrates. The protein exhibits high conformational flexibility to allow for structural rearrangements in binding and effluxing substrates [19]. Substrate-bound images reveal the capacity for P-gp to distinguish stereoisomers and simultaneously bind multiple substrates at overlapping binding sites. The ability to bind substrates in close proximity to one another provides a mechanistic rationale for observed functional interactions between coadministered substrates (e.g. allosteric, competitive and noncompetitive inhibition, and cooperativity) [10,21,22].

Tissue distribution and function

P-gp is expressed in a polarized manner in the plasma membrane of cells in barrier and elimination organs, where it has protective and excretory functions [23]. It plays an important role in first-pass elimination of orally administered drugs to limit their bioavailability by effluxing drugs from the lumen-facing epithelia of the small intestine and colon, and from the bile-facing canaliculi of the liver. It eliminates substrates from the systemic circulation at the urine-facing side of the brush border membrane of proximal tubules in the kidney, and again through biliary excretion. It restricts the permeability of drugs into ‘sanctuary’ organs from the apical or serosal side of blood–tissue barriers (e.g. blood–brain, blood–cerebral spinal fluid, blood–placenta, blood–testis barriers) [24]. P-gp expression in the adrenal cortex is thought to play a role in hormone transport and homeostasis, and glucorcorticoid resistance [5,25]. In lymphocytes and other immunological and blood components, P-gp putatively plays a role in viral resistance and in trafficking cytokines and enveloped viruses [5,26]. P-gp is also thought to be important for steroid partitioning and lipid homeostasis in the periphery and central nervous system [25,27,28]. Intracellular P-gp with unknown function has been detected in the endoplasmic reticulum, vesicles, and the nuclear envelope, and has been associated with cell trafficking machinery [29]. Relevant to the clinical challenge of MDR, P-gp is overexpressed in numerous tissues transformed by cancer.

Physiological role

P-gp was discovered in 1970 by Biedler *et al.* [30] who observed the phenomenon of MDR conferred by a cell surface protein in mammalian cell lines. This membrane protein conferred a 2500-fold increase in drug resistance to actinomycin D and cross-resistance to a

single exposure of mithramycin, vinblastine, vincristine, puromycin, daunomycin, demecolcine, and mitomycin C. The 170 kD phosphoglycoprotein, or 'permeability' glycoprotein, was identified as the cause for reduced cellular drug exposure [31] by its active extrusion of drugs from the cell [32,33]. The physiological impact of this multidrug efflux pump was appreciated in 1994 by Schinkel *et al.* [34] who observed a 100-fold increase in the penetration of antiparasitic medication, ivermectin, into the brain of genetically engineered mice lacking *abcb1.* Animals naturally deficient for *abcb1* were also found to exhibit neurological and fetal drug toxicity because of a breach in the blood–brain and blood–placenta barriers in which P-gp is normally active [35,36]. A 4-bp deletion (*ABCB1-1 Delta*) was subsequently identified as the cause of the nonfunctioning allele in dogs [36], which led to the proposed dosing changes in veterinary medicine [37,38]. In humans, spontaneous deletion of *ABCB1* has not been described, but a nonfunctional variant was found in two heterozygous individuals in which a single nucleotide polymorphism (SNP), T3587G, results in an isoleucine to serine change at residue 1196 in the second ATP-binding domain of P-gp [39]. However, in one heterozygous subject the SNP was not shown to affect the clearance of the P-gp substrate, SN-38, after parenteral irinotecan administration [39,40]. The frequency of the 3587G allele was 1 : 300 in a Japanese population; therefore, homozygotes with two copies of the nonfunctioning 1196Ser allele would be very rare (1 : 100 000).

Numerous common coding variants in *ABCB1* have been studied for their potential influence on P-gp expression, function, and disease risk. Genetic associations with molecular or clinical phenotypes have largely been inconsistent (see *ABCB1* genetics) [41–43]. As a result, no adjustments in drug dosing have been recommended for individuals carrying sequence variants of *ABCB1* in humans, and replication studies are needed to understand the influence of *ABCB1* genetics on disease susceptibility. Current clinical considerations for P-gp are therefore related to its important role in (i) MDR and (ii) drug–drug interactions, derived primarily from its broad substrate specificity and variable intrinsic and drug-induced expression [44].

Compounds that interact with P-gp

P-gp recognizes and effluxes a multitude of structurally and biochemically unrelated substrates (cyclic, linear, basic, uncharged, zwitterionic, negatively charged, hydrophobic, aromatic, nonaromatic, amphipathic) from 250 to 4000 molecular weight [10,29,45], sufficiently indeterminate to predict in drug design [7]. Substrates include xenobiotics, endogenous compounds [e.g. peptides (including β-amyloids), steroid hormones, lipids, phospholipids, cholesterol, and cytokines] [22], pharmaceuticals [46], neutraceuticals (e.g. St John's wort), dietary compounds (e.g. grapefruit juice, green tea) [47,48], and other compounds, which may also modulate P-gp activity [49] (Table 1). P-gp compounds can act as substrates, inhibitors, inducers, and repressors; and citations refer to P-gp compounds as being in more than one category, depending on the circumstance [10]. Modulation of *ABCB1* gene expression and/or P-gp activity by various mechanisms consequently influences P-gp-mediated drug disposition.

Repressors of P-gp, including certain antineoplastic agents that act at nuclear receptors [73], or endotoxin [74], cobalamin [50], and atorvastatin [75,76], potentiate the action of substrates; whereas rifampin (rifampicin) [51] and cell stress signals induce P-gp-mediated drug resistance [29,50,75]. Another mechanism for P-gp-related pharmacoresistance to cytotoxic agents is hypothesized to relate to the cell stress signals they induce [52,77]. Upregulation of *ABCB1* gene expression can occur at gene promoter sequences through transactivation [10,47,78], for example, by the pregnane X receptor (*NR1I2*) gene in response to substrates that may have overlapping specificity for P-gp [29]; or induction can

occur independent of nuclear receptors [79]. Alternatively, epigenetic inactivation of P-gp can occur by DNA methylation at specific nucleotide sequences within the promoter sequence, called CpG islands, as has been observed in some cancer tissues [80]; or downregulation of P-gp can also occur by mechanisms other than by DNA methylation, for example, in response to cobalamin, a vitamin B-12 derivative [50].

Drug interactions

Many studies have characterized the interactions among P-gp compounds, as concomitant administration can substantially alter the pharmacokinetics of the compounds involved [81]. Research has focused on both the deleterious and beneficial effects of interactions among P-gp compounds: (i) interactions that potentially affect drug safety and efficacy [22], and (ii) interactions exploited to optimize drug delivery (see MDR).

Drug safety and efficacy are major health concerns, particulary for drugs with a narrow therapeutic index and/or large clinical effect [82]. A number of drug interactions of clinical relevance are cited as warnings in the drug labels by the Federal Drug Administration. For example, the drug label for the contraceptive, Trinessa (Watson Pharma, Inc.), warns against potential drug inefficacy when coadministered with compounds that induce P-gp (e.g. rifampin, St John's wort, protease inhibitors, carbamazepine, and barbiturates). The drug label for the antidiarrheal, loperamide (Imodium, McNeil Consumer Healthcare), warns against neurotoxic side effects when coadministered with P-gp inhibitors (e.g. quinidine, ritonavir) as this gut-targeted optiate relies upon P-gp to prohibit intestinal absorption and entry into the central nervous system [83].

Interactions between compounds are substrate-specific, concentration-dependent [22], and tissue-specific [84]. For example, unlike the drug-potentiating interaction between quinine [85,86] or ritonavir [87] on loperamide, the potent P-gp inhibitor, tariquidar, does not produce the same analgesic effects, despite its efficient inhibition of P-gp in lymphocytes. This is presumably because of tissue-specific factors [84]. Concentration is another important determinant of drug interactions. For example, at the therapeutic concentration for the β blocker and P-gp substrate, propranolol (Innopran Xl, Reliant Pharmaceuticals Inc.), modulation of P-gp by other compounds does not affect propranolol disposition. Other influences include key pharmacokinetic genes that affect the disposition of substrates for P-gp. For example, P-gp and cytochrome P450 3A4 metabolizing enzyme (*CYP3A4*) overlap in tissue distribution and specificity for a substantial number of substrates, inducers, and inhibitors [88]. Furthermore, genes responsible for the disposition of a drug can act synergistically [89]. Marchetti *et al.* cite clinically relevant drug interactions influenced by the interplay of *ABCB1* with other genes in the disposition of P-gp compounds, such as paclitaxel and cyclosporine A (CsA) (through *CYP3A4* inhibition), digoxin and rifampin (through *CYP3A4* induction), and topotecan and elacridar (through *ABCG2* inhibition) [90].

Multi-drug resistance

Drug resistance by multiple mechanisms [46,52,91–93] accounts for more than 90% treatment failure in metastatic cancer [92,94]. MDR from intrinsic (drug-naive) and acquired (drug-induced) overexpression of P-gp [93] is a notable impediment to brain-targeted therapies (e.g. antiepileptics, neuroantiretrovirals) and chemotherapies [7,73,95,96]. P-gp expression is predictive of between 30 and 40% of treatment failure in epilepsy [5,47,97] and is correlated with drug nonresponse in acute myeloid leukemia [98], childhood neuroblastoma [99] and sarcoma [100], and other cancers [101]. The relationship between P-gp expression with nonresponse to chemotherapy and drug-induced upregulation of P-gp according to tumor type is reviewed nicely by Takara *et al.* [46].

Known interactions between substrates and modulators of P-gp have been exploited in drug development and treatment protocols to overcome low drug delivery. Inhibitors of P-gp, such as formulary excipients [e.g. tocopherol (vitamin E preparation, TPGS 1000) and Cremophor EL] [53–55] and approved drugs, are clinically used to enhance the delivery of P-gp substrates. Verapamil and CsA are examples of the first-generation of 'P-gp reversal agents' [46] used in combination with antineoplastic agents, such as doxorubicin, vincristine, and paclitaxel to enhance bioavailability [102–106]. However, dose-limiting toxicity of early reversal agents and formulary excipients has led to the development of second-generation antagonists of P-gp, such as valspodar (PSC833), with ten-fold greater potency for P-gp and less side effects [91,107,108].

Substrate interactions with other pharmacokinetic genes affecting the absorption, distribution, metabolism, elimination (ADME) of drugs play a significant role in the effectiveness of P-gp reversal agents. Substrate specificity for multiple ADME genes can be advantageous or disadvantageous in adjunct therapy. For example, the mechanism by which both CsA and valspodar enhance the bioavailability of paclitaxel is owed in part to their inhibition of *CYP3A4* [109,110], *ABCC2* [111], and other elimination-pathway genes (e.g. *CYP2J2*) [112] for paclitaxel. In contrast, nonspecific inhibition of multiple elimination-pathway genes involved in drug clearance can lead to side effects associated with the prolonged half life of the primary drug. As more is known about the gene expression profile of specific pathological conditions, P-gp reversal agent use can be optimized. For example, where redundant drug resistance mechanisms are operant, as with *ABCB1, ABCC1* (MRP1) and *ABCG2* (BCRP) in acute myeloid leukemia [52,113], inhibition of multiple MDR genes can be beneficial. Characterization of the genes responsible for pharmacoresistance in a particular disease or disease stage is used to inform drug treatment (see P-gp-guided therapy). Also, third-generation P-gp reversal agents [e.g. tariquidar (XR9576), zosuquidar (LY335979), laniquidar (R101933), and ONT-093 (OC-144-093)] with greater specificity for Pgp and less affinity for other ADME genes have been developed [91,114]. A number of the newer-generation Pgp reversal agents [e.g. tariquidar, valspodar, zosuquidar, ONT-093, elacridar (GF120918, GG918), and CBT-1] has shown promise in *in vitro* and early trials for epilepsy and cancer treatments [91,96,115–117].

P-gp-guided therapy

Techniques to characterize the mechanisms of drug resistance that are operant in individual patients inform treatment with P-gp antagonists as adjuncts in the appropriate case. Single photon emission computed tomography analysis of the P-gp substrate, ^{99m}Tc sestamibi, is used to probe P-gp-positive cells as a way to predict pharmacoresistance to antiepileptic [96] and antitumor drugs [118,119]. This technique is shown to be a cost-effective method for pre-selecting responders to lung cancer treatment [56]. ^{99m}Tc sestamibi is also used to monitor the efficacy of P-gp reversal agents in sensitizing pharmacoresistant cells to P-gp substrates [120]. A phase I clinical trial using vinblastine and valspodar reversal agent, and ^{99m}Tc sestamibi imaging to monitor the sensitization of P-gp-positive cells, showed increased ^{99m}Tc sestamibi retention in tumor cells of metastatic renal carcinoma patients (and therefore presumably, cytotoxic agent, vinblastine) [118]. Tariquidar/taxane/anthracycline polytherapy guided by serial ^{99m}Tc sestamibi tumor scans is currently in a phase II clinical trial for breast cancer with acquired pharmacoresistance (search Clinical trial ID: NCT00048633 at *http://clinicaltrials.gov*). Results to date show that cancers exhibiting *de novo* pharmacoresistance (drug naive), such as leukemias, myelomas, lymphomas, and breast and ovarian cancers, are most amenable to P-gp modulation with reversal agents as adjunct therapy.

ABCB1 genetics

Disease-causing mutations in 14 of the ABC superfamily members have been described, as in *CFTR* (ABCC7) for cystic fibrosis, *ABCA4* for macular degeneration, *ABCC2* and *ABCB11* for biliary dysfunction, and *ABCA1, ABCG5*, *ABCG8*, and *ABCD1* for fatty acid/lipid disorders [4]. A large corpus of the literature about sequence variations for *ABCB1* exists, however there is no clear consensus regarding the contribution of *ABCB1* variation to disease risk [41,121,122]; and despite evidence for interindividual variability in *ABCB1* expression and function [14,123,124], the genetic contribution is unclear [41]. A great number of studies have been carried out to establish the role of *ABCB1* genetics in various phenotypes such as P-gp expression, function, drug response, and disease susceptibility with little consensus. Here we limit mentioning to genotype–phenotype associations that are substantiated by study replication, meaningful sample size, and appropriate multitesting correction. See Leschziner *et al*. [41] for a detailed review of the controversial literature regarding genetic association of *ABCB1* SNPs and haplotypes with P-gp expression, activity, drug response, and disease risk.

As of 30 April 2009 for build 130 of the Single Nucleotide Polymorphism database (dbSNP) [14], there are 1279 SNPs in the *ABCB1* gene region, 62 of which are coding (22 synonymous, 41 nonsynonymous, and one in the start codon). The number and frequency of SNPs observed varies by ethnicity. Excluding SNPs below 5% allele frequency, there are approximately 124 SNPs observed in Caucasians, 134 in African–Americans, 153 in Chinese, and 166 in Japanese (see HapMap release 27 at www.hapmap.org). Additional information is available at the University of California, San Francisco Pharmacogenetics of Membrane Transporters Database (pharmacogenetics.ucsf.edu).

About 2.6 times fewer (n=4) SNPs occur in the transmembrane domains compared with the intracellular and extracellular regions of the protein. None of the 3′ untranslated region SNPs are reported to alter mRNA stability [14]. The three most common SNPs in the protein coding region are rs1128503 (1236T > C, Gly412Gly), rs2032582 (2677T>G/A, Ser893Ala/Thr), and rs1045642 (3435T > C, Ile1145Ile) [125], according to the National Center for Biotechnology Information build 130 of dbSNP. These three SNPs have been the focus of many pharmacokinetic and disease association studies with controversial results [41].

Common coding SNPs

Rs1128503 (1236T>C, mRNA 1654T>C, Gly412Gly)

According to dbSNP, the C allele of the synonymous (Gly412Gly) SNP, rs1128503 (1236T>C), ranges in allele frequency from 30 to 93% depending upon the ethnic population, with C being the minor allele in Asians, and T being the minor allele in Africans. Although many studies have undertaken characterizing potential phenotypic associations for this silent SNP, the literature bears no consensus [41]. As a brief illustration, studies found increased drug exposure or drug response associated with the 1236 CC genotype [126], the 1236 TT genotype [127,128], or no genetic effect was found with regard to rs1128503 [129].

Rs2032582 (2677T>G/A, mRNA 3095T>G/A, Ser893Ala/Thr)

The triallelic SNP, rs2032582 (2677T > G/A, Ser893Ala/ Thr), has been well studied because it is a common amino acid change in P-gp. The 893 serine-bearing 2677T allele frequency varies as much as 2–65% among world populations, according to data from the International HapMap project (www.hapmap.org). The frequency of 893Ala/Ala homozygotes (2677 GG genotype) is greater than 81% in African populations, compared with 10–32% in American Indians, Mexicans, Italians, Asians, and Caucasians. According

to dbSNP, the 893 threonine-bearing 2677A allele is relatively uncommon [130,131], ranging from 0 to 17% in different ethnic populations.

Despite a large number of studies testing potential phenotypic associations with this nonsynonymous SNP, the literature is inconclusive [41,57,132]. To illustrate briefly, evidence exists in favor of [133,134] and against [135,136] the association of the 893Ser allele with altered P-gp activity and expression [41]; 893Ser has been associated with an increase [127,131], decrease [133], and no change [129,137–141] in drug exposure and drug effect [41]. Studies for clinical outcome and disease risk are similarly discordant [41]. As a brief example, research in drug treatment and disease risk for the related conditions of inflammatory bowel disease, Crohn's disease, and ulcerative colitis has implicated the 893Ala allele [142], the 893Ser/Ser genotype [143], and has shown no genotypic effect with regard to rs2032582 [144,145].

Rs1045642 (3435T>C, mRNA 3853T>C, Ile1145Ile)

The synonymous SNP, rs1045642 (3435T>C), exhibits larger interethnic allele frequency differences, with the 3435C allele ranging between 34 and 90% across populations [57,58,132]. In 2000, a study by Hoffmeyer *et al*. [146] implicated the 3435T allele with altered P-gp function, showing association of the 3435 TT genotype with low expression of P-gp in the gut and increased plasma levels of digoxin relative to the 3435 CC genotype. This finding generated much interest in this silent mutation with regard to P-gp expression and activity; however, replication studies have not borne out this and many other phenotypic associations [41]. To illustrate briefly, studies have associated the 3435 TT genotype with decreased [125,147–149] and increased [58] expression of P-gp, and no genotypic effect [135]. Likewise, studies have shown increased drug exposure associated with the 3435T allele or TT genotype [150–152], the 3435 CC genotype [148,153,154], and no genetic effect with regard to rs1045642 [137,140,141,152,155–158]. Association studies for clinical outcomes are similarly inconclusive. Briefly, there is evidence for [159,160] and against [161] the association of 3435 CC with drug response in epilepsy, and no genetic effect with regard to rs1045642 [162,163].

ABCB1 haplotypes

Closely positioned sequence variants tend not to segregate independently with each generation because of linkage disequilibrium (LD). As a result, multiple variant alleles are inherited together on the same physical chromatid in a particular pattern. That is to say that for linked variant alleles, the occurrence of one variant allele informs the valence of other alleles with a given predictability. For example, the three most common coding SNPs at nucleotides 1236, 2677, and 3435 are in high LD [15] and are observed most frequently as either the 893Ala-containing CGC haplotype or 893Ser-containing TTT haplotype in most ethnic groups [133,139,164]. Other observed haplotypes extend beyond the exonic region of *ABCB1* [165]. Leschziner *et al*. [15] observed LD extending 75 kb, linking 3′ variant alleles of *ABCB1* to coding variant alleles of the adjacent ABC transporter gene, *ABCB4*.

Haplotype structure relates to the location of recombination hot spots and ancestry-specific patterns of LD [165,166]. Tang *et al*. [164] observed ethnic-specific LD blocks at the *ABCB1* locus that are 80, 60, and 40 kb in length and distinguish Chinese, Malay, and Indian populations, respectively. Similarly, comparison of the mutation rate between Beninese Africans (one variant per 224 bp) and African–Americans (one variant per 172 bp) reflects an admixture in the US cohort that differentiates the *ABCB1* haplotype structure in these populations [167]. Accordingly, haplotype frequencies differ by ethnic group. For example, the 893Ser-containing TTT haplotype occurs approximately 2–5-fold less often in African– Americans [133,139] than in Caucasians [133,139] and Asians [164].

A haplotype by definition is not bound by a gene region, but gene-specific haplotypes can acquire allelic designations in the literature. Sequence analysis of *ABCB1* in different ethnic groups has been performed [15,40,133,139,164,167,168] and led to the designation of 'star alleles' [40,133,139], as explained by Robarge *et al.* [169]. Briefly, the designation of *ABCB1* star alleles follows rules established by the Cytochrome P450 Allele Nomenclature Committee and others for naming haplotypes observed for cytochrome P450, uridinediphosphate-glucuronosyltransferase, *N*-acetyltransferase, and aldehyde dehydrogenase [169,170] genes. Star alleles are defined relative to an arbitrarily established reference sequence, denoted as *1. *ABCB1**1 contains 1236C, 2677G (893Ala), and 3435C. Many star allele designations for *ABCB1* are currently not harmonized in the literature. To illustrate briefly, *ABCB1**2, as defined by Kim *et al.* [133], harbors three coding variants, namely 1236T, 2677T (893Ser), and 3435T; whereas *ABCB1**2, as named by Kroetz *et al.* [139], contains 3435T [and is a reference for 1236C and 2677G (893Ala)]. *ABCB1**13 per Kroetz *et al.* [139] [1236T, 2677T (893Ser), 3435T, and three intronic SNPs] is most similar to *ABCB1**2 defined by Kim *et al.* [133] as they are indistinguishable in terms of the coding region and amino acid sequence.

The vast majority of haplotype studies for *ABCB1* do not take into account all segregating sites that are used to distinguish *ABCB1* star alleles, but interrogate a select few variants. Genotyping the three most common *ABCB1* SNPs at 1236, 2677, and 3435 captures a large portion of observed population haplotypes [133,139,171]. Haplotype association studies for *ABCB1* have been inconclusive [41]. To illustrate briefly, the 893Ser-bearing TTT (1236, 2677, 3435) haplotype was associated with increased irinotecan levels [40], but enhanced fexofenadine elimination [133] and increased pharmacoresistance to antiepileptic treatment was associated with homozygous 893-Ala-bearing CGC/CGC individuals in one study [172], but with CGC and 893Ser-bearing TTT haplotypes in another study [173]. However, worth mention is the replication of an association between the 893Ser-bearing TTT (1236, 2677, 3435) haplotype and increased digoxin exposure in 195 Europeans [174] and in a small study of 12 Chinese [175].

To investigate the regulatory impact of promoter variants on functional phenotypes, haplotype analysis of the promoter region has also been performed [13,149,171,176]. Wang et al. [13] observed a haplotype formed from eight low-frequency variants (< 5% minor allele frequency) in the promoter region that accounted for 85% of all haplotypes observed in five ethnic groups. They functionally characterized promoter haplotypes observed in Chinese, Malays, Indians, European Americans, and African–Americans using an in-vitro reporter assay and found significant ethnic-specific differences in promoter activity, although activity differed by the cell line used in the assay (presumably because of cell-specific regulatory factors). Other work has been done to understand the relationship between regulatory and coding variants for *ABCB1* and their potential association with endo-phenotypes. Takane *et al.* [149] showed that variation in promoter haplotype activity was independent of variation at the synonymous 3435 SNP, and the methylation status of the proximal promoter did not correlate with *ABCB1* mRNA expression. Jiang *et al.* [171] found an association between the promoter methylation status and variation in coding SNPs for *ABCB1*. They showed that lower promoter methylation was associated with the 3435 TT and 893Ala-containing 2677 genotypes, whereas the 893Ser-containing TTT (1236, 2677, 3435) haplotype was associated with higher methylation. More research is needed to elucidate the functional relevance of regulatory variants for *ABCB1* and their potential value to predicting P-gp-related phenotypes.

Despite much work to ascertain the genetic contribution of *ABCB1* on drug disposition and disease susceptibility, the accumulation of studies to date are unclear. Until data are amassed

to form a consensus about the role of genetics in P-gp-related phenotypes, the primary clinical focus on P-gp relates to its role in (i) MDR and (ii) drug–drug interactions [44].

Additional information is presented at the Pharmacogenomics Knowledge Base (PharmGKB) website (www.pharmgkb.org) in a search for *ABCB1*, accession number PA267, and at www.pharmgkb.org/search/annotatedGene/abcb1/index.jsp.

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Table 1

Compounds that interact with P-glycoprotein

P-gp substrates
Actinomycin D, Aldosterone, ALLM peptide, ALLN peptide, Amitriptyline, Amprenavir, Atorvastatin, β-amyloid, Bromperidol, Calcein acetoxymethylester, Carbamazepine, Celiprolol, Chloropromazine, Clopidogrel, Cimetidine, Citalopram, Colchicine, Corticosterone, Cortisol, Cyclosporine A, Daunorubicin, Dexamethasone, Digoxin, Diltiazem, Docetaxel, Domperidon, Doxycycline, Doxorubicin, Erythromycin, Etoposide, Fexofenadine, Grapefruit juice, Gramacidin D, Gramacidin S, Imatinib, Indinavir, Irinotecan, Itraconazole, Ivermectin, Ketoconazole, Lamotrigine, Lansoprazole, Levetiracetam, Levofloxacin, Loperamide, Losartan, Lovastatin, Melphalan, Methylprednisolone, Mevinolin, Mitomycin C, Mitoxantrone, Morphine, Nelfinavir, Omeprazole, Ondansetron, Paclitaxel, Pantoprazole, Pentazocine, Phenobarbital, Phenothiazine, Phenytoin, Propanolol, Quinidine, Ranitidine, Rifampicin, Ritonavir, Saquinavir, short chain lipids, Simvastatin, Sirolimus, Sparfloxacin, Tacrolimus, Talinolol, ^{99m}Tc-MIBI, Teniposide, Terfenadine, Tetracycline, Topotecan, Valspodar, Vecuronium, Verapamil, Vinblastine, Vincristine
P-gp inhibitors
Amiodarone, Amitriptyline, Astemizole, Atorvastatin, Bepridil, Biricodar, Bromocriptine, Carotenoids, Carvedilol, Chlorpromazine, Clarithriomycin, Cobalamin, Cortisol, Cremophor EL, Curcumin, Cyclosporine A, Desipramine, Dietary antioxidants, Diltiazem, Dipyridamole, Disulfiram, Elacridar, Erlotinib, Erythromycin, Felodipine, Fluoxetine, Flupenthixol, Fluphenazine, Gefitinib, Haloperidol, Indinavir, Itraconazole, Ketoconazole, Laniquidar, Lansoprazole, Leupeptin, Lonafarnib, Maprotiline, Mefloquine, Midazolam, Mifepristone, Natural diterpenes, Natural triterpenes, Nelfinavir, Nicardipine, Nitrendipine, ONT-093, Omeprazole, Pantoprazole, Paroxetine, Pentazocine, Progesterone, Propafenone, Quinidine, Quinine, Reserpine, Ritonavir, Saquinavir, Sertraline, Simvastatin, Sirolimus, Spironolactone, Tacrolimus, Tamoxifen, Tariquidar, Terfenadine, Tetrabenzine, Tocopherol, Valinomycin, Valspodar, Vanadate, Verapamil, Vinblastine, XR9051, Zosuquidar
P-gp inducers/stimulators
Amiodarone, Amprenavir, Bromocriptine, Chlorambucil, Cisplatin, Clotrimazole, Colchicine, Cyclosporine A, Daunorubicin, Dexamethasone, Diltiazem, Doxorubicin, Efavirenz, Erythromycin, Etoposide, FCME peptide, Flurouracil, GGCME peptide, Hydroxyurea, Insulin, Indinavir, Methotrexate, Midazolam, Mitoxantrone, Morphine, Nelfinavir, Nicardipine, Nifedipine, Phenytoin, Phenothiazine, Prenylcysteines, Probenecid, Reserpine, Retinoid acid, Rifampicin, Ritonavir, Saquinavir, St John's wort, Tacrolimus, Tamoxifen, Verapamil, Vinblastine, Vincristine, Yohimbine
References: [3,5,10,22,43,50–72]