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RESEARCH PAPER

ABCG2 and *SLCO1B1* gene polymorphisms in the Croatian population

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ABSTRACT

Background: Organic anion-transporting polypeptide 1B1 (OATP1B1) and the ATP-binding cassette subfamily G member 2, ABCG2, are important transporters involved in the transport of endogenous substrates and xenobiotics, including drugs. Genetic polymorphisms of these transporters have effect on transporter activity. There is significant interethnic variability in the frequency of allele variants.
Aim: To determined allele and genotype frequencies of *ABCG2* and *SLCO1B1* genes in Croatian populations of European descent.
Subjects and methods: A total of 905 subjects (482 women) were included. Genotyping for *ABCG2* c.421C > A (rs2231142) and for *SLCO1B1* c.521T > C (rs4149056), was performed by real-time polymerase chain reaction (PCR) using TaqMan® DME Genotyping Assays.
Results: For *ABCG2* c.421C > A, the frequency of CC, CA and AA genotypes was 81.4%, 17.8% and 0.8% respectively. The frequency of variant *ABCG2* 421 A allele was 9.7%. For *SLCO1B1* c.521T > C, the frequency of TT, TC and CC genotypes was 61.7%, 34.8% and 3.5% respectively. The frequency of variant *SLCO1B1* 521 C allele was 20.9%.
Conclusion: The frequency of the ABCG2 and SLCO1B1 allelic variants and genotypes in the Croatian population is in accordance with other European populations. Pharmacogenetic analysis can serve to individualise drug therapy and minimise the risk of developing adverse drug reactions.

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Introduction

Membrane-bound proteins (transporters), which control access of important nutrients and ions into the cell, excrete cellular waste, environmental toxins and other xenobiotics, are also important determinants in the absorption, distribution and excretion of drugs (International Transporter Consortium 2010). Through the mechanisms of uptake and excretion, transporters play an important role in modulating the adverse effects of these compounds on the body. While metabolic enzymes are predominantly found in the liver and intestine, transporters are located in many tissues, including intestinal, renal and hepatic, and affect drug pharmacokinetics (PK) and pharmacodynamics (PD). Depending on the transmission direction across the cell membrane, the transporters are divided into those that carry in (influx) or take out (efflux) substrates from the cell (Franke et al. 2010). They also differ in transmission mode depending on energy because they can transfer substrates with or without energy consumption. Furthermore, similar to metabolising enzymes, transporters can be inhibited, and some of them are also inducible (Endres et al. 2006; Tirona 2011; Bruhn and Cascorbi 2014; Bruckmueller and Cascorbi 2021a).

According to the HUGO Gene Nomenclature Committee (HGNC), there are more than 660 transporters that can be classified into one of two superfamilies: ATP-binding cassette (ABC) transporters or Solute Carriers (SLC) (HGNC 2022). For more than two decades, The International Transporter Consortium representing scientists from academia, industry, and regulatory bodies, have been examining transporters' relevance for PK and PD (Huang et al. 2010; Hillgren et al. 2013; Zamek-Gliszczynski et al. 2018). Variability in drug exposure and response can be modulated by a transporter's gene polymorphism and drug–drug interactions (DDIs) (Endres et al. 2006; Yee et al. 2018).

The two very important polymorphic transporters associated with the variable pharmacokinetics of drug substrates are the ATP-binding cassette subfamily G member 2 (ABCG2), known as the breast cancer resistance protein (BCRP), encoded by the *ABCG2* gene, and an organic anion transporting polypeptide 1B1 (OATP1B1), encoded by the *SLCO1B1* gene. Genetic variations of these two transporters, which vary across populations, can serve as genetic markers

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in the individualisation and optimisation of pharmacotherapy. The genotyping of *ABCG2* and *SLCO1B1* can help achieve optimal therapeutic effects since the phenotypes associated with genetic variations contribute to differences in PK, PD and adverse drug reactions (ADRs) risk (Hirota et al. 2020; Turner, Fontana, et al. 2020; Turner, Radman, et al. 2020) and the influence on drug–drug, drug–gene and drug–drug–gene interactions are also observed (Verbeurgt et al. 2014; Malki and Pearson 2020; Bruckmueller and Cascorbi 2021b). All of the above can have a significant impact on the efficacy and safety of pharmacotherapy with the drug substrates. Clinically relevant drug substrates of BCRP/ABCG2 are cytostatics, such as camptothecin analogues (diflomotecan, irinotecan, topotecan), methotrexate, mitoxantrone, tyrosine kinase inhibitors (TKIs, e.g. erlotinib, gefitinib, imatinib, nilotinib), hypolipidemic (rosuvastatin, ezetimibe, fibrates), proton pump inhibitors (PPIs, e.g. pantoprazole), anticoagulants (apixaban and rivaroxaban), and cyclosporine (Mao and Unadkat 2015; Hira and Terada 2018; Heyes et al. 2018; Safar et al. 2019). Clinically relevant drug substrates of OATP1B1 are antibacterial drugs (benzylpenicillin, cefditoren, rifampicin), cytostatics (SN-38, pazopanib), protease inhibitors (darunavir, lopinavir) and hypolipidemics (atorvastatin, pravastatin, rosuvastatin, ezetimibe) (Niemi et al. 2011; Gessner et al. 2019).

The genetic structure of the Croatian population agrees with its geographical position at the crossroads of Central and Southeast Europe, on the coast of the Adriatic Sea. The majority of the inhabitants of Croatia are Croats (90.4%), followed by Serbs, Bosnians, Italians, Albanians, Hungarians, Slovenes, etc. Moreover, different studies testify that chromosome variants of Croatians can be adequately explained within typical European maternal and paternal genetic landscapes, while the observed structuring of Y chromosomal variance reveals an evident Slavic component in the paternal gene pool of Croatian men (Peričić, Barać Lauc et al. 2005; Perićić, Lauc et al. 2005).

Given that a clear link has been established between genetic defects in drug-metabolising enzymes and drug transporters and their impact on the efficacy and toxicity of certain drugs, the clinical guidelines for healthcare professionals have been developed and published by different working groups and organisations (Wilke et al. 2012; Ramsey et al. 2014; Cooper-DeHoff et al. 2022; DPWG 2022) to reduce the incidence of ADRs and associated costs. It has been documented for ADRs to be the fourth leading cause of death in hospitalised patients in the United States (Lazarou et al. 1998). Consequently, some of the guidelines have been included in Patient Information Leaflets (PILs) and Summaries of Product Characteristics (SmPCs) by regulatory bodies, such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Ehmann et al. 2015; Skvrce et al. 2020; FDA 2021; PharmGKB 2021).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international consortium with the aim of transferring knowledge and using pharmacogenomic testing results for clinical purposes. One of the obstacles to implementing pharmacogenomic testing in clinical practice is the difficulty in transferring genetic results into specific drug prescribing decisions. The CPIC's goal is to address this barrier to the clinical implementation of pharmacogenomic tests by creating and publishing freely available, peer-reviewed, evidence-based, updated and detailed guidelines for application in clinical practice (CPIC 2022). The most recent CPIC guidelines published in January 2022 replace the original 2012 guidelines and the updates from 2014 (Wilke et al. 2012; Ramsey et al. 2014; Cooper-DeHoff et al. 2022). In addition to the gene-based guideline for prescribing simvastatin based on SLCO1B1 genotype, recommendations based on *SLCO1B1* (simvastatin, rosuvastatin, atorvastatin, pravastatin, pitavastatin, fluvastatin, and lovastatin), *CYP2C9* (fluvastatin) and *ABCG2* (rosuvastatin) genotype, were added with the purpose of reducing the risk of statin-associated musculoskeletal symptoms. Furthermore, the guidelines are specifically used in cases when the results of pharmacogenomic tests are available to achieve the best possible clinical results with the most suitable statin in its optimal dose (Cooper-DeHoff et al. 2022).

BCRP/ABCG2

The ATP-binding cassette subfamily G member 2, ABCG2 (breast cancer resistance protein, BCRP, first discovered in breast cancer), is an efflux transporter expressed in the apical cell membranes of the placenta, brain, gastrointestinal tract, bile ducts, gallbladder, hepatocytes, renal tubules, stem cells, adrenal gland, prostate, testes, ovaries, uterus, central nervous system, endothelium of veins and capillaries and retinal capillary endothelial cells (Mao and Unadkat 2015; Fohner et al. 2017). It primarily functions as an apical efflux pump in enterocytes, as a canalicular efflux pump transporting substrates from hepatocytes into the bile, and as a transporter in the brain microvascular endothelial cells, renal proximal tubular cells and placental syncytiotrophoblasts. Therefore, this transporter contributes to the absorption, distribution, and elimination of compounds and tissue protection against xenobiotic exposure (Poirier et al. 2014).

The ABCG2 is considered the major determinant of renal and extrarenal urate secretion, and reduced-function *ABCG2* variants are linked to the risk for developing gout and hyperuricaemia (Matsuo et al. 2011; Fohner 2017). In addition, it is proven that ABCG2 has a crucial protective role in lowering cadmium's intracellular concentration, which could be negatively altered by the Q141K genetic variant (Wen et al. 2021). At first, it was thought that ABCG2 substrates include a wide range of cytostatics, such as mitoxantrone, irinotecan, methotrexate and tyrosine kinase inhibitors (TKIs) such as imatinib, gefitinib and nilotinib. However, BCRP substrates are not limited to chemotherapeutics but include different drugs like erlotinib, prazosin, rosuvastatin, cimetidine, apixaban, sulfasalazine, etc. (Giacomini et al. 2013; Mao and Unadkat 2015; Hira and Terada 2018; Heyes et al. 2018; Safar et al. 2019; Toyoda et al. 2019; Svedberg et al. 2020).

Many studies have highlighted the *ABCG2* c.421C > A variant as a determinant of pharmacokinetics, and the efficacy and toxicity of several drugs (Keskitalo, Pasanen, et al. 2009; Giacomini et al. 2013; Miroševic Skvrce et al. 2013; Hirota et

al. 2020; Mirošević Skvrce et al. 2015; Horsey et al. 2016; Hirota et al. 2020; Ganoci et al. 2021; Merćep et al. 2022). Single nucleotide polymorphism of *ABCG2* c.421C > A (rs2231142, p.Q141K) results in its reduced activity (Giacomini et al. 2013) – mRNA expression is maintained, but protein expression and function are reduced by 50-70% due to enhanced susceptibility to proteasomal degradation (Kondo et al. 2004; Furukawa et al. 2009). The frequency of the *ABCG2* variant allele in populations of European descent is estimated at around 10–15% (Robey et al. 2009; Sakiyama et al. 2014). The variant has a low incidence in individuals of African descent (2%), however, the incidence of about 30% has been established in the populations of East Asia, including Chinese and Japanese (Keskitalo, Pasanen, et al. 2009; Sakiyama et al. 2014; Hirota et al. 2020). First of all, the variant was associated with changes in response to the xanthine oxidase inhibitor, allopurinol, and statins (simvastatin, rosuvastatin and fluvastatin). The area under the curve (AUC) of inactive simvastatin lactone was 111% higher, and for fluvastatin and atorvastatin, 72% higher in subjects with *ABCG2* 421 A/A genotype compared to concentrations recorded in the carriers of 421 C/C genotype (Hofman et al. 2019). This increase is most likely due to the increased bioavailability of orally administered drugs due to a decrease in the efflux transporter function of the BCRP associated with the *ABCG2* 421 A/A genotype. Furthermore, the Keskitalo group reported that subjects with *ABCG2* 421 A/A genotype had a 72% greater mean area under the curve for atorvastatin and a 144% greater mean area under the curve for rosuvastatin than the ones who carried *ABCG2* 421 C/C genotype (Keskitalo, Zolk, et al. 2009). A study on the Japanese population showed that individuals with one variant allele for *ABCG2* 421 C > A had a 55% increase in atorvastatin's oral bioavailability compared to the wild type homozygotes (Tsamandouras et al. 2017). A recent meta-analysis on rosuvastatin pharmacokinetics showed that subjects carrying *ABCG2* 421 A variant allele have significantly increased AUC0-∞ and Cmax values compared to subjects with the CC genotype (Song et al. 2022). Similarly, a case-control study has shown the *ABCG2* c.421C > A variant allele was associated with adverse events of rosuvastatin (Merćep et al. 2022). Klarica Domjanovic et al. also revealed that interaction between variant *ABCG2* 421 A allele and the antiepileptic drug valproate was observed. Variant *ABCG2* 421 A allele and valproate interact in their effects on the disposition of lamotrigine. Lamotrigine mono-treated variant allele carriers (vs. wild type homozygotes) had 25% lower troughs, but they had 70% higher lamotrigine troughs when cotreated with valproate. Moreover, valproate increases lamotrigine troughs by 2.3-fold in wild type homozygotes and 5.2-fold in variant allele carriers (Klarica Domjanović et al. 2018). Another study showed that risperidone exposure and clinical response is conditional on the *ABCG2* 421 C > A polymorphism (Ganoci et al. 2021). A study in hypertensive breastfeeding women found that concentrations of nifedipine in breast milk in *ABCG2* 421 C/A genotype carriers were approximately three times greater than in *ABCG2* 421 C/C genotype carriers (Malfará et al. 2019). In addition, the variant is associated with the harmful effects of various anti-cancer drugs. It has been shown that *ABCG2* 421 C > A polymorphism had a significant impact on the induction of severe thrombocytopenia as the most common ADR of sunitinib and gefitinib (Cusatis et al. 2006; Low et al. 2016), while it was also associated with clinically significant changes in pharmacokinetics/pharmacodynamics of sulfasalazine (Gotanda et al. 2015). The real-world study linking genotype data of Finnish biobanks suggested possible association of *ABCG2* c.421C > A variant with bleeding events in apixaban and dabigatran users (Lähteenmäki et al. 2021). These results are in line with findings from studies of *ABCG2 c.421C > A* effect on plasma concentrations and apixaban clearance (Ueshima et al. 2018; Gulilat et al. 2020).

Due to the high frequency of alleles, especially in Asian populations, and the fact that the transporter is a determinant of the pharmacokinetics of many drugs, it is very likely that this variant will be increasingly important in personalised medicine (Robey et al. 2009; Miroševic Skvrce et al. 2013; Mirošević Skvrce et al. 2015; Hirota et al. 2020).

OATP1B1

Organic anion-transporting polypeptide 1B1 (OATP1B1; also known as OATP-C, OATP2, and liver-specific transporter 1), expressed on the basolateral membrane of human hepatocytes, represents one of the main influx transporters (Kalliokoski and Niemi 2009; Giacomini et al. 2010; Klaassen and Aleksunes 2010). OATP1B1, encoded by the *SLCO1B1* gene, is responsible for uptake into the liver of mainly weakly acidic drugs and endogenous compounds e.g. statins, methotrexate, rifampicin, SN-38 (the active metabolite of irinotecan), valsartan, bosentan, enalapril, HIV protease inhibitors and bilirubin, bile acids (taurocholic acid), conjugated steroids, and leukotriene C4 (Kalliokoski and Niemi 2009; Giacomini et al. 2010; Klaassen and Aleksunes 2010). More than 40 nonsynonymous variants (nsSNPs) have been identified in this transporter's gene, some of which result in reduced transport function (Kalliokoski and Niemi, 2009). For two genetic polymorphisms, *SLCO1B1* c.388A > G (p.Asn130Asp; rs2306283) and *SLCO1B1* c.521T > C (p.Val174Ala; rs4149056), it has been detected how they can change the transport capacity of OATP1B1 (Hagenbuch and Meier 2003; Hagenbuch and Meier 2004; Kalliokoski and Niemi 2009; Niemi et al. 2011; Horsey et al. 2016; Hirota et al. 2020; Turner, Radman, et al. 2020). *SLCO1B1* c.521T > C results in a change of the amino acid sequence, Val147Ala, and is associated with decreased membrane expression of the transporter, with consequently reduced transport capacity (Niemi et al.2011). Furthermore, this variant increases systemic exposure to simvastatin (221% increase in area under the curve, AUC, for 521 C/C homozygous patients) (Pasanen, Neuvonen et al. 2006). Therefore for individuals with reduced function of OATP1B1 who receive simvastatin, the Clinical Pharmacogenetics Implementation Consortium recommends a lower dose of simvastatin or use of alternative statins, such as rosuvastatin or pravastatin which are less affected by the *SLCO1B1* polymorphism (Niemi et al. 2011;

Kalliokoski and Niemi 2009; Elsby et al. 2012; Wilke et al. 2012). Besides statins, for drugs such as bosentan (Treiber et al. 2007), valsartan (Song et al. 2021), rifampicin (Li et al. 2012; Litjens et al. 2020) and methotrexate (Bielen et al. 2018; Roszkiewicz et al. 2021; Schulte et al. 2021), this variant might have a crucial role in toxicity. This is especially important in comedication with cyclosporine, which is a proven OATP1B1 inhibitor (Launay-Vacher et al. 2005; Treiber et al. 2007). Furthermore, a study on Chinese autoimmune disease patients demonstrated a significant relationship between *SLCO1B1* 521 T > C polymorphism and dose-adjusted plasma levels of mycophenolic acid, an active metabolite of mycophenolate mofetil, in which the carriers of *SLCO1B1* 521 C/C genotype showed much higher dose-adjusted plasma levels of mycophenolic acid than the others (Shu et al. 2021). In addition, it was reported that *SLCO1B1* 521 T > C polymorphism might have an impact on the pharmacokinetics of exemestane since the statistically significant differences between AUCs in carriers of different *SLCO1B1* 521 T > C genotypes were found (Gregory et al. 2017), while the association of response to menopausal hormone therapy and the respective polymorphism was also reported. It is considered that the bioavailability of conjugated oestrogens has an influence on the incidence of night sweats, where it was shown that women with *SLCO1B1* 521 T/C genotype had a greater decrease in night sweats than those with *SLCO1B1* 521 T/T genotype (Moyer et al. 2018). Another study on angiotensin-converting enzyme inhibitor (ACEI) enalapril reported that male patients who were carriers of *SLCO1B1* 521 C/C genotype had a higher risk of developing the ACEI induced cough as ADR (vs. wild type homozygotes) (Luo et al. 2015). Taking all of the above into account, rs4149056 polymorphism has great importance since the frequency of allele C for the European populations is approximately 16% (obtained from The 1000 Genomes database) (The 1000 Genomes database 2021).

In this study, we determined the frequency of the most important *ABCG2* and *SLCO1B1* gene variants in the Croatian population of European descent.

Subjects and methods

A total of 905 anonymised subjects of European descent, all Croatian citizens, 482 women and 423 men (the median age of 56 years; range 1-95 years), were included in the study. We collected the data from the subjects that were genotyped in the Zagreb University Hospital Centre over a period of 5 years. Most often it was pre-emptive testing within the framework of pharmacogenetic projects including the ongoing project "Pharmacogenomics in prediction of cardiovascular drugs adverse reaction". Study was approved by the institutional Ethics Committee and written informed consent was obtained from all patients.

For genotyping of *SLCO1B1* c.521T > C and *ABCG2* c.421C > A, 3–6 mL of peripheral blood samples were collected in K_3-EDTA tubes. Genomic DNA was extracted from whole blood by QIAamp® method (Qiagen, Hilden, Germany). Genotyping was performed using TaqMan® Drug Metabolism Genotyping Assay (TaqMan® DME) for *SLCO1B1* c.521T > C (ID: C__30633906_10; rs4149056) and *ABCG2* c.421C > A (ID: C__15854163_70; rs2231142) (Applied Biosystems, Carlsbad, CA, USA) on the 7500 Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA), according to the manufacturer's instructions. All genotyping methods are part of the routine diagnostics with method validation and/or participation in external quality assurance (EQA) programs. Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). The allele and genotype frequencies were estimated using the gene counting method.

The Hardy-Weinberg equilibrium (HWE) was tested with the online HWE calculator Gene Calc at the level of significance of 0.05 (Bińkowski and Miks 2018).

Results

Genotype frequencies of *SLCO1B1* c.521T > C and *ABCG2* c.421C > A analysed in this study are presented in Table 1. The allele frequencies of the investigated polymorphisms are shown in Table 2. Finally, the frequency of possible combinations of *SLCO1B1* c.521T > C and *ABCG2* c.421C > A genotypes among the investigated subjects in the Croatian population are shown in Table 3.

Distribution of *ABCG2 c.421C > A* (rs2231142) and *SLCO1B1 c.521T > C* (rs4149056) were consistent with Hardy Weinberg's law with HWE $p = 0.85694$ and $p = 0.30453$, repectively.

For *SLCO1B1* c.521T > C, 558 (61.7%) subjects were carriers of 521 T/T genotype, 315 (34.8%) subjects were carriers of 521 T/C genotype, while 32 (3.5%) subjects were carriers of

Table 1. Genotype frequencies of *ABCG2* c.421C > A and *SLCO1B1* c.521T > C in the Croatian population and data on European populations from the 1000 Genomes database (The 1000 Genomes database 2021).

Gene	Number of subjects, n	Genotype	Number of subjects, n	Observed frequency, Croatians (this study)	EUR[a] European (total)	CEU[a] Utah Residents (CEPH)	TSI[a] Tuscans in Italy	IBS[a] Iberian population	GBR[a] British in England	FIN[a] Finnish in Finland
ABCG2	905	421C/C	737	0.814	0.823	0.778	0.888	0.860	0.747	0.828
		421C/A	161	0.178	0.165	0.212	0.103	0.140	0.220	0.162
		421A/A	7	0.008	0.012	0.010	0.009	0.000	0.033	0.010
SLCO1B1	905	521T/T	558	0.617	0.698	0.717	0.607	0.776	0.725	0.667
		521T/C	315	0.348	0.282	0.273	0.355	0.215	0.264	0.303
		521C/C	32	0.035	0.020	0.010	0.037	0.009	0.011	0.030

[a]Allele frequencies were acquired from the 1000 Genomes database (http://www.1000genomes.org/); CEU, Utah residents with Northern and Western European ancestry from the CEPH collection.

Table 2. Allele frequencies of *ABCG2* c.421C > A and *SLCO1B1* c.521T > C in the Croatian population and data on worldwide populations from the Genome Aggregation Database (gnomAD) (gnomAD 2022).

Gene -allele	NCBI dbSNP ID	Nucleotide change	Number of subjects (n)	Croatians[a]	EUR[b]	FIN[b]	AFR[b]	EAS[b]	SAS[b]	AMR[b]	AJ[b]	Other[b]
ABCG2 c.421C > A	rs2231142	c.421C > A	905	$C = 0.90331$	$C = 0.891$	$C = 0.929$	$C = 0.969$	$C = 0.679$	$C = 0.910$	$C = 0.864$	$C = 0.934$	$C = 0.899$
				$A = 0.09669$	$A = 0.109$	$A = 0.071$	$A = 0.031$	$A = 0.321$	$A = 0.090$	$A = 0.136$	$A = 0.066$	$A = 0.101$
SLCO1B1 c.521T > C	rs4149056	c.521T > C	905	$T = 0.79061$	$T = 0.844$	$T = 0.788$	$T = 0.972$	$T = 0.874$	$T = 0.950$	$T = 0.888$	$T = 0.820$	$T = 0.834$
				$C = 0.20939$	$C = 0.157$	$C = 0.212$	$C = 0.028$	$C = 0.126$	$C = 0.050$	$C = 0.112$	$C = 0.180$	$C = 0.166$

[a]Observed frequencies in this study; [b]Data acquired from the Genome Aggregation Database (gnomAD): EUR: non-Finnish European; FIN: Finnish; AFR: African/African American; EAS: East Asian; SAS: South Asian; AMR: Latino/Admixed American; AJ: Ashkenazi Jewish.

521 C/C genotype. The frequency of variant *SLCO1B1* allele in a total of 905 subjects was $C = 0.20939$.

For *ABCG2* c.421C > A, 737 (81.4%) subjects were carriers of 421 C/C genotype, 161 (17.8%) subjects were carriers of 421 C/A genotype, and 7 (0.8%) subjects were carriers of 421 A/A genotype. The frequency of variant *ABCG2* allele in a total of 905 subjects was $A = 0.09669$. Moreover, the most common combination of *SLCO1B1* c.521T > C and *ABCG2* c.421C > A genotypes is *SLCO1B1* 521 T/T and *ABCG2* 421 C/C (50.1%), while the *SLCO1B1* 521 C/C and *ABCG2* 421 A/A combination is the least represented (0.11%).

Discussion

Since there is strong scientific evidence on the importance of BCRP/ABCG2 and OATP1B1 for the pharmacokinetics of various endogenous and xenobiotic substrates, pharmacogenetics of OATP1B1 and BCRP/ABCG2 in the Croatian population was investigated. Both transporters show significant genetic variability, and the frequency of polymorphisms *SLCO1B1* c.521T > C and *ABCG2* c.421C > A has a large population and ethnic variability. Therefore, the analysis of these two polymorphisms may serve to individualise and optimise pharmacotherapy with drug substrates and minimise the risk of side effects. All subjects included in the study were of European descent, all Croatian citizens from different parts of Croatia, and were good representatives of a mixed Croatian population of European descent. According to obtained results, the frequencies of investigated alleles and genotypes are similar to other populations of European descent as per the 1000 Genomes database (The 1000 Genomes database 2021), Genome Aggregation Database (gnomAD 2022) and other published results (Pasanen et al. 2008; Xiao et al. 2020).

BCRP/ABCG2

Genotyping of *ABCG2* c.421C > A variant revealed the frequency of variant allele A of 9.7%, which is similar to data obtained in individuals of European descent (10–15% respectively) (Robey et al. 2009; Brunham et al. 2012; Sakiyama et al. 2014). According to the data obtained from the 1000 Genomes database (The 1000 Genomes database 2021) and Genome Aggregation Database (gnomAD 2022) the variant allele *ABCG2* 421 A is the most common in East Asians (30%) and Latin Americans (23%), while it is the rarest in the African population (3%). Data from our study are comparable to other European populations, especially the Finnish population (9.1%), but are slightly higher than data on Tuscan Italians (6.1%) and the Iberian (7.0%) population (The 1000 Genomes database 2021). The frequency of the variant allele *ABCG2* 421 A is reported to be the highest in the British (14.3%) population (The 1000 Genomes database 2021). This transporter has now been recognised as one of the key drug transporters involved in clinically relevant drug disposition (FDA 2017, EMA 2012). A large number of ABCG2 inhibitors have been identified (Mao and Unadkat 2015) and some convincing data point to ABCG2 as an important

Table 3. Frequencies of possible combinations of *SLCO1B1* c.521T > C and *ABCG2* c.421C > A genotypes in the Croatian population.

ABCG2 c.421C > A genotype	*SLCO1B1* c.521T > C genotype	Number of subjects (n)	Frequency of genotype combination (%)
C/C	T/T	453	50.06
C/A	T/T	103	11.38
A/A	T/T	2	0.22
C/C	T/C	259	28.62
C/A	T/C	52	5.75
A/A	T/C	4	0.44
C/C	C/C	25	2.76
C/A	C/C	6	0.66
A/A	C/C	1	0.11

mediator of drug-drug interactions in humans (International Transporter Consortium 2010).

A personalised approach to treatment and administration based on pharmacogenetic analysis can improve patients' adherence to medication. Choosing the right drug and dose minimises the risk of developing various side effects that are the main reason for discontinuation of therapy and non-cooperation of patients, which could result in deteriorating health (Scarpini et al. 2012).

OATP1B1

The variant allele *SLCO1B1* 521 C is more common in European (15%), than in Asian (14%) and African (1%) populations (Tirona et al. 2001; Nozawa et al. 2002; Jada et al. 2007; Link et al. 2008; Donnelly et al. 2011; Grapci et al. 2015; Turongkaravee et al. 2021). One study showed an even higher frequency for the European population (18%) (Pasanen et al. 2008). The frequency of the variant *SLCO1B1* 521 C allele in our study on the Croatian population is slightly higher than in previously mentioned studies, about 20.9% for variant allele C. In comparison with data obtained from the 1000 Genomes database (The 1000 Genomes database 2021) and Genome Aggregation Database (gnomAD 2022), our results correspond to the data obtained on the Tuscan Italian population, which is a neighbouring country to Croatia (21.5% respectively), but are slightly higher than data obtained on Utah residents, British, Finnish and Iberian populations (The 1000 Genomes database 2021). Data obtained on the Macedonian and Albanian populations in another study show frequencies of variant allele C of 14.0% and 12.0%, respectively (Grapci et al. 2015); slightly lower than our results. Still, studies on Finnish (20.0%) (Pasanen, Backman et al. 2006), Dutch (18.0%) (Brunham et al. 2012) and Israeli (20.0%) populations (Pasanen et al. 2008) show higher frequencies that are in agreement with results obtained in our study on the Croatian population. Genotype frequencies reflect the results described above – it is indicated that patients who are statin takers and who are carriers of the CC and TC genotypes have a higher risk for myopathy development than those who are TT genotype carriers (Turongkaravee et al. 2021).

In conclusion, the *ABCG2* c.421C > A and *SLCO1B1* c.521T > C gene variants show significant interindividual variability and are therefore good candidates for pharmacogenetic analysis in clinical practice. They can serve in predicting the variable pharmacokinetics of substrate drugs and in minimising the risk of drug side effects.

Ethics approval

Study was approved by the Ethics committee of the University Hospital Centre Zagreb and Zagreb University School of Medicine (approval number 380-59-10106-20-111/125 and 02/21 AG). All procedures performed in the study were in accordance with the 1964 Declaration of Helsinki and its later amendments.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[CPIC] Clinical Pharmacogenetics Implementation Consortium 2022. [accessed 2022 Feb 22]. www.cpicpgx.org/.

[DPWG] Dutch Pharmacogenetics Working Group 2022. Pharmacogenetic recommendation text 20220201. [accessed 2022 March 23]. https://www.knmp.nl/media/1058.

[EMA] European Medicines Agency 2012., London, UK: guideline on the investigation of drug interactions CPMP/EWP/560/95/rev. 1 Corr. 2**. [accessed 2022 March 22]. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf.

[FDA] 2017. US Food and Drug Administration: guidance for industry: drug interaction studies—study design, data analysis, implications for dosing, and labeling recommendations. [accessed 2022 March 22]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

[FDA] US Food and Drug Administration 2021. Table of pharmacogenomic biomarkers in drug labels. [accessed 20022 March 22]. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

[gnomAD] Genome Aggregation Database 2022. [accessed 2022 March 22]. https://gnomad.broadinstitute.org/.

[PharmGKB] The Pharmacogenomics Knowledgebase 2021. Drug label annotations. [accessed 2022 Feb 22]. https://www.pharmgkb.org/labelAnnotations.

Bielen L, Kralj I, Ćurčić E, Vodanović M, Boban A, Božina N. 2018. Acute kidney injury, agranulocytosis, drug-induced liver injury, and posterior reversible encephalopathy syndrome caused by high-dose

methotrexate-possible role of low activity ABC and SLC drug transporters. Eur J Clin Pharmacol. 74(9):1191–1192.
Bińkowski J, Miks S. 2018. Gene-Calc [Computer software]. www.gene-calc.pl.
Bruckmueller H, Cascorbi I. 2021a. ABCB1, ABCG2, ABCC1, ABCC2, and ABCC3 drug transporter polymorphisms and their impact on drug bioavailability: what is our current understanding? Expert Opin Drug Metab Toxicol. 17(4):369–396.
Bruckmueller H, Cascorbi I. 2021b. Drug-Drug-Gene Interactions: a Call for Clinical Consideration. Clin Pharmacol Ther. 110(3):549–551.
Bruhn O, Cascorbi I. 2014. Polymorphisms of the drug transporters ABCB1, ABCG2, ABCC2 and ABCC3 and their impact on drug bioavailability and clinical relevance. Expert Opin Drug Metab Toxicol. 10(10): 1337–1354.
Brunham LR, Lansberg PJ, Zhang L, Miao F, Carter C, Hovingh GK, Visscher H, et al. 2012. Differential effect of the rs4149056 variant in *SLCO1B1* on myopathy associated with simvastatin and atorvastatin. Pharmacogenomics J. 12(3):233–237.
Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, Gong L, et al. 2022. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 111(5):1007–1021.
Cusatis G, Gregorc V, Li J, Spreafico A, Ingersoll RG, Verweij J, Ludovini V, et al. 2006. Pharmacogenetics of ABCG2 and adverse reactions to gefitinib. J Natl Cancer Inst. 98(23):1739–1742.
Donnelly LA, Doney AS, Tavendale R, Lang CC, Pearson ER, Colhoun HM, McCarthy MI, Hattersley AT, et al. 2011. Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. Clin Pharmacol Ther. 89(2):210–216.
Ehmann F, Caneva L, Prasad K, Paulmichl M, Maliepaard M, Llerena A, Ingelman-Sundberg M, Papaluca-Amati M. 2015. Pharmacogenomic information in drug labels: european Medicines Agency perspective. Pharmacogenomics J. 15(3):201–210.
Elsby R, Hilgendorf C, Fenner K. 2012. Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther. 92(5):584–598.
Endres CJ, Hsiao P, Chung FS, Unadkat JD. 2006. The role of transporters in drug interactions. Eur J Pharm Sci. 27(5):501–517.
Fohner AE, Brackman DJ, Giacomini KM, Altman RB, Klein TE. 2017. PharmGKB summary: very important pharmacogene information for ABCG2. Pharmacogenet Genomics. 27(11):420–427.
Franke RM, Gardner ER, Sparreboom A. 2010. Pharmacogenetics of drug transporters. Curr Pharm Des. 16(2):220–230.
Furukawa T, Wakabayashi K, Tamura A, Nakagawa H, Morishima Y, Osawa Y, Ishikawa T. 2009. Major SNP (Q141K) variant of human ABC transporter ABCG2 undergoes lysosomal and proteasomal degradations. Pharm Res. 26(2):469–479.
Ganoci L, Trkulja V, Živković M, Božina T, Šagud M, Lovrić M, Božina N. 2021. ABCB1, ABCG2 and CYP2D6 polymorphism effects on disposition and response to long-acting risperidone. Prog Neuropsychopharmacol Biol Psychiatry. 104:110042.
Gessner A, König J, Fromm MF. 2019. Clinical Aspects of Transporter-Mediated Drug-Drug Interactions. Clin Pharmacol Ther. 105(6): 1386–1394.
Giacomini KM, Balimane PV, Cho SK, Eadon M, Edeki T, Hillgren KM, Huang SM, International Transporter Consortium, et al. 2013. International Transporter Consortium commentary on clinically important transporter polymorphisms. Clin Pharmacol Ther. 94(1): 23–26.
Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, International Transporter Consortium, et al. 2010. Membrane transporters in drug development. Nat Rev Drug Discov. 9(3):215–236.
Gotanda K, Tokumoto T, Hirota T, Fukae M, Ieiri I. 2015. Sulfasalazine disposition in a subject with 376C > T (nonsense mutation) and 421C > A variants in the ABCG2 gene. Br J Clin Pharmacol. 80(5): 1236–1237.
Grapci AD, Dimovski AJ, Kapedanovska A, Vavlukis M, Eftimov A, Matevska Geshkovska N, Labachevski N, et al. 2015. Frequencies of single-nucleotide polymorphisms and haplotypes of the SLCO1B1 gene in selected populations of the western balkans. Balkan J Med Genet. 18(1):5–21.
Gregory BJ, Chen SM, Murphy MA, Atchley DH, Kamdem LK. 2017. Impact of the OATP1B1 c.521T > C single nucleotide polymorphism on the pharmacokinetics of exemestane in healthy post-menopausal female volunteers. J Clin Pharm Ther. 42(5):547–553.
Gulilat M, Keller D, Linton B, Pananos AD, Lizotte D, Dresser GK, Alfonsi J, et al. 2020. Drug interactions and pharmacogenetic factors contribute to variation in apixaban concentration in atrial fibrillation patients in routine care. J Thromb Thrombolysis. 49(2):294–303.
Hagenbuch B, Meier PJ. 2003. The superfamily of organic anion transporting polypeptides. Biochim Biophys Acta. 1609(1):1–18.
Hagenbuch B, Meier PJ. 2004. Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. Pflugers Arch. 447(5):653–665.
Heyes N, Kapoor P, Kerr ID. 2018. Polymorphisms of the Multidrug Pump ABCG2: a Systematic Review of Their Effect on Protein Expression, Function, and Drug Pharmacokinetics. Drug Metab Dispos. 46(12): 1886–1899.
Hillgren KM, Keppler D, Zur AA, Giacomini KM, Stieger B, Cass CE, Zhang L, International Transporter Consortium 2013. Emerging transporters of clinical importance: an update from the International Transporter Consortium. Clin Pharmacol Ther. 94(1):52–63.
Hira D, Terada T. 2018. BCRP/ABCG2 and high-alert medications: biochemical, pharmacokinetic, pharmacogenetic, and clinical implications. Biochem Pharmacol. 147:201–210.
Hirota T, Fujita Y, Ieiri I. 2020. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol. 16(9):809–822.
Hofman J, Sorf A, Vagiannis D, Sucha S, Kammerer S, Küpper JH, Chen S, et al. 2019. Brivanib Exhibits Potential for Pharmacokinetic Drug-Drug Interactions and the Modulation of Multidrug Resistance through the Inhibition of Human ABCG2 Drug Efflux Transporter and CYP450 Biotransformation Enzymes. Mol Pharm. 16(11):4436–4450.
Horsey AJ, Cox MH, Sarwat S, Kerr ID. 2016. The multidrug transporter ABCG2: still more questions than answers. Biochem Soc Trans. 44(3): 824–830.
Huang SM, Zhang L, Giacomini KM. 2010. The International Transporter Consortium: a collaborative group of scientists from academia, industry, and the FDA. Clin Pharmacol Ther. 87(1):32–36.
Jada SR, Xiaochen S, Yan LY, Xiaoqiang X, Lal S, Zhou SF, Ooi LL, Chowbay B. 2007. Pharmacogenetics of *SLCO1B1*: haplotypes, htSNPs and hepatic expression in three distinct Asian populations. Eur J Clin Pharmacol. 63(6):555–563.
Kalliokoski A, Niemi M. 2009. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol. 158(3):693–705.
Keskitalo JE, Pasanen MK, Neuvonen PJ, Niemi M. 2009. Different effects of the ABCG2 c.421C > A SNP on the pharmacokinetics of fluvastatin, pravastatin and simvastatin. Pharmacogenomics. 10(10):1617–1624.
Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, Niemi M. 2009. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther. 86(2):197–203.
Klaassen CD, Aleksunes LM. 2010. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. Pharmacol Rev. 62(1):1–96.
Klarica Domjanović I, Lovrić M, Trkulja V, Petelin-Gadže Ž, Ganoci L, Čajić I, Božina N. 2018. Interaction between ABCG2 421C > A polymorphism and valproate in their effects on steady-state disposition of lamotrigine in adults with epilepsy. Br J Clin Pharmacol. 84(9):2106–2119.
Kondo C, Suzuki H, Itoda M, Ozawa S, Sawada J, Kobayashi D, Ieiri I, et al. 2004. Functional analysis of SNPs variants of BCRP/ABCG2. Pharm Res. 21(10):1895–1903.
Lähteenmäki J, Vuorinen A-L, Pajula J, Harno K, Lehto M, Niemi M, Gils M. 2021. Pharmacogenetics of Bleeding and Thromboembolic Events in Direct Oral Anticoagulant Users. Clin Pharma and Therapeutics. 110(3):768–776.

Launay-Vacher V, Izzedine H, Deray G. 2005. Statins' dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients. Int J Cardiol. 101(1):9–17.

Lazarou J, Pomeranz BH, Corey PN. 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 279(15):1200–1205.

Li LM, Chen L, Deng GH, Tan WT, Dan YJ, Wang RQ, Chen WS. 2012. SLCO1B1 *15 haplotype is associated with rifampin-induced liver injury. Mol Med Rep. 6(1):75–82.

Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, SEARCH Collaborative Group, et al. 2008. SLCO1B1 variants and statin-induced myopathy–a genomewide study. N Engl J Med. 359(8): 789–799.

Litjens CHC, van den Heuvel JJMW, Russel FGM, Aarnoutse RE, Te Brake LHM, Koenderink JB. 2020. Rifampicin Transport by OATP1B1 Variants. Antimicrob Agents Chemother. 64(10):e00955-20.

Low SK, Fukunaga K, Takahashi A, Matsuda K, Hongo F, Nakanishi H, Kitamura H, et al. 2016. Association Study of a Functional Variant on ABCG2 Gene with Sunitinib-Induced Severe Adverse Drug Reaction. PLoS One. 11(2):e0148177.

Luo JQ, He FZ, Wang ZM, Sun NL, Wang LY, Tang GF, Liu MZ, et al. 2015. SLCO1B1 Variants and Angiotensin Converting Enzyme Inhibitor (Enalapril)-Induced Cough: a Pharmacogenetic Study. Sci Rep. 5:5: 17253.

Malfará BN, Benzi JRL, de Oliveira Filgueira GC, Zanelli CF, Duarte G, de Carvalho Cavalli R, de Moraes NV. 2019. ABCG2 c.421C > A polymorphism alters nifedipine transport to breast milk in hypertensive breastfeeding women. Reprod Toxicol. 85:1–5.

Malki MA, Pearson ER. 2020. Drug-drug-gene interactions and adverse drug reactions. Pharmacogenomics J. 20(3):355–366.

Mao Q, Unadkat JD. 2015. Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport–an update. Aaps J. 17(1):65–82.

Matsuo H, Takada T, Ichida K, Nakamura T, Nakayama A, Suzuki H, Hosoya T, Shinomiya N. 2011. ABCG2/BCRP dysfunction as a major cause of gout. Nucleosides Nucleotides Nucleic Acids. 30(12): 1117–1128.

Merćep I, Radman I, Trkulja V, Božina T, Šimičević L, Budimir E, Ganoci L, Božina N. 2022. Loss of function polymorphisms in SLCO1B1 (c.521T > C, rs4149056) and ABCG2 (c.421C > A, rs2231142) genes are associated with adverse events of rosuvastatin: a case-control study. Eur J Clin Pharmacol. 78(2):227–236.

Miroševic Skvrce N, Božina N, Zibar L, Barišic I, Pejnovic L, Macolic Šarinic V. 2013. CYP2C9 and ABCG2 polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case-control study. Pharmacogenomics. 14(12):1419–1431.

Mirošević Skvrce N, Macolić Šarinić V, Šimić I, Ganoci L, Muačević Katanec D, Božina N. 2015. ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study. Pharmacogenomics. 16(8):803–815.

Moyer AM, de Andrade M, Faubion SS, Kapoor E, Dudenkov T, Weinshilboum RM, Miller VM. 2018. SLCO1B1 genetic variation and hormone therapy in menopausal women. Menopause. 25(8):877–882.

Niemi M, Pasanen MK, Neuvonen PJ. 2011. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol Rev. 63(1):157–181.

Nozawa T, Nakajima M, Tamai I, Noda K, Nezu J, Sai Y, Tsuji A, Yokoi T. 2002. Genetic polymorphisms of human organic anion transporters OATP-C (SLC21A6) and OATP-B (SLC21A9): allele frequencies in the Japanese population and functional analysis. J Pharmacol Exp Ther. 302(2):804–813.

Pasanen MK, Backman JT, Neuvonen PJ, Niemi M. 2006. Frequencies of single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide 1B1 *SLCO1B1* gene in a Finnish population. Eur J Clin Pharmacol. 62(6):409–415.

Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. 2006. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics. 16(12):873–879.

Pasanen MK, Neuvonen PJ, Niemi M. 2008. Global analysis of genetic variation in SLCO1B1. Pharmacogenomics. 9(1):19–33.

Peričić M, Barać Lauc L, Martinović Klarić I, Janićijević B, Rudan P. 2005. Review of Croatian genetic heritage as revealed by mitochondrial DNA and Y chromosomal lineages. Croat Med J. 46(4):502–513.

Pericić M, Lauc LB, Klarić IM, Rootsi S, Janićijevic B, Rudan I, Terzić R, et al. 2005. High-resolution phylogenetic analysis of southeastern Europe traces major episodes of paternal gene flow among Slavic populations. Mol Biol Evol. 22(10):1964–1975.

Poirier A, Portmann R, Cascais AC, Bader U, Walter I, Ullah M, Funk C. 2014. The need for human breast cancer resistance protein substrate and inhibition evaluation in drug discovery and development: why, when, and how? Drug Metab Dispos. 42(9):1466–1477.

Ramsey LB, Johnson SG, Caudle KE, Haidar CE, Voora D, Wilke RA, Maxwell WD, McLeod HL, et al. 2014. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther. 96(4):423–428.

Robey RW, To KK, Polgar O, Dohse M, Fetsch P, Dean M, Bates SE. 2009. ABCG2: a perspective. Adv Drug Deliv Rev. 61(1):3–13.

Roszkiewicz J, Michałek D, Ryk A, Swacha Z, Szmyd B, Smolewska E. 2021. SLCO1B1 variants as predictors of methotrexate-related toxicity in children with juvenile idiopathic arthritis. Scand J Rheumatol. 50(3): 213–217.

Safar Z, Kis E, Erdo F, Zolnerciks JK, Krajcsi P. 2019. ABCG2/BCRP: variants, transporter interaction profile of substrates and inhibitors. Expert Opin Drug Metab Toxicol. 15(4):313–328.

Sakiyama M, Matsuo H, Takada Y, Nakamura T, Nakayama A, Takada T, Kitajiri S, et al. 2014. Ethnic differences in ATP-binding cassette transporter, sub-family G, member 2 (ABCG2/BCRP): genotype combinations and estimated functions. Drug Metab Pharmacokinet. 29(6): 490–492.

Scarpini F, Cappellone R, Auteri A, Puccetti L. 2012. Role of genetic factors in statins side-effects. Cardiovasc Hematol Disord Drug Targets. 12(1):35–43.

Schulte RR, Choi L, Utreja N, Van Driest SL, Stein CM, Ho RH. 2021. Effect of SLCO1B1 Polymorphisms on High-Dose Methotrexate Clearance in Children and Young Adults With Leukemia and Lymphoblastic Lymphoma. Clin Transl Sci. 14(1):343–353.

Shu Q, Fan Q, Hua B, Liu H, Wang S, Liu Y, Yao Y, et al. 2021. Influence of SLCO1B1 521T > C, UGT2B7 802C > T and IMPDH1 -106G > A Genetic Polymorphisms on Mycophenolic Acid Levels and Adverse Reactions in Chinese Autoimmune Disease Patients. Pharmgenomics Pers Med. 14:713–722.

Skvrce NM, Krivokapić S, Božina N. 2020. Implementation of pharmacogenomics in product information. Pharmacogenomics. 21(7):443–448.

Song G, Chung JE, Yee J, Lee KE, Park K, Gwak HS. 2021. Effects of SLCO1B1 and SLCO1B3 Genetic Polymorphisms on Valsartan Pharmacokinetics in Healthy Korean Volunteers. JPM. 11(9):862.

Song Y, Lim HH, Yee J, Yoon HY, Gwak HS. 2022. The Association between ABCG2 421C > A (rs2231142) Polymorphism and Rosuvastatin Pharmacokinetics: A Systematic Review and Meta-Analysis. Pharmaceutics. 14(3):501.

Svedberg A, Jacobs L, Vikingsson S, Gréen H. 2020. The influence of ABCG2 polymorphism on erlotinib efflux in the K562 cell line. Pharmacol Res Perspect. 8(2):e00581.

The 1000 Genomes database 2021. The 1000 Genomes database [accessed Feb 21]. http://www.1000genomes.org/.

Tirona RG, Leake BF, Merino G, Kim RB. 2001. Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. J Biol Chem. 276(38):35669–35675.

Tirona RG. 2011. Molecular mechanisms of drug transporter regulation. Handb Exp Pharmacol. 201:373–402.

Toyoda Y, Takada T, Suzuki H. 2019. Inhibitors of Human ABCG2: from Technical Background to Recent Updates With Clinical Implications. Front Pharmacol. 10:208.

Treiber A, Schneiter R, Häusler S, Stieger B. 2007. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. Drug Metab Dispos. 35(8):1400–1407.

Tsamandouras N, Guo Y, Wendling T, Hall S, Galetin A, Aarons L. 2017. Modelling of atorvastatin pharmacokinetics and the identification of

the effect of a BCRP polymorphism in the Japanese population. Pharmacogenet Genomics. 27(1):27–38.

Turner RM, Fontana V, FitzGerald R, Morris AP, Pirmohamed M. 2020. Investigating the clinical factors and comedications associated with circulating levels of atorvastatin and its major metabolites in secondary prevention. Br J Clin Pharmacol. 86(1):62–74.

Turner RM, Radman I, Bozina N, Alfirevic A. 2020. Pharmacogenetics and statin-related myopathy: what do we know? Pharmacogenomics. 21(12):821–825.

Turongkaravee S, Jittikoon J, Lukkunaprasit T, Sangroongruangsri S, Chaikledkaew U, Thakkinstian A. 2021. A systematic review and meta-analysis of genotype-based and individualized data analysis of SLCO1B1 gene and statin-induced myopathy. Pharmacogenomics J. 21(3):296–307.

Ueshima S, Hira D, Kimura Y, Fujii R, Tomitsuka C, Yamane T, Tabuchi Y, et al. 2018. Population pharmacokinetics and pharmacogenomics of apixaban in Japanese adult patients with atrial fibrillation. Br J Clin Pharmacol. 84(6):1301–1312.

Verbeurgt P, Mamiya T, Oesterheld J. 2014. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. Pharmacogenomics. 15(5): 655–665.

Wen X, Kozlosky D, Zhang R, Doherty C, Buckley B, Barrett E, Aleksunes LM. 2021. BCRP/*ABCG2* Transporter Regulates Accumulation of Cadmium in Kidney Cells: role of the Q141K Variant in Modulating Nephrotoxicity. Drug Metab Dispos. 49(8):629–637.

Wilke RA, Ramsey LB, Johnson SG, Maxwell WD, McLeod HL, Voora D, Krauss RM, Roden DM, Clinical Pharmacogenomics Implementation Consortium (CPIC), et al. 2012. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. Clin Pharmacol Ther. 92(1):112–117.

Xiao Q, Zhou Y, Lauschke VM. 2020. Ethnogeographic and inter-individual variability of human ABC transporters. Hum Genet. 139(5): 623–646.

Yee SW, Brackman DJ, Ennis EA, Sugiyama Y, Kamdem LK, Blanchard R, Galetin A, et al. 2018. Influence of Transporter Polymorphisms on Drug Disposition and Response: A Perspective From the International Transporter Consortium. Clin Pharmacol Ther. 104(5):803–817.

Zamek-Gliszczynski MJ, Taub ME, Chothe PP, Chu X, Giacomini KM, Kim RB, Ray AS, International Transporter Consortium, et al. 2018. Transporters in Drug Development: 2018 ITC Recommendations for Transporters of Emerging Clinical Importance. Clin Pharmacol Ther. 104(5):890–899.