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PharmGKB summary: very important pharmacogene information for *SLC22A1*

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Introduction

Organic cationic transporter 1 (OCT1, encoded by gene *SLC22A1*) is one of the three similar polyspecific cationic transporters mediating the uptake of many organic cations from the blood into epithelial cells. *SLC22A1* is located in a cluster on chromosome 6 and contains seven exons and six introns. It can produce several alternatively spliced mRNA isoforms [1]. Similar to other members of the SLC22 family, the OCT1 protein contains 12 predicted α -helical transmembrane domains and a long hydrophilic loop between transmembrane domains 1 and 2 [2,3]. OCT1 is one of the major hepatic-uptake transporters located on the sinusoidal membrane of hepatocytes. It has substrate selectivity for a variety of endogenous ligands (dopamine, serotonin, choline), as well as cationic drugs, such as metformin, cimetidine, imatinib, oxaliplatin, tramadol, and agmatine [2,4–8]. This PharmGKB summary discusses *SLC22A1* and its pharmacogenomic importance. A fully interactive version of this short review, with links to individual paper annotations can be found at: <http://www.pharmgkb.org/gene/PA329#tabview=tab3&subtab=33>.

Expression

SLC22A1 is predominantly expressed in the liver and, to a lesser extent, in the adrenal gland, lung, kidney, as well as other tissues [9,10]. Constitutive expression of *SLC22A1* may be mediated by transcription factors. For example, transcriptional activation of *SLC22A1* can be mediated by binding of hepatocyte nuclear factor 4- α to DNA response elements adjacent to

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the gene [5]. Hepatocyte nuclear factor 1 may be an even stronger regulator of *SLC22A1* in the human liver, as high HNF1 expression is significantly correlated with high OCT1 expression in human liver samples. Further, electrophoretic mobility shift and chromatin immunoprecipitation assays confirmed the specific binding of HNF1 to the intron 1 evolutionary conserved region of *SLC22A1* [11]. In addition, the ubiquitously expressed and constitutively active transcriptional factor USF1 was shown to bind to the proximal promoter region and to modulate the basal expression of OCT1 [12]. Further, studies demonstrated that *SLC22A1* gene expression may also be induced by PPAR agonist receptors α and γ [13]. In a separate study, rifampin was reported to induce OCT1 expression and hepatic uptake of metformin, which in turn led to enhanced glucose-lowering properties [14]. Rifampin could therefore be considered a potential inducer of *SLC22A1*.

SLC22A1 may also be regulated through epigenetic silencing. A recent report showed that DNA methylation of *SLC22A1* is associated with reduced *SLC22A1* expression levels in human hepatocellular carcinoma [15]. Given the potential for anticancer drugs to act as substrates of *SLC22A1*, the study proposed that methylation of *SLC22A1* may result in substantial variability of treatment response to various anticancer drugs.

Drug–drug interactions

OCTs play an important role in transporting many commonly used drugs. Drug–drug interaction (DDI) by inhibition of OCT transporters may be clinically relevant. Proton pump inhibitors have been shown to inhibit metformin uptake by OCT1 and other OCTs in a concentration dependent manner *in vitro*, but they themselves are not substrates of these transporters [16]. More recently, treatment of MDCK-OCT1 and HepG2 cells with sitagliptin and metformin resulted in a reduced level of phosphorylated AMPK, suggesting that the inhibitory potential of sitagliptin on OCT1 may attenuate the first step of metformin action [17]. However, it is important to consider that HepG2 cell lines do not endogenously express OCT1, thus the results of this study should be interpreted carefully. In a study by Ahlin and colleagues, metformin uptake was reported to be inhibited by concomitantly administered drugs that inhibit OCT1 (such as verapamil and amitriptyline) at clinically relevant concentrations in the OCT1-reference, V408M but especially in M420del. The increased sensitivity of OCT1 variants to drug inhibition suggests that reduced OCT1 function can lead to an enhanced risk for DDIs in individuals carrying these variants [18]. Despite strong evidence from the described in-vitro studies, it is important to note that there has not yet been an in-vivo study investigating these potential DDIs with OCT1.

Important variants of *SLC22A1*

A number of *SLC22A1* polymorphisms have been associated with functional changes in protein activity, as well as drug disposition, response, and toxicity. The role of such variants is summarized in Table 1. Four nonsynonymous *SLC22A1* variants that have most extensively been studied are rs12208357, rs34130495, OCT1 420 deletion (rs35167514, rs34305973, rs35191146, rs72552763), and rs34059508. All four variants may impact the pharmacokinetics and pharmacodynamics of metformin, tropisetron, ondansetron, morphine, and tramadol [4,22,23,34].

c.181C > T; p.Arg61Cys (rs12208357)

This nonsynonymous missense variant is located in exon 1, on the first large extracellular loop of the protein. It is present in about 7.2% of Caucasians. The variant allele results in a residue change from arginine to cysteine, which results in loss of OCT1 protein function. This is associated with reduced uptake of metformin and 1-methyl-4-phenylpyridinium (MPP(+)) [3,34]. In a study by Shu *et al.*, confocal microscopy revealed that this variant resulted in a more diffuse pattern of localization on the plasma membrane compared with the reference allele [34].

c.1201G > A; p.Gly401Ser (rs34130495)

This nonsynonymous missense variant is located in exon 7. This residue belongs to a stretch of five amino acids that are highly conserved within the superfamily of facilitative transporters, indicating that this residue might be essential for basal transporter activity [6]. This variant is relatively rare, and is found in less than 1% of Caucasians and African Americans. A residue change from glycine to serine is observed, which results in a complete loss of OCT1 function, reducing metformin and MPP + uptake [34].

OCT1 Met420 deletion (p.M420del) (rs72552763)

The OCT1 Met420 deletion occurs in exon 7. It is a deletion of three bases (ATG) at codon 420 (represented by rs72552763). In database of single nucleotide polymorphisms (dbSNP), there are three other dbSNP IDs (rs35167514; rs34305973; rs35191146) representing single-base deletions of A, T, and G, respectively, although none of the single-base deletions exist alone. We think that all three rsIDs (rs35167514; rs34305973; rs35191146) should be merged into rs72552763, which represents the deletion of ATG at codon 420. The Met420 deletion variant is quite common and has a frequency of ~18.5% in Caucasians and 5% in African Americans. This common variant also resulted in reduced OCT1 function, reducing metformin uptake by altering the kinetics (decreasing V_{max}) of metformin in HEK293 cells [34].

c.1393G > A, p.Gly465Arg (rs34059508)

This nonsynonymous missense variant occurs in exon 9. This variant is also quite rare and appears at a rate of less than 1% when combining all ethnicities. This loss-of-function variant results in an amino acid change from glycine to arginine, reducing metformin and MPP + uptake [34]. It has also been shown that OCT1-G465R has reduced expression on the plasma membrane of MDCK cells compared with reference OCT1 [3].

Please note that some of the loss-of-function polymorphisms exist only within specific haplotype combinations, for example, in Arg465 or Arg88 in Caucasians always occurs in a haplotype with the deletion of Met420. These combination alleles are also called OCT1*5 and OCT1*6, respectively, in a number of publications [4,23,24].

Clinical associations between *SLC22A1* variant alleles and drug disposition, response, and toxicity

Metformin and type 2 diabetes

The role of *SLC22A1* polymorphisms in the clinical pharmacology of metformin has been extensively studied. Several genetic polymorphisms have been identified to be clinically significant predictors of metformin exposure and response. Table 1 summarizes the clinically relevant OCT1 variants. Of particular note are four variants, rs12208357, rs34130495, OCT1 420 deletion (rs72552763), and rs34059508. *In vitro*, all four polymorphisms were found to be associated with reduced metformin uptake and altered levels of phosphorylated AMPK in HEK293 cells [34]. Shu and colleagues [19,34] initially characterized these polymorphisms in healthy volunteer studies. In one study, carriers of any one of the four reduced-function OCT1 alleles showed a higher area under the plasma concentration–time curve, higher maximal plasma concentration ($C_{\max}$), and lower oral volume of distribution (V/F) [19]. In another study by Shu *et al.* [34], the glucose-lowering effect of metformin was significantly reduced in individuals carrying at least one reduced-function OCT1 allele according to the glucose tolerance tests.

In a study with healthy volunteers, carriers of reduced-function OCT1 alleles had higher renal clearances [20]. In a separate study by Christensen *et al.* [25], the number of reduced-function OCT1 alleles (including the OCT1 420 deletion SNP rs72552763) was associated with decreased metformin steady-state trough concentrations and increased HbA1c levels. Finally, in a study by Becker and colleagues, the minor allele rs622342 (with a population frequency of 27% in Caucasians) was associated with a reduction in HbA1c levels [28,29,35]. It is important to highlight a few controversies that underlie the findings on genetic variants in metformin pharmacokinetics and response. For example, none of the variants found relevant in the study by Shu and colleagues reached statistical significance in Becker's Rotterdam study. In the Rotterdam study, only an intronic variant (rs622342) was found to be significant. Further, in the paper by Christensen and colleagues, the finding on OCT1 deletion and metformin exposure level was opposite to that observed in the study by Shu and colleagues. Overall, more reproducibility by independent research groups is required for OCT1 variants to be clinically actionable.

SLC22A1 variants have also been associated with metformin-related side effects. A study by Tarasova and colleagues identified two coding variants, rs36056065 and rs628031, that were associated with the occurrence of side effects of metformin. Particularly, the authors observed that the presence of either variant may predispose a patient toward an increase in GI-related side effects following metformin therapy [26].

Metformin and polycystic ovary syndrome

In addition to being the first therapeutic option for type 2 diabetes, metformin is also used to treat polycystic ovary syndrome in women. The four aforementioned OCT1 coding variants (rs12208357, rs34130495, the OCT1 420 deletion, and rs34059508) were also studied in women with polycystic ovary syndrome. In this study, carriers of a reduced-function OCT1

variant were likely to have reduced lipid (total cholesterol and triglycerides) and insulin responses [21].

Imatinib and chronic myeloid leukemia

Previous studies have shown that patients with low expression or activity of OCT1 have a lower probability of achieving cytogenetic or molecular remission to chronic myeloid leukemia (CML). Improved progression-free survival and overall survival was also observed in patients with higher OCT1 expression [36]. In a study by Giannoudis *et al.* [7], the effect of polymorphisms rs628031 (Met408Val) and rs35191146 (420Del) on imatinib uptake and clinical efficacy was investigated. In CML cell lines transfected with the M420del and/or rs628031 (M408V), M420del significantly decreased imatinib uptake. Several papers found the uptake of imatinib through OCT1 to be controversial. For example, Ann Nies and colleagues showed through transport and inhibition studies that overexpression of functional OCT1 did not lead to increased accumulation of imatinib. They go on to conclude that cellular uptake of imatinib is independent of OCT1 and therefore OCT1 is not a valid biomarker for imatinib resistance [37]. In a separate study, the hOCT1 M420 deletion (rs35191146) was linked to clinical outcome of imatinib-treated CML. Patients with this polymorphism showed an increased probability of imatinib treatment failure. In a separate study by Kim *et al.*, CML patients carrying the GG genotype for SNP rs683369 were found to be at a higher risk for loss of response or treatment failure to imatinib therapy [31].

Sorafenib and hepatocellular carcinoma

There have been recent studies suggesting the importance of OCT1 in the development of hepatocellular carcinoma (HCC). First, there may be downregulation of SLC22A1 protein expression in HCC compared with normal adjacent tissue [15]. Second, sorafenib, a tyrosine kinase inhibitor approved for the treatment of HCC, has been recently suggested to be a substrate of OCT1 [38]. However, this finding has not been confirmed, as other authors could not measure OCT1-mediated uptake of sorafenib [39]. A more recent study explored the role of OCT1 in sorafenib chemoresistance in HCC cell lines, specifically investigating two novel alternatively spliced variants. The paper concluded that these variants, coupled with decreased OCT1 expression, may affect the ability of sorafenib to reach active intracellular levels in the tumor [40].

Antiemetic (antinausea) drugs

A study by Tzvetkov *et al.* [22] investigated the impact of OCT1 polymorphisms on the pharmacokinetics and clinical outcome of the antiemetic drugs tropisetron and ondansetron. In this study, overexpression of wild-type OCT1 led to significant increases in tropisetron uptake but did not affect the uptake of ondansetron. Clinically, patients were genotyped for five variants already studied in other indications, rs12208357, rs34130495, OCT1 420 deletion, rs34059508, and rs5598055. Carriers of two loss-of-function OCT1 alleles had higher plasma concentrations and higher clinical efficacy compared with carriers of fully active OCT1.

Morphine and tramadol

OCT1 variants have been associated with responses to pain medications [23]. Morphine is a substrate of OCT1 [23]. Carriers of loss-of-function OCT1 polymorphisms had a 56% higher mean area under the plasma concentration–time curve of morphine compared with noncarriers [23]. Among children, morphine clearance was significantly lower in homozygote carriers of loss-of-function OCT1 variants [24]. Another study showed that hepatic reuptake of *O*-desmethyltramadol, but not the prodrug tramadol, is mediated by SLC22A1 (OCT1). Individuals carrying the loss-of-function SLC22A1 variants had significantly higher plasma concentrations of *O*-demethyltramadol and significantly longer miosis, a surrogate marker for the opioidergic effect [4].

SLC22A1/OCT1 polymorphisms in other areas of research

Three *SLC22A1* polymorphisms have been linked to disease progression in patients with primary biliary cirrhosis (PBC) [30]. The three variants rs683369, rs2282143, and rs622342 were found to be associated with jaundice-type progression in Japanese PBC patients on the basis of a minor allele recessive genotype model. A genome-wide association study including 2782 advanced prostate cancer patients and 4458 controls identified the *SLC22A1* variant rs651164 to be a susceptibility locus, with the minor allele A resulting in an odds ratio of 0.87 [32]. The polymorphism rs622342, linked to metformin response and PBC disease progression, was also shown in a separate study to be linked to the efficacy of antiparkinsonian drugs. The minor allele of this SNP was associated with a higher prescribed dose of levodopa, a known substrate of OCT1 [29]. In the same study, this SNP was associated with increased mortality in patients with Parkinson's disease. Interestingly, in a separate genome-wide association study on plasma lipids in 100 000 individuals with European ancestry, the minor allele of *SLC22A1* SNP, rs1564348, was associated with low-density lipoprotein levels at a genome-wide level. Further experimental studies are needed to validate the role of OCT1 in modulating low-density lipoprotein levels.

Conclusion

SLC22A1 (OCT1) plays an important role in hepatic uptake of many commonly used drugs. Several *SLC22A1* (OCT1) polymorphisms may have clinical consequences. Polymorphisms in *SLC22A1* have been identified to significantly alter metformin exposure and response. However, it is important to consider the lack of replication by multiple independent research groups, and for this reason, clinical application of these variants should be exercised with caution. Polymorphisms may also affect clinical response to imatinib. However, as with metformin, without scientific consensus on the role of OCT1 in imatinib uptake, conclusions should be drawn with caution. Overall, larger sample sizes are clearly needed to validate the role of *SLC22A1* polymorphisms in drug disposition, response, and toxicity. Further, in-vivo DDI studies are also needed to corroborate the DDIs that have been observed *in vitro* to warrant clinical consideration of high-affinity OCT1 substrates that are concomitantly prescribed. Future work on OCT1 will also need to address the role of epigenetics, as well as other more rare variants, on response variability.

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Table 1Summary of clinical impact of *SLC22A1* (OCT1) polymorphisms

Polymorphism	MAF	Drug	Indication	Clinical phenotype	References
Arg61Cys (rs12208357)	~7.2% (EA) [19]	Metformin	Type II diabetes	↑AUC ↑ C _{MAX} ↑CL _r ↓ Vd ↓ OGTT	[19,20] ^a
		Metformin	PCOS	↓ Lipid response ↓ Insulin response	[21] ^a
		Tropisetron	Nausea	↑Cp ↓ Vomiting episodes	[22] ^b
		Morphine	Pain	↑AUC	[23,24] ^b
		Ondansetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
		Tramadol	Pain	↑Cp of metabolite ↑Miosis	[4] ^c
Gly401Ser (rs34130495)	1.1% (EA) [19]	Metformin	Type II diabetes	↑AUC ↑ C _{max} ↑CL _r ↓ Vd ↓ OGTT	[19,20]
		Metformin	PCOS	↓ Lipid response ↓ Insulin response	[21]
		Tramadol	Pain	↑Cp of metabolite ↑Miosis	[4]
		Morphine	Pain	↑AUC	[23,24]
		Tropisetron	Nausea	↑Cp ↓ Vomiting episodes	[22] ^b
		Ondansetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
Met420del	~18.5% (EA) [19]	Metformin	Type II diabetes	↑AUC ↑ C _{max} ↑CL _r ↓ Vd ↓ OGTT ↓ Trough C _{ss}	[19,20,25]
		Metformin	PCOS	↓Lipid response ↓ Insulin response	[21]
		Tramadol	Pain	↑Cp of metabolite ↑Miosis	[4]
		Morphine	Pain	↑AUC	[23,24]
		Tropisetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
		Ondansetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
Gly465Arg rs34059508	4% (EA) [19]	Imatinib	CML	↑Probability of imatinib failure ^d	[7]
		Metformin	Type II diabetes	↑AUC ↑ C _{max} ↑CL _r ↓ Vd ↓ OGTT	[19,20]
		Metformin	PCOS	↓Lipid response ↓ Insulin response	[21]
		Tropisetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
rs36056065	41% (EA) [26]	Ondansetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
		Metformin	Type II diabetes	↑GI side effects	[26]
Met408Val (rs628031)	42% (EA) [26]	Metformin	Type II diabetes	↑GI side effects	[26]
Cys88Arg [27](rs55918055)	<1% (EA)	Tropisetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
		Morphine	Pain	↑AUC	[23,24]
		Ondansetron	Nausea	↑Cp ↓ Vomiting episodes	[22]
rs622342	37% (EA) [28]	Metformin	Type II diabetes	↓HbA1c	[28]
		Levodopa	Parkinson's	↑Prescribed dose ↑ mortality	[29]
		NA ^e	PBC	↑Disease progression	[30]
Pro341Leu (rs2282143)	5.7% (dbSNP) (All)	NA ^e	PBC	↑Disease progression	[30]
Phe160Leu (rs683369)	25% (EA) (dbSNP)	NA ^e	PBC	↑Disease progression	[30]
		Imatinib	CML	↑Treatment failure	[31]
rs651164	35% (EA) (dbSNP)	NA ^e	Prostate cancer	↓Prostate cancer susceptibility	[32]
rs1564348	17% (EA) (dbSNP)	NA ^e	LDL	↑LDL	[33]

All, all ethnic groups consider for MAF; AUG, drug exposure; CLr, renal clearance; CML, chronic myeloid leukemia; Css, Concentration at steady state; Cp, plasma concentration; EA, European American; GI, gastrointestinal; LDL, low-density lipoprotein; MAF, minor allele frequency; OGTT, oral glucose tolerance test; PBC, primary billiary cirrhosis; PCOS, polycystic ovary syndrome; SNP, single nucleotide polymorphism; Vd, Volume of distribution.

^a Carriers of at least one of four OCT1 polymorphisms showed phenotype R61C, G401S, 420del, or G465R.

^b Carriers of at least one of five OCT1 polymorphisms showed phenotype Arg61Cys, Cys88Arg, Gly401Ser, Gly465Arg, or 420del.

^c Carriers of at least one of four OCT1 polymorphisms showed phenotype Arg61Cys, Cys88Arg, Gly401Ser, or Gly465Arg.

^d Specific variant in this study was rs35191146.

^e Polymorphism was associated with disease or another phenotype, independent of drug impact.