

Review

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# Impact of genetic variants in the solute carrier (SLC) genes encoding drug uptake transporters on the response to anticancer chemotherapy

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## Abstract

Cancer drug resistance constitutes a severe limitation for the satisfactory outcome of these patients. This is a complex problem due to the co-existence in cancer cells of multiple and synergistic mechanisms of chemoresistance (MOC). These mechanisms are accounted for by the expression of a set of genes included in the so-called resistome, whose effectiveness often leads to a lack of response to pharmacological treatment. Additionally, genetic variants affecting these genes further increase the complexity of the question. This review focuses on a set of genes encoding members of the transportome involved in drug uptake, which have been classified into the MOC-1A subgroup of the resistome. These proteins belong to the solute carrier (SLC) superfamily. More precisely, we have considered here several members of families SLC2, SLC7, SLC19, SLC22, SLCO, SLC28, SLC29, SLC31, SLC46, and SLC47 due to the impact of their expression and genetic variants in anticancer drug uptake by tumor cells or, in some cases, general bioavailability. Changes in their expression levels and the appearance of genetic variants can contribute to the Darwinian selection of more resistant clones and, hence, to the development of a more malignant phenotype. Accordingly, to address this issue in future personalized medicine, it is necessary to characterize both changes in resistome genes that can affect their



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function. It is also essential to consider the time-dependent dimension of these features, as the genetic expression and the appearance of genetic variants can change during tumor progression and in response to treatment.

**Keywords:** Cancer, chemotherapy, pharmacogenetics, single nucleotide alteration, single nucleotide polymorphism, transportome

## INTRODUCTION

One of the main problems in cancer treatment is the poor response of many tumors to standard drug regimens. This situation can be partly explained by the existence of complex and varied mechanisms of chemoresistance (MOC), such as those leading to a reduction in the intracellular concentration of active antitumor agents<sup>[1]</sup>. The reduction of intracellular drug concentrations by impaired uptake markedly affects the overall effectiveness because the mechanism of action of many anticancer agents takes place inside cells, frequently inhibiting essential processes required for tumor cell survival<sup>[1]</sup>. Besides drug uptake, other mechanisms also contribute to the refractoriness of tumors to currently available antitumor chemotherapy, such as changes in the intracellular metabolism of antitumor drugs and prodrugs, alteration of the molecular targets, increased repair of drug-induced DNA damage, change in the balance between proapoptotic and antiapoptotic factors, modification of tumor microenvironment, and phenotypic transformations of tumor cells<sup>[2,3]</sup>.

Here, we have gathered the available information on the impact on cancer chemoresistance of genetic variants affecting part of the so-called “transportome,” i.e., the set of transporters expressed at a given time. The subset of transportome accounting for drug uptake belongs to the superfamily of solute carriers (SLC) proteins. Genetic variants in *SLC* genes have been associated with interindividual differences regarding drug efficacy and toxicity<sup>[4]</sup>. The transfer of anticancer agents across the plasma membrane of tumor cells and, hence, their effectiveness depends on the function of these proteins<sup>[5]</sup>. Consequently, variants affecting these genes could modify the response of tumor cells to their substrates. The relevance of some of these proteins in the transport of anticancer drugs has already been described<sup>[6]</sup>. Transporters encoded by the *SLC22A* gene family can accept various antitumor drugs of cationic, anionic, or zwitterionic nature as substrates. Organic anion-transporting polypeptides (OATP) encoded by *SLCO* genes transport some drugs of anionic or zwitterionic nature. In addition, certain members of the *SLC28A* and *SLC29A* gene families encode transporters capable of facilitating concentrative (CNT, concentrative nucleoside transporters) and equilibrative (ENT, equilibrative nucleoside transporters) cellular uptake of nucleoside analogs, such as gemcitabine and cytarabine<sup>[7]</sup>, as well as fluoropyrimidines like 5'-deoxy-5-fluorouridine<sup>[8]</sup>. However, they do not transport other antitumor drugs commonly used related compounds, such as 5-fluorouracil (5-FU). Moreover, the copper transporter 1 (CTR1, *SLC31A1*) mediates the cellular uptake of cisplatin. The role of other SLC transporters in the uptake of antitumor drugs is restricted to specific drugs<sup>[5]</sup>.

The occurrence of genetic mutations in tumor cells, driven by stochastic events, favors the selection of tumor cells that adapt to pharmacological pressure, thereby increasing tumor heterogeneity. Furthermore, in a heterogeneous population of tumor cells, Darwinian evolutionary selection can act on those showing phenotypic variation induced *de novo* as well as those carrying pre-existing variants<sup>[9]</sup>. Selected clones may advantageously expand, contributing to the transformation into a more chemoresistant phenotype.

In this study, we have followed the Human Genome Variation Society (HGVS) nomenclature for the description of genetic variants, according to the recommendations of the HGVS Variant Nomenclature Committee (HVNC) (<https://varnomen.hgvs.org/>), updated on May 1, 2020, which operates under the

auspices of the Human Genome Organization (HUGO). Single nucleotide polymorphisms (SNP) have been considered substitutions in a population with a frequency higher than 1%. In contrast, single nucleotide changes without frequency limitation that can arise in tumor cells have been termed single nucleotide variations (SNV). Some of the information contained in this review has been collected from databases such as the Pharmacogene Variation Consortium (<https://www.pharmvar.org>), the ClinicalGenome (ClinGen) resource (<https://clinicalgenome.org/>), the PharmGKB database (<http://www.pharmgkb.org/>), the COSMIC database (<https://cancer.sanger.ac.uk/cosmic>), and the NCBI database of single nucleotide polymorphisms (dbSNP) (<https://www.ncbi.nlm.nih.gov/snp/>). The clinical significance of the various gene variants has primarily been evaluated based on the information on pharmacogenomics provided by the PharmGKB database. This database gathers studies on the phenotypic effects of the variants, assigning a score ranging from 1 to 4 based on the level of evidence, with level 1 indicating the highest criteria are met. In most cases, the clinical annotation was at level 3, which indicates a low level of evidence supporting the variant-drug association. This is because there is only one study annotated in PharmGKB, several studies have failed to replicate the association, or the annotation is based on preliminary evidence. In some cases, the level of evidence was 4, which describes variant-drug combinations where the evidence does not support a conclusive association between the variant and the phenotype.

## THE SLCO FAMILY OF ORGANIC ANION TRANSPORTING POLYPEPTIDES

OATPs constitute a superfamily of proteins that mediate the transport of amphiphilic substrates across the plasma membrane of animal cells. Although more than 300 OATP proteins have been identified, only a few have been well-characterized in humans and rodents<sup>[10]</sup>. Based on amino acid identity, the 11 known human OATPs have been classified into six families, containing those with more than 40% identity and ten subfamilies that encompass proteins with more than 60% identity<sup>[11]</sup>. OATPs carry out the sodium-independent uptake of a wide range of amphiphilic organic anions and, less frequently, neutral or cationic compounds<sup>[11]</sup>. They can transport a broad range of substrates with significant overlapping specificity among members of this family. These carriers are expressed in many different types of healthy cells. This expression is heterogeneously preserved in cancers derived from them. Herein lies their importance, as OATPs are involved in the uptake of some anticancer drugs, mainly negatively charged compounds<sup>[12]</sup>.

OATP1A2 (*SLCO1A2*) is expressed mainly in the apical membrane of epithelial cells of the biliary tree, gallbladder, and digestive tract<sup>[13]</sup>. The highest levels of OATP1A2 expression in cancer cells are found in gliomas, testicular germ cell tumors, and squamous cell lung carcinoma<sup>[5]</sup>. This transporter has a broad substrate specificity that includes endogenous substrates, drugs, and other xenobiotics with anionic, neutral, or cationic nature. Regarding antitumor drugs, *in vitro* studies have reported that OATP1A2 may be involved in the uptake of methotrexate<sup>[12,14]</sup> and imatinib<sup>[15]</sup>. Moreover, there is evidence that some *SLCO1A2* genetic variants cause a reduced or complete loss of the ability to transport these drugs. This is the case of the intronic variants g.21420471C>T (rs4149009) and g.21488004C>T (rs3764043), which could have a clinical impact on the treatment of leukemias<sup>[16,17]</sup> [Figure 1 and Table 1].

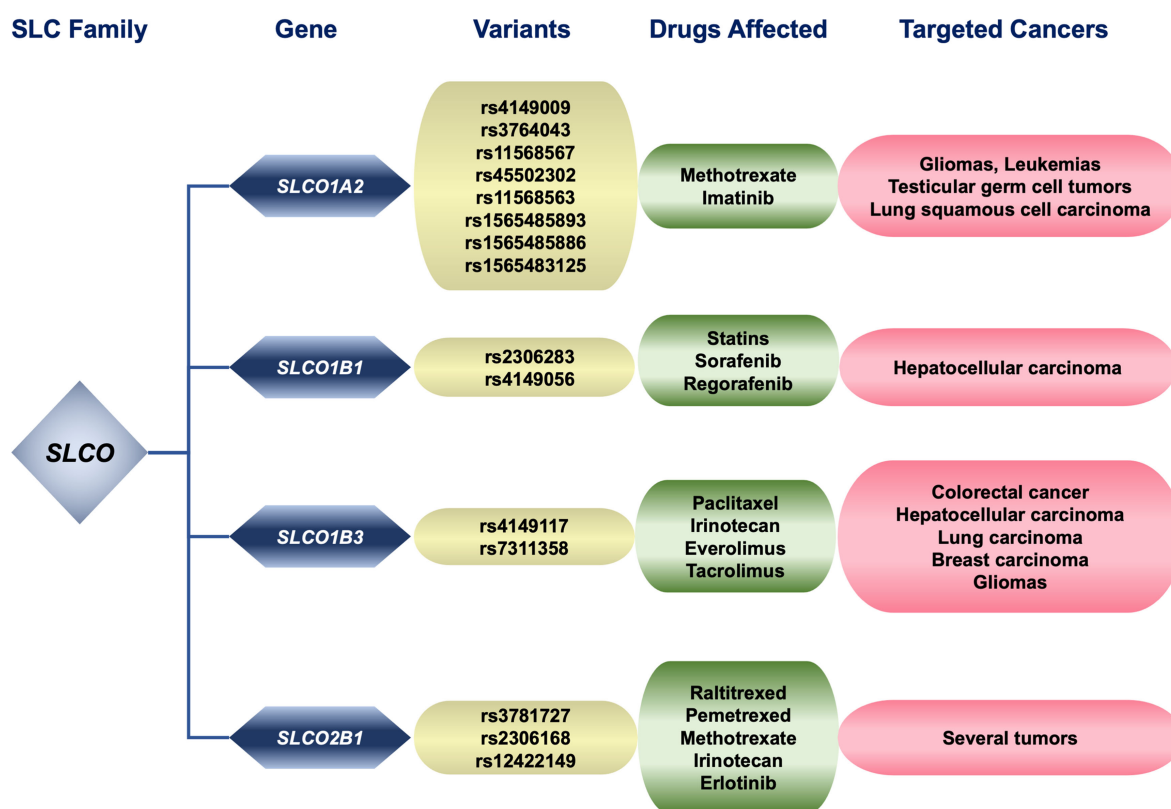
According to the PharmGKB pharmacogenomics database, the clinical relevance of these variants is low, with a level of evidence of 3 on a scale from 1 to 4, where level 1 meets the highest criteria.

A study of 141 children with acute lymphoblastic leukemia showed that the presence of the rs4149009 variant altered the pharmacokinetics of methotrexate<sup>[18]</sup>. Similarly, another analysis of 34 patients with chronic myeloid leukemia and 100 controls reported that the rs3764043 variant alters the pharmacokinetics of imatinib<sup>[16]</sup>. Because only one clinical study has been carried out for each variant, their clinical relevance is still low. Moreover, variants affecting the ORF, such as c.382A>T (p.Asn128Tyr, rs11568567), c.404A>T

**Table 1. Clinically relevant genetic variants of members of the SLCO family of SLC in the pharmacokinetics, efficacy, or toxicity of antitumor drugs**

Variant	Drug	Targeted tumor	Alteration	Study size	Ethnicity	Ref.	
SLCO1A2	rs4149009	Methotrexate	Lymphoblastic leukemia	Pharmacokinetics	141	East Asian	[18]
	rs3764043	Imatinib	Chronic myeloid leukemia	Pharmacokinetics	134	East Asian	[16]
SLCO1B1	rs2306283	Irinotecan	Colorectal carcinoma	Efficacy	137	East Asian	[19]
		Methotrexate	Lymphoblastic leukemia	Pharmacokinetics	499	European	[20]
		Sorafenib	Hepatocellular carcinoma	Toxicity	114	European	[21]
	rs4149056	Docetaxel	Breast carcinoma	Toxicity	50	European	[22]
		Methotrexate	Lymphoblastic leukemia	Pharmacokinetics	48	Near Eastern	[23]
		Methotrexate	Lymphoblastic leukemia	Efficacy	317	East Asian	[24]
		SN-38	Non-small cell lung cancer	Pharmacokinetics	107	East Asian	[25]
		Sorafenib	Hepatocellular carcinoma	Toxicity	114	European	[21]
SLCO1B3	rs4149117	Paclitaxel	Non-small cell lung cancer	Toxicity	194	East Asian	[26]
		Sunitinib	Gastrointestinal stromal tumors	Efficacy	127	European	[27]
	rs7311358	Docetaxel	Nasopharyngeal neoplasms	Pharmacokinetics	50	East Asian	[28]
		Paclitaxel	Non-small cell lung cancer	Toxicity	194	East Asian	[26]

SLCO: Family of organic anion transporting polypeptides (OATPs encoded by SLCO genes); SLC: solute carrier.



**Figure 1.** Relationship between genetic variants of pharmacologically relevant members of the SLC family SLCO, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier.

(p.Asn135Ile, rs45502302), c.516A>T/C (p.Glu172Asp, rs11568563), c.550G>A (p.Glu184Lys, rs1565485893), c.553G>A (p.Asp185Asn, rs1565485886), and c.862G>A (p.Asp288Asn, rs1565483125),

encode proteins that are not expressed in the plasma membrane or generate truncated inactive proteins<sup>[29]</sup>. However, no clinical impact of these variants has been reported, possibly because the contribution of other SLC transporters to the uptake of these drugs is higher than that of OATP1A2.

OATP1B1 (*SLCO1B1*) and OATP1B3 (*SLCO1B3*) are considered among the most clinically relevant transporters by the International Transporter Consortium (ITC) guidelines due to their role in drug uptake and disposition<sup>[30]</sup>. These proteins are expressed almost exclusively (OATP1B1) or abundantly (OATP1B3) in the sinusoidal membrane of hepatocytes<sup>[31]</sup>. As for their expression in tumors, both transporters have high levels in hepatocellular carcinoma (HCC) cells<sup>[5]</sup>. In addition, the expression of a splice variant of *SLCO1B3*, termed the cancer-type isoform, has been detected mainly in tumors derived from the gastrointestinal tract<sup>[32-34]</sup>. The clinical relevance of OATP1B1 and OATP1B3 as transport systems for antitumor agents in cancer cells is considered low due to their almost restricted localization to liver cells and limited substrate specificity for anticancer agents. Both transporters can mediate the uptake of taxanes (paclitaxel and docetaxel)<sup>[35]</sup> and other antitumor drugs that are not commonly used in treating HCC<sup>[36]</sup>.

For this reason, the evaluation of OATP1B3 expression in HCC could be helpful before deciding whether to use anticancer drug substrates of this carrier in the personalized treatment of these patients<sup>[36]</sup>. When expressed in HEK293 cells *in vitro*, both OATPs can transport a wide range of tyrosine kinase inhibitors (TKIs)<sup>[37]</sup>. However, their relevance *in vivo* needs to be clarified because the transport of these drugs appears to be restricted to their conjugates with glucuronic acid<sup>[38]</sup>. OATP1B1, but not OATP1B3, has been reported to be involved in the transport of regorafenib, a TKI used in second-line treatment of advanced liver cancer, which has not responded to sorafenib<sup>[39]</sup>. OATP1B3 can also interact, although whether transport takes place is controversial, with mTOR inhibitors, such as everolimus<sup>[40]</sup> and tacrolimus<sup>[41]</sup>, used against lung<sup>[42]</sup> and breast carcinomas<sup>[43]</sup> and gliomas<sup>[44]</sup>. The low expression of OATP1B3 in these tumors may be related to their low sensitivity to these drugs.

Approximately 200 variants relevant to drug transport have been described for the *SLCO1B1* gene<sup>[45]</sup>. Some are highly prevalent, such as c.388A>G (p.Asn130Asp, rs2306283). The c.521T>C variant (p.Val174Ala, rs4149056) leads to diminished transport activity attributable to decreased plasma membrane expression and phosphorylation status<sup>[46]</sup>. The most significant clinical relevance of these SNPs concerns their impact on statin uptake<sup>[47]</sup>. They have a moderate effect on the pharmacokinetics, drug response, and toxicity of some antitumor drugs [Figure 1 and Table 1]<sup>[48]</sup>. These variants have been associated with increased side effects after treatment of HCC patients with sorafenib. Still, no association with patient survival has been found in a study with 114 HCC patients<sup>[21]</sup>. In another study which included 499 children with acute lymphoblastic leukemia, both variants were shown to affect pharmacokinetics and response to methotrexate<sup>[20]</sup>.

*SLCO1B1* is one of the critical genes involved in the implementation of pharmacogenomics. Based on the studies on the impact of variants of this gene, numerous dosing recommendations based on genotype or whether a drug is indicated or contraindicated have been implemented in clinical guidelines<sup>[49]</sup>. However, the most critical clinical annotations on *SLCO1B1* pharmacogenetics in clinical guidelines and Food and Drug Administration (FDA)-approved drug labels all refer to statins<sup>[45]</sup>. Further studies with other OATP1B1 substrates, such as thiazolidinediones, antibiotics, antihypertensives, antidiabetics, and antitumor agents, are needed to reach the relevance of the statin studies.

*SLCO1B3* is also highly polymorphic, and based on the results of *in vitro* experiments, many genetic variants associated with reduced transport activity or expression have been described<sup>[50]</sup>. Among them, the most

clinically relevant common variants are c.334T>G (p.Ser112Ala, rs4149117) and c.699G>A (p.Met233Ile, rs7311358) [Figure 1 and Table 1]<sup>[50]</sup>. Both have been described to lead to altered cellular localization and a reduced ability to transport taxanes so that their expression in tumor cells may contribute to interindividual variability in the pharmacokinetics of the drug and, therefore, to its antitumor activity as demonstrated in a study of 194 patients with non-small cell lung cancer treated with chemotherapy including paclitaxel<sup>[26]</sup>. In another study of patients with unresectable liver metastases from colorectal cancer treated with irinotecan (a substrate of OATP1B3) and other OATP1B3 non-transported drugs (oxaliplatin and 5-FU), the presence of these variants has been linked to altered pharmacokinetics of irinotecan, resulting in reduced hepatic detoxification and consequently increasing its adverse effects, such as neutropenia and diarrhea<sup>[51]</sup>. More studies are needed for the level of evidence of an association between *SLCO1B3* variant-drug combinations to be considered higher.

Recently, the ITC guidelines have included OATP2B1 (*SLCO2B1*) among the transporters of emerging clinical relevance due to its essential role in drug absorption and disposition<sup>[30]</sup>. OATP2B1 shows widespread tissue expression, being particularly abundant in the liver and intestine<sup>[52]</sup>. Recent proteomic data indicate that OATP2B1 has a similar expression to OATP1B3 in the liver<sup>[53]</sup>, suggesting that its importance in hepatic uptake may have been underestimated. Its expression in tumors is relatively high in most types of cancer, except in acute myeloid leukemia (AML)<sup>[5]</sup>. Although OATP2B1 has a broad substrate specificity among anionic organic compounds, both endogenous and xenobiotics<sup>[31,54]</sup>, few of its substrates are antitumor drugs. OATP2B1 has been demonstrated to play a role in the intestinal absorption of antifolate drugs such as raltitrexed, pemetrexed, and methotrexate<sup>[55]</sup>, as well as the most active metabolite of irinotecan, SN-38<sup>[56]</sup>.

Numerous TKIs are inhibitors of OATP2B1, most notably erlotinib, but whether they are substrates of this transporter is unknown<sup>[57]</sup>. Results from *in vitro* experiments have shown that several *SLCO2B1* variants affect protein expression or function, such as g. 75204976T>C (rs3781727), c.1457C>T (p.Ser486Phe, rs2306168), c.935G>A/T (p.Arg312Gln/Leu, rs12422149), but its clinical relevance for antitumor drugs has not yet been found<sup>[58]</sup>.

Although other members of the OATP family are expressed in some types of tumors and can transport antitumor drugs, such as OATP1C1 (*SLCO1C1*), which transports docetaxel<sup>[59]</sup>, OATP4C1 (*SLCO4C1*), methotrexate<sup>[60]</sup>, and OATP5A1 (*SLCO5A1*), satraplatin<sup>[61]</sup>, their role in cancer chemoresistance is poorly understood.

## THE SLC22 FAMILY

Within the SLC superfamily of transporter proteins, the SLC22 family plays critical roles in physiology, pharmacology, and toxicology due to its ability to transport a wide variety of substrates and the expression of some of its members in crucial organs involved in drug disposition, such as the intestine, liver, and kidney<sup>[62]</sup>. Not all twenty-four transporters of the SLC22 family have been well characterized<sup>[63]</sup>. Phylogenetic studies have classified them into six subfamilies, of which the three best known are those of organic cation transporters (OCT), organic cation/carnitine transporters (OCTN), and organic anion transporters (OAT), in addition to others less well-known, such as OAT-like, OAT-related, and OCT/OCTN-related transporters<sup>[63,64]</sup>. A common feature of all SLC22 proteins is their structure, which consists of 12 transmembrane domains (TMD) with three highly conserved areas that are important for their function: a large extracellular loop at the beginning, between TMD1 and TMD2; another large intracellular loop in the central region, between TMD6 and TMD7; and motifs in TMD9 and TMD10 that are crucial for the transport activity of the protein<sup>[65]</sup>. Current U.S. FDA and European Medicines Agency (EMA) guidelines consider OCT transporters as proteins of great importance in pharmacology<sup>[48,63]</sup>.

## OCTs

OCT1 (*SLC22A1*) is primarily a hepatic uptake transporter expressed in the sinusoidal membrane of hepatocytes, where it mediates the uptake from portal blood of a wide variety of endogenous compounds and cationic drugs<sup>[66]</sup>. OCT1 promiscuously transports structurally diverse endogenous organic cations, such as thiamine, choline, and cationic neurotransmitters, and many commonly used drugs, such as metformin, ranitidine, sumatriptan, or lamivudine<sup>[64]</sup>. Among the antitumor drugs, irinotecan, mitoxantrone, oxaliplatin, paclitaxel, imatinib, and sorafenib have been described as OCT1 substrates<sup>[67,68]</sup>.

The results obtained from *in vitro* and *in vivo* studies, as well as in numerous clinical investigations, support the functional impact of some genetic variants of OCT1 on the pharmacokinetics and chemotherapeutic response of drugs that are substrates of this transporter [Figure 2 and Table 2].

The information from the PharmGKB pharmacogenomics database, indicate that the clinical relevance of these variants is placed third in the range from 1 to 4.

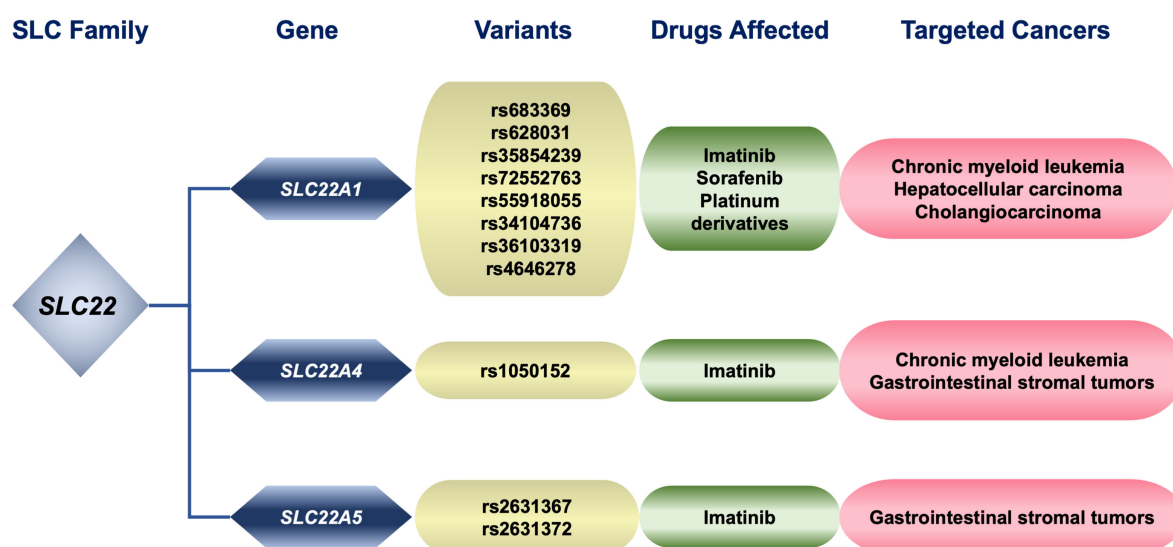
Global genetic analyses have shown marked inter-ethnic variability regarding *SLC22A1* variants affecting OCT1 activity<sup>[76]</sup>. Imatinib, whose uptake has been shown to depend on OCT1<sup>[77]</sup>, is a potent inhibitor of the BCR-ABL tyrosine kinase and has therefore been used in the treatment of chronic myeloid leukemia (CML), where this aberrant fusion protein is very frequent (> 95% of cases). Thus, OCT1 expression and activity may be a critical determinant of intracellular drug levels<sup>[78]</sup>; indeed, the OCT1 expression level has been suggested to be a valuable biomarker for predicting the success of imatinib-based therapy in CML patients<sup>[79,80]</sup>. A meta-analysis found a significant association between the presence of the *SLC22A1* variant c.480G>A/C/T (p.Leu160Phe, rs683369) and a lower response rate to imatinib in CML patients<sup>[71]</sup>. Other authors reported in a study with 278 Asian CML patients that the presence of the SNP c.1222A>C/G (p.Met408Val, rs628031) together with the intron variant g.Chr6:160139868insGTAAGTTG (rs35854239), an 8-bp insertion variant that duplicates the splicing motif 8 bp downstream of the original splicing motif, and the SNP c.1260\_1262del (p.Met420del, rs72552763) increase the probability of developing resistance to imatinib<sup>[81]</sup>. Consistent with this information, another study with 167 CML patients in the chronic phase revealed that patients with the rs628031 variant, both in homozygosis and heterozygosis, and additional rare genotypes had worse event-free survival and overall survival (OS) compared to patients with only the rs628031 variant<sup>[82]</sup>. The relevance of these results is limited because they could not be replicated in other trials. For example, the presence of the SNP rs628031 was only significantly correlated with imatinib pharmacokinetics when it was part of a haplotype that included rs3798168 and rs628031<sup>[72]</sup>.

On the other hand, in liver tumors, both in HCC and cholangiocarcinoma (CCA), many *SLC22A1* genetic variants have been found, both SNVs and aberrant splicing forms, which result in reduced or even abolished transporter function, when truncated proteins are generated<sup>[83]</sup>. For instance, in a high proportion (40%) of HCC analyzed, at least one aberrant splicing variant (often exon 10 skipping) has been reported<sup>[83]</sup>. Other examples of inactivating variants found in these tumors are c.262T>C/A (p.Cys88Ser/Arg, rs55918055), c.566C>T (p.Ser189Leu, rs34104736), c.659G>C/T (p.Gly220Ala/Val, rs36103319), and c.859C>G/T (p.Arg287Gly/Trp, rs4646278). These SNVs and others, such as c.262delT (p.Cys88Alafs\*16) and c.181delCGinsT (p.Arg61Serfs\*10), result in lower uptake of sorafenib (an oral multikinase inhibitor used for the treatment of HCC) and, therefore, lower induced cytotoxicity<sup>[83]</sup>. Similarly, the presence of OCT1 in the plasma membrane of tumor cells has been associated with a better outcome in HCC patients treated with sorafenib<sup>[84]</sup>. Similar variants have also been described in CCA. Although sorafenib is not currently included in the standard treatment of CCA, *in vitro* studies have demonstrated that the uptake of other drugs, such as platinum derivatives used in first-line pharmacological regimes, is affected by the appearance of inactivating variants of OCT1<sup>[85]</sup>.

**Table 2. Clinically relevant genetic variants of members of the SLC22A family of SLC in the pharmacokinetics, efficacy, or toxicity of antitumor drugs**

Variant	Drug	Targeted tumor	Alteration	Study size	Ethnicity	Ref.	
SLC22A1	rs683369	Imatinib	Chronic myeloid leukemia	Efficacy	60	European	[69]
		Imatinib	Gastrointestinal stromal tumors	Toxicity	118	East Asian	[70]
rs628031	Imatinib	Chronic myeloid leukemia	Efficacy	642	Multiple groups	[71]	
	Imatinib	Chronic myeloid leukemia	Pharmacokinetics	38	East Asian	[72]	
	Imatinib	Gastrointestinal stromal tumors	Toxicity	38	European	[73]	
SLC22A4	rs1050152	Imatinib	Chronic myeloid leukemia	Efficacy	189	Multiple groups	[74]
		Imatinib	Gastrointestinal stromal tumors	Efficacy	54	European	[75]
SLC22A5	rs2631367	Imatinib	Gastrointestinal stromal tumors	Efficacy	54	European	[75]
	rs2631372	Imatinib	Gastrointestinal stromal tumors	Efficacy	54	European	[75]

SLC: Solute carrier.



**Figure 2.** Relationship between genetic variants of pharmacologically relevant members of the SLC family 22, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier; SLCO: family of organic anion transporting polypeptides (OATPs encoded by *SLCO* genes).

Most studies on the clinical implications of *SLC22A1* variants have been focused on the antidiabetic drug metformin and the TKI imatinib<sup>[67-69,71,82,86]</sup>. However, it is essential to note the need to replicate the results obtained. Therefore, the clinical utility of these variants in cancer chemotherapy should be approached with caution at present. Larger sample sizes are needed to validate the role of *SLC22A1* variants in anticancer drug disposition, response, and toxicity.

OCT2 (*SLC22A2*) is mainly expressed in the kidney, located at the basolateral plasma membrane of proximal tubule cells<sup>[66]</sup>. It works with multidrug and toxin extrusion proteins MATE1 (*SLC47A1*) and MATE2 (*SLC47A2*) to eliminate many cationic and zwitterionic endogenous compounds and drugs in the urine<sup>[87]</sup>. Metformin and platinum derivatives are among the most relevant clinical substrates<sup>[66]</sup>.



More than fourteen genetic variants have been found in the *SLC22A2* gene<sup>[88]</sup>. However, the impact of these variants on chemotherapy response may be negligible because renal carcinoma expresses low OCT2 levels compared to normal kidney tissue<sup>[89]</sup>, and the antitumor drugs described as OCT2-substrates (ifosfamide and platinum derivatives)<sup>[85,90]</sup> are not used in the treatment of renal carcinoma.

*SLC22A3* missense variants are rare throughout all populations, and none of all OCT3 variants described so far result in a complete loss of function, nor have they been associated with changes in pharmacokinetics or pharmacodynamics<sup>[91]</sup>. Only the SNVs c.1110G>T (p.Met370Ile, rs137958808) and c.1199C>A/T (p.Thr400Asn/Ile, rs8187725) have functional consequences *in vitro* and show a partially reduced uptake of well-characterized substrates<sup>[91]</sup>. Although there is no described connection between *SLC22A3* variants and response to chemotherapy in patients, it has been reported that some genetic variants of *SLC22A3* in the 5'-flanking region may modulate OCT3 expression<sup>[92]</sup>.

### OCTNs

OCTN1 (*SLC22A4*) and OCTN2 (*SLC22A5*) are transporters of carnitine, acetylcholine, and ergothioneine widely distributed in the organism. OCTN1 is abundantly expressed in the digestive tract and biliary system, as well as in the bone marrow, prostate, lung, and kidney. In contrast, OCTN2 is mainly expressed in the kidney, intestine, and prostate<sup>[93]</sup>. Regarding antitumor drugs, OCTN1 participates in the uptake of mitoxantrone<sup>[94]</sup>, doxorubicin<sup>[94]</sup>, oxaliplatin<sup>[95]</sup>, imatinib<sup>[15]</sup>, and nucleoside derivatives, such as cytarabine, 2'-deoxycytidine, and gemcitabine<sup>[96]</sup>. On the other hand, the substrate specificity concerning antitumor drugs for OCTN2 is more restricted, including, for instance, etoposide<sup>[97]</sup> and imatinib<sup>[15]</sup>.

A relationship between some OCTN1/2 polymorphisms and the prognosis of some gastrointestinal tumors treated with imatinib has been established<sup>[75]</sup> [Figure 2]. In this line, in patients with gastrointestinal stromal tumors treated with imatinib, the time to progression period was significantly improved in carriers of the C allele of the *SLC22A4* variant c.1507C>T (p.Leu503Phe, rs1050152), as well as in carriers of the minor alleles of the *SLC22A5* variants c.-207C>G/A/T (rs2631367) and c.-2087G>C (rs2631372), both located at the promoter, suggesting that OCTN1 and OCTN2 activity or expression may predict the efficacy of imatinib chemotherapy<sup>[98]</sup>. Some *SLC22A4* variants can modulate imatinib response in patients with CML, where this drug is also used. For instance, an association has been found between the SNP rs1050152 of OCTN1 and the response to imatinib in CML patients<sup>[74]</sup>.

### OATs

These proteins are mainly expressed in the kidneys and liver and at lower levels, in the brain, placenta, prostate, and testis<sup>[99]</sup>. Regarding their activity, OATs can transport small and negatively charged endogenous compounds, including metabolites, signaling molecules, nutrients, gut microbiome products, antioxidants, and uremic toxins. Among their substrates are antivirals, antibiotics, nonsteroidal anti-inflammatory drugs, antihypertensives, diuretics, and many other clinically relevant drugs (for a review<sup>[100]</sup>). However, OATs have a scarce impact on antitumor drug uptake. In this line, although different genetic and splice variants have been described, no information is available on the effect of these variants in antitumor drug response.

Methotrexate, used in the treatment of several cancers (uterus, breast, and lung carcinomas, certain cancers of the head and neck, and some lymphomas and leukemias), has been described as a substrate of OAT1 (*SLC22A6*)<sup>[101]</sup> and OAT2 (*SLC22A7*)<sup>[102]</sup>. Moreover, OAT2 can participate in the uptake of irinotecan<sup>[103]</sup> and probably 5-FU<sup>[104]</sup>, which is consistent with the fact that the high expression of this transporter has been proposed as a predictor of effectiveness for 5-FU-based chemotherapeutic regimens such as FOLFOX (5-FU/leucovorin/oxaliplatin) in metastatic colorectal cancer<sup>[105]</sup>. Several genetic polymorphisms have been

described in the *SLC22A7* gene<sup>[106]</sup>, and a splice variant containing an additional nucleotide sequence of the intron 1 (TCCCAG) between exons 1 and 2 of the open reading frame has been detected in liver, kidney, and pancreas in approximately the same proportion of expression as the wild-type transporter. The peptide encoded by this variant is not functional because it is retained intracellularly and consequently lacks transport activity<sup>[107]</sup>. However, the impact of these OAT2 genetic variants on drug response has yet to be elucidated.

## THE SLC28A AND SLC29A FAMILIES OF NUCLEOSIDE TRANSPORTERS

The *SLC28* and *SLC29* gene families encode transporters accounting for the uptake of natural nitrogen bases, nucleosides, and nucleotides. They are the main pathways to crossing the plasma membrane for many purine and pyrimidine analogs used in anticancer therapies for various tumors<sup>[108-111]</sup>.

### CNTs

CNTs include three members of Na<sup>+</sup>-dependent secondary active transporters. CNT1 (*SLC28A1*) is predominantly found in the apical membrane of epithelial cells in the small intestine, liver, and kidney<sup>[112]</sup>. It mediates the uptake of pyrimidine nucleosides, including fluoropyrimidines such as gemcitabine<sup>[113]</sup>, and hypomethylating nucleoside analogs with antitumor activity, such as cytarabine, azacytidine, decitabine, and zebularine<sup>[114-117]</sup>. In addition to the loss of CNT1 expression identified in solid tumors and leukemias, where nucleoside analogs are used as first-line treatment agents<sup>[115,118,119]</sup>, several genetic variants have been associated with a worse outcome in patients with different types of cancer [Figure 3 and Table 3].

According to the PharmGKB pharmacogenomics database, the clinical relevance of these variants is low, with a level of evidence of 3, or 4 in the case of *SLC29A3*, on a scale from 1 to 4, where level 1 meets the highest criteria.

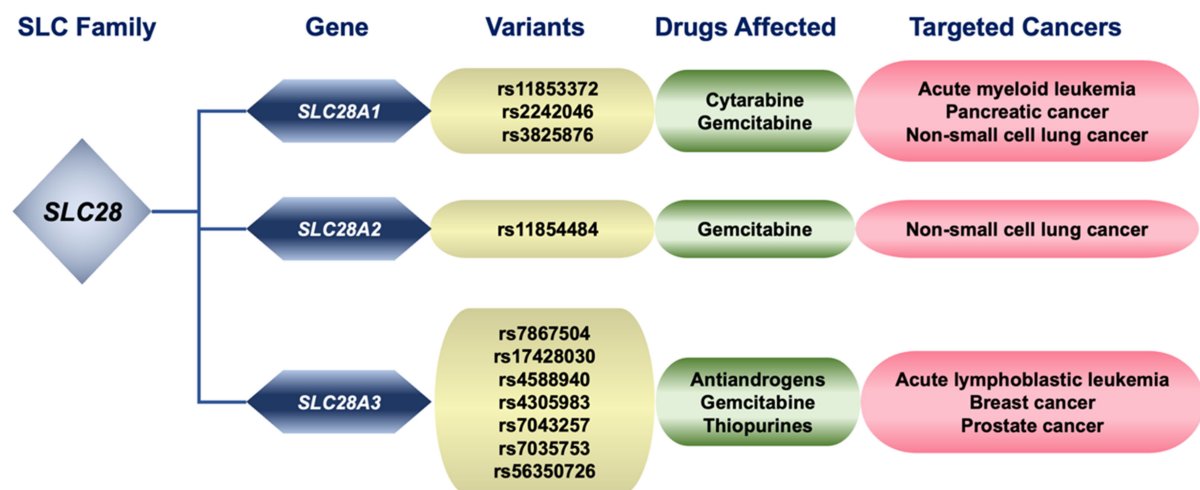
Thus, the *SLC28A1* intronic variant c.795+4320T>A (rs11853372) has been associated with low-intracellular cytarabine levels in cancer cells collected from children with leukemia<sup>[127]</sup>. A study with a heterogeneous cohort of patients with solid tumors treated with gemcitabine revealed that the rs11853372 variant was associated with impaired clearance of 2',2'-difluoro-2'-deoxycytidine triphosphate and hence could influence gemcitabine response<sup>[128]</sup>. However, these studies are not considered sufficient evidence for clinical relevance by international pharmacogenomics consortia. However, there are two variants that have a moderate clinical impact. In patients with non-small cell lung cancer (NSCLC) treated with gemcitabine-based therapy, the non-synonymous *SLC28A1* variant c.1561G>A/T (p.Asp521Asn/Tyr, rs2242046) has been associated with increased myelotoxicity due to an increased gemcitabine absorption<sup>[120]</sup>. Another intron variant, c.277+2103G>A (rs3825876), has demonstrated a higher risk of neutropenia in advanced pancreatic cancer patients treated with this drug<sup>[121]</sup>.

In contrast to CNT1, CNT2 (*SLC28A2*), whose expression is high in the intestinal tract, biliary system, and kidney, prefers purine nucleosides as substrates. A limited impact of CNT2 on tumor sensitivity to drugs transported by this transporter is expected due to its low expression in most tumor types<sup>[5]</sup>. Nevertheless, in some cancers, for instance, gastric, colorectal, endometrial, or lung adenocarcinomas, it has been shown that impaired expression or activity of CNT2 can affect the activity of the antitumor nucleoside analogs<sup>[129]</sup>. A study conducted on Asian populations regarding the association of gemcitabine pharmacology with the prognosis of patients with NSCLC has suggested that the *SLC28A2* variant c.65C>A/G/T (p.Pro22Gln/Arg/Leu, rs11854484) is associated with better outcomes. However, the reason for this relationship has yet to be elucidated<sup>[120]</sup>. Furthermore, an SNP in the promoter region of *SLC28A2* (c.-146T>A; rs2413775), which induces increased transcription of this gene, has been suggested to play a role in the interindividual variability of pharmacokinetics and pharmacological effects of nucleoside analogs<sup>[130]</sup>.

**Table 3. Clinically relevant genetic variants of members of the SLC28A and SLC29A families of SLC in the pharmacokinetics, efficacy, or toxicity of antitumor drugs**

Variant	Drug	Targeted tumor	Alteration	Study size	Ethnicity	Ref.
SLC28A1 rs2242046	Gemcitabine	Non-small cell lung cancer	Toxicity	53	East Asian	[120]
rs3825876	Gemcitabine	Pancreatic cancer	Toxicity	294	European	[121]
SLC28A2 rs11854484	Gemcitabine	Non-small cell lung cancer	Efficacy	53	East Asian	[120]
SLC28A3 rs7867504	Gemcitabine	Solid tumors	Pharmacokinetics	40	American	[122]
SLC29A1 rs9394992	Tipiracil, trifluridine	Colorectal carcinoma	Efficacy	179	Multiple groups	[123]
	Gemcitabine	Pancreatic cancer	Toxicity	149	Multiple groups	[124]
rs747199	Gemcitabine	Breast carcinoma	Efficacy	85	East Asian	[125]
rs760370	Gemcitabine	Breast carcinoma	Efficacy	85	East Asian	[125]
	Gemcitabine	Pancreatic cancer	Efficacy	149	Multiple groups	[124]
	Tipiracil, trifluridine	Colorectal carcinoma	Efficacy	179	Multiple groups	[123]
SLC29A3 rs780668	Gemcitabine	Non-small cell lung cancer	Efficacy	88	Multiple groups	[126]

SLC: Solute carrier.

**Figure 3.** Relationship between genetic variants of pharmacologically relevant members of the SLC family 28, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier.

Another member of this group of transporters is CNT3 (*SLC28A3*), which has a broad substrate selectivity. Indeed, it does not discriminate between purine and pyrimidine nucleosides and can also transport various drugs with antitumor activity, such as gemcitabine, floxuridine, and zebularine<sup>[131]</sup>. Its expression, which is elevated in carcinomas derived from the gastrointestinal tract, pancreas, ovaries, and cervix, squamous cell carcinoma of the lung, mesothelioma, and testicular tumors, is considered a valuable predictive biomarker for the response of leukemias to chemotherapy based on cytarabine<sup>[132]</sup> or thiopurines<sup>[133]</sup>. Regarding genetic modifications, several *SLC28A3* variants have been associated with resistance to antitumor drugs [Figure 3]. The variant c.267A>T/G/C (p.Thr89Thr, rs7867504) was associated with clinical outcomes in patients with metastatic breast cancer receiving gemcitabine plus paclitaxel chemotherapy<sup>[125]</sup>. Moreover, several intronic SNPs: c.60+1868T>C (rs17428030), c.61-13251T>G (rs4588940), c.60+11038T>C (rs4305983), c.60+1815A>G (rs7043257), c.-45-89G>C (rs7035753), may reduce response to thiopurines of childhood acute lymphoblastic leukemia (ALL)<sup>[134]</sup>. A study carried out on a Korean population with metastatic

prostate cancer has found that the variant c.1538A>T/G (p.Tyr513Phe/Cys, rs56350726) was associated with metastasis and progression of castration-resistant prostate cancers, probably due to a less efficient transport androgen-deprivation therapy<sup>[135]</sup>.

## ENTs

The *SLC29* gene family encodes four different ENT proteins. ENT1 (*SLC29A1*) is highly expressed in most types of cancers<sup>[5]</sup>, where it carries out most of the facilitative uptake by tumor cells of natural nucleosides and nucleoside-derived drugs, such as gemcitabine or cytarabine<sup>[136,137]</sup>. Several studies have suggested potential contributions of *SLC29A1* genetic variants [Figure 4 and Table 3]: c.946-207893C>A (rs3734703), c.-162+228A>C (rs693955), c.30-549T>C (rs324148), and c.29+913C>T (rs9394992) to the cytarabine resistance and clinical outcomes in patients with AML receiving cytarabine<sup>[138-140]</sup>. Moreover, c.-55+441G>A (rs747199) has been associated with a poorer response of breast carcinomas to gemcitabine and paclitaxel<sup>[125]</sup>. Low ENT1 expression is related to the presence of the intronic variant c.1260-201A>C (rs760370), which has been suggested as a prognostic marker in patients with colorectal cancer treated with trifluridine<sup>[141]</sup>.

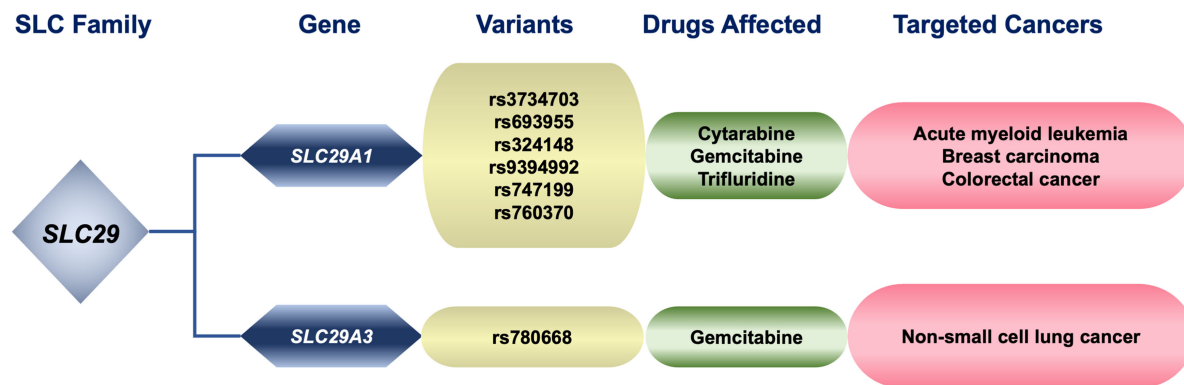
Although ENT2 (*SLC29A2*) and ENT1 are thought to play an essential role in the uptake of antitumor purine and pyrimidine analogs, ENT2 has a more restricted tissue expression profile. High *SLC29A2* mRNA levels are found in the digestive tract and tumors derived from these tissues<sup>[5]</sup>.

Although the genetic variability of ENT3 (*SLC29A3*), which has a high affinity for adenosine, is very low compared to ENT1, and hence, variations in its coding sequence are expected to have a low impact on the clinical response to drugs taken up by this transporter, the expression of the *SLC29A3* variant c.473C>T (p.Ser158Phe, rs780668) seems to correlate with the outcome of NSCL patients treated with gemcitabine<sup>[126]</sup> [Figure 4].

## SLC31 FAMILY OF COPPER TRANSPORTERS

Proteins encoded by the *SLC31* genes, together with ATP7A and ATP7B P-type ATPases, regulate cellular copper levels. CTR1 (*SLC31A1*), expressed at the plasma membrane, is involved in the uptake of monovalent copper by the cells, whereas CTR2 (*SLC31A2*), located in intracellular membranes, is involved in vacuolar accumulation<sup>[142]</sup>. CTR1, which has higher substrate affinity than CTR2, is ubiquitously expressed in the body, with the highest levels found in the liver, gastrointestinal tract, kidney, and choroid plexus. Although CTR1 is expressed in many types of cancers, the highest levels are found in tumors derived from tissues where CTR1 expression is high<sup>[5]</sup>. In addition to copper, CTR1 can also transport other metals such as cadmium, silver, zinc, and cobalt<sup>[142]</sup>. Its interest in cancer pharmacology is based on the ability of this transporter to mediate the uptake of platinum-derived antitumor drugs such as cisplatin, oxaliplatin, and carboplatin<sup>[143,144]</sup>. Accordingly, CTR1 expression is clinically more relevant in tumors whose treatments include platinum derivatives, which is the case of reproductive, respiratory, and most gastrointestinal cancers<sup>[5,145]</sup>.

Few genetic variants of *SLC31A1* have been described in healthy tissues, and there is no evidence supporting any impact of these altered proteins on the pharmacokinetics, response, and toxicity of the drugs transported by CTR1<sup>[146]</sup>. According to the COSMIC database of mutations in cancer, *SLC31A1* is mutated in less than 1% of samples, reaching 2.1% in HCC, 2.0% in CCA, and 1.8% in endometrial carcinoma<sup>[147]</sup>. Most studies on the relevance of *SLC31A1* variants in cancer chemoresistance have been carried out in patients with NSCLC, a type of cancer treated with platinum derivatives [Figure 5 and Table 4].

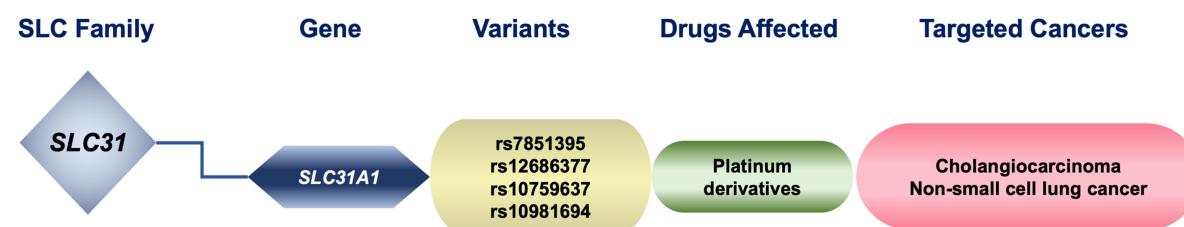


**Figure 4.** Relationship between genetic variants of pharmacologically relevant members of the SLC family 29, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier.

**Table 4.** Clinically relevant genetic variants of members of other families of SLC in the pharmacokinetics, efficacy, or toxicity of antitumor drugs

Variant	Drug	Targeted tumor	Alteration	Study size	Ethnicity	Ref.
SLC31A1 rs7851395	Carboplatin, cisplatin	Non-small cell lung cancer	Efficacy	282	East Asian	[148]
rs10759637	Platinum compounds	Non-small cell lung cancer	Efficacy	1004	East Asian	[149]
rs10981694	Cisplatin	Non-small cell lung cancer	Toxicity	204	East Asian	[150]
	Cisplatin	Testicular neoplasms	Toxicity	196	American	[151]
SLC7A5 rs4240803	Melphalan	Myeloma	Toxicity	135	American	[152]
SLC19A1 rs1051266	Methotrexate	Lymphoblastic leukemia	Efficacy	31	Latino	[153]
	Methotrexate	Osteosarcoma	Efficacy	62	European	[154]
	Methotrexate	Lymphoblastic leukemia	Toxicity	95	East Asian	[155]
	Methotrexate	Osteosarcoma	Toxicity	37	East Asian	[156]

SLC: Solute carrier.



**Figure 5.** Relationship between genetic variants of pharmacologically relevant members of the SLC family 31, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier.

In the scale of the PharmGKB pharmacogenomics database, the clinical relevance of these variants is for 3 *SLC31A1* and *SLC7A5*, and 4 in the case of *SLC19A1*.

Although intron variants are not expected to alter the protein structure (unless they favor aberrant splicing), they can markedly affect the expression levels. Thus, g.116002464A>G (rs7851395) and g.116004033C>A (rs12686377) cause CTR1 downregulation<sup>[148]</sup>, which has been associated with a worse response of NSCLC patients to platinum derivative therapy<sup>[148]</sup>. A similar association has been reported for the germinal SNP g.116025024A>C (rs10759637), which affects the 3'-UTR region of *SLC31A1* mRNA and reduces the

expression of the transporter. Following intravenous administration of the platinum drug, the presence of the rs10759637 variant results in decreased platinum uptake in tissues and its accumulation in bone marrow and peripheral blood, and is therefore associated with increased platinum resistance in the tumor and the occurrence of hematological toxicity such as thrombocytopenia<sup>[149]</sup>. The intron variant g.113224129T>G (rs10981694) has also been associated with cisplatin-induced ototoxicity in patients with NSCLC, and it has been suggested that detection of its presence before treatment could be considered when choosing cisplatin treatment in these patients<sup>[150]</sup>. CCA is another cancer treated with drug combinations that include cisplatin. Although no association has been found between the presence of the SNP rs12686377 of *SLC31A1* and patient response, when this SNP appears with *ERCC1* variants, it could predict a lack of response to treatment with gemcitabine plus cisplatin<sup>[157]</sup>.

## THE SLC47 FAMILY OF MULTIDRUG AND TOXIN EXTRUSION TRANSPORTERS

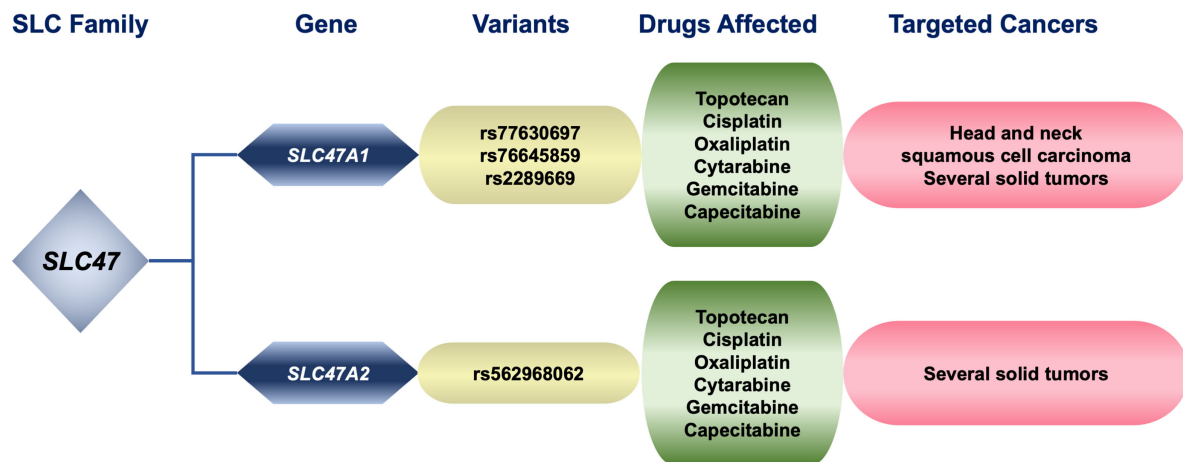
MATE1 and MATE2 are bidirectional H<sup>+</sup>/organic cation transporters<sup>[158,159]</sup>. MATE1 was identified in 2005 as a mammalian ortholog of the MATE bacterial family that confers resistance to multiple drugs<sup>[158]</sup>. MATE1 is highly expressed in the liver and kidney in humans and localizes to the canalicular membrane of hepatocytes and the apical membrane of proximal tubular cells. Additionally, MATE1 is also expressed in skeletal muscle and other tissues<sup>[160]</sup>. MATE2 pre-mRNA can generate two major alternative splicing variants. The long one (MATE2-B) is a non-functional variant ubiquitously expressed in all tissues except the kidney. The short variant (MATE2-K) is translated into an active transporter with kidney-specific expression<sup>[161]</sup>. Functionally, MATE1 and MATE2-K work together as a detoxification system by mediating renal tubular secretion of intracellular ionic compounds across the brush border membranes<sup>[158]</sup>.

The endogenous substrates of MATE1 and MATE2 include the organic cations creatinine, guanidine, and thiamine, organic anions, such as estrone sulfate, and neutral steroids, such as corticosterone<sup>[158,159,161]</sup>. In addition, it has been shown that around 30 drugs in clinical use were identified as MATE substrates. These include antineoplastic drugs such as topotecan<sup>[159]</sup>, cisplatin, oxaliplatin<sup>[162,163]</sup>, cytarabine, gemcitabine, and capecitabine<sup>[164]</sup>. More information is needed on the impact of MATE expression and impaired functions due to genetic variants in drug handling by tumor cells because, up to now, most studies have been focused on their role in the pharmacokinetics of anticancer agents. More than 16,000 SNPs and SNVs are currently listed for *SLC47A* genes in the NCBI-SNP database, most located in non-coding regions and just over 2,200 in exons. Although most studies of MATE1 and MATE2 pharmacogenetics have been performed for metformin<sup>[86]</sup>, a similar impact could be extrapolated to anticancer drugs transported by these proteins [Figure 6]. In a study with a cohort of patients with kidney damage, two *SLC47A1* variants have been found: c.191G>A (Gly64Asp, rs77630697) and c.1438G>A (p.Val480Met, rs76645859) and one in *SLC47A2*: c.740G>T (p.Gly211Val, rs562968062), which cause a loss of protein function. Increased accumulation of oxaliplatin has been found in the kidney, with subsequent nephrotoxicity suggesting that it could be caused by loss of function<sup>[165]</sup>. One study has linked the presence of *SLC47A1* variants to cisplatin-induced toxicity. In an adult cohort of patients with head and neck squamous cell carcinoma who received cisplatin treatment, the presence, in homozygosity or heterozygosity, of the *SLC47A1* variant g.19560030G>A (rs2289669) was found to predispose to cisplatin-induced toxicity<sup>[166]</sup>.

## OTHER SLC TRANSPORTERS

### Facilitative glucose transporters

The first four members of the SLC2A subfamily are facilitative transporters of hexoses, mainly glucose. Facilitative glucose transporter 1 (GLUT1, gene *SLC2A1*) is the major glucose transporter in the brain, placenta, and erythrocytes<sup>[167]</sup>. GLUT2 (gene *SLC2A2*) is a low-affinity, high-capacity transporter, which, besides being involved in glucose transport by the liver and kidney, acts as a glucose sensor by mediating



**Figure 6.** Relationship between genetic variants of pharmacologically relevant members of the SLC family 47, substrate drugs affected by changes in these proteins, and cancers treated with these compounds. SLC: Solute carrier.

glucose uptake by beta pancreas cells<sup>[167]</sup>. GLUT3 (*SLC2A3*) is involved in glucose transport by the placenta and brain, while GLUT4 (*SLC2A4*) is the insulin-sensitive transporter expressed in skeletal muscle, heart, and adipose tissue<sup>[167]</sup>. Enhanced expression of GLUTs has been observed in several types of cancer<sup>[168]</sup>. For instance, GLUT1 upregulation has been reported in HCC<sup>[169]</sup>, pancreatic tumors<sup>[170,171]</sup>, cervical squamous cell carcinoma<sup>[172]</sup>, prostate cancer, and several other cancers<sup>[168]</sup>. This is clinically relevant because glucose uptake is required for cancer development, progression, and metastasis. Regarding chemoresistance, evidence suggests a link between glycolysis and DNA repair mechanisms, as the glycolytic pathway provides metabolites that play an essential role in DNA metabolism<sup>[173]</sup>. Accordingly, glucose transporter inhibitors can be used in cancer therapy to enhance the cytostatic effect of DNA-damaging drugs like cisplatin<sup>[168]</sup>. The presence of *SLC2A1* genetic variants, such as g.43426591C>T (rs3738514), g.43392250C>G/T (rs4658), and g.43387302C>G/T (rs841844), has been associated with the overall toxicity of platinum-based chemotherapy in lung cancer patients<sup>[174]</sup>. In HCC, high expression of GLUT2 has been associated with poorer outcomes<sup>[175,176]</sup>. Furthermore, an elevated GLUT2 expression has also been found in more invasive versions of ductal carcinoma, tubular colon carcinoma, pancreatic adenocarcinoma, and pulmonary mesothelioma<sup>[177]</sup>. Whether *SLC2A2* genetic variants have an impact on the development of resistance to anticancer drugs and other malignant characteristics of these tumors is yet unknown.

### Amino acid transporters

The L-type amino acid transporter 1 (LAT1; *SLC7A5*)<sup>[178]</sup>, which preferentially transports large neutral amino acids, including most essential amino acids, is overexpressed in several types of cancer<sup>[178,179]</sup>. Some studies have suggested that LAT1 expression correlates with cancer cell growth and proliferation<sup>[180]</sup>, which has led to the proposal of LAT1 as a potential prognostic biomarker in different types of cancer<sup>[181,182]</sup>. Moreover, LAT1 is an appealing target for pharmacologically manipulating the uptake of cancer drugs and prodrugs, such as melphalan and acivicin<sup>[183-185]</sup>. Several compounds that specifically inhibit LAT1, like the novel tyrosine analog nanvuranlat (JPH203), have been developed to treat several types of solid tumors<sup>[186-188]</sup>. Genetic variants of *SLC7A5* have been associated with cancer pharmacology. Thus, the variant g.87889203G>A/C/T (rs4240803), both in homozygosis and heterozygosis, has been related to a decreased risk of melphalan-induced gastrointestinal toxicity in patients with multiple myeloma treated with this drug<sup>[152]</sup> [Table 4].

## Folate transporters

Since folate is required for cancer cell proliferation, folate transporters play a relevant role in the response to antifolate drugs. Namely, two transporters must be considered: reduced folate transporter 1 (RFC1, *SLC19A1*), which is the primary transporter responsible for folate uptake widely expressed in the body<sup>[189,190]</sup>, and the proton-coupled folate transporter (PCFT, *SLC46A1*)<sup>[191]</sup>. RFC1 mediates high-affinity transport by tumor cells of antifolate chemotherapeutic agents, such as methotrexate and pemetrexed<sup>[192,193]</sup>, raltitrexed, and pralatrexate<sup>[194,195]</sup>. These drugs can also be transported, although to a lesser extent, by PCFT<sup>[194,196,197]</sup>.

High expression of RFC1 has been detected in NSCLC, squamous cell carcinoma, neuroblastoma, colorectal carcinoma, and urothelial bladder carcinomas<sup>[198-200]</sup>. Because antifolates are essential drugs in the treatment of numerous cancers, including pediatric ALL, osteogenic sarcoma, lymphoma, breast cancer, non-small cell lung cancer, and malignant pleural mesothelioma<sup>[201-203]</sup>, the appearance in tumor cells of *SLC19A1* variants associated with altered transport of these anticancer drugs, can result in poorer responses in these patients<sup>[204]</sup>. For instance, the SNP g.46957794T>C/G (rs1051266) has been associated with increased severity of adverse effects of methotrexate in patients with precursor cell lymphoblastic leukemia<sup>[205]</sup>. Moreover, the SNP g.46957794T>C/G (rs1051266), both in homozygosis and heterozygosis, has been associated with decreased plasma concentrations of methotrexate in children with osteosarcoma<sup>[156]</sup>. Finally, the SNP g.46948827G>A/C/T (rs4818789) is associated with a decreased risk of adverse effects when treated with cyclosporine and methotrexate in people with hemopoietic stem cell transplant<sup>[206]</sup>.

## CONCLUSION

Besides the complexity of the clinical problem posed by diverse and synergistic MOCs accounting for the lack of response of many cancers to pharmacological treatments, the available evidence supports the existence of a higher degree of complexity due to the appearance of genetic variants in the elements forming part of the resistome. The present review highlights the clinical impact of a subset of MOC genes belonging to the transportome, and more precisely, these transporters involved in drug uptake, which has been classified as MOC-1A subtype<sup>[1,2]</sup>. The presence of variants favoring the resistance acts as a Darwinian selection factor, thus contributing to developing a more malignant phenotype during cancer progression. Accordingly, the effort to achieve the desirable horizon of more personalized medicine to treat cancer patients requires the identification of this issue in all its dimensions, i.e., not only measuring the expression levels of every gene involved in the resistome but also characterizing the different variants that can affect their function. It is also essential to consider the time-dependent aspect of these features, as the genetic expression and the appearance of genetic variants can change during tumor progression and in response to treatment.

At present, evidence for the existence of an association between genetic variant-drug combinations is limited to genes encoding uptake transporters for antitumor drugs. Further research supporting such associations is needed to reach the level seen with more studied drugs, such as statins. For these drugs, a personalized genetic information influences the adjustment of their prescription, and clinical guidelines recommend testing each individual for genetic characteristics before drug administration.

## DECLARATIONS

### Authors' contributions

Literature mining: SLC22 family (Lozano E), SLCO (Briz O), SLC28 and SLC29 (Herraez E), SLC31 (Perez-Silva L), SLC47 (Ortiz-Rivero S), other SLCs (Serrano MA)



Writing the draft: General aspects (Marin JJG, Briz O), SLC22 family (Lozano E), SLCO (Briz O), SLC28 and SLC29 (Herraez E), SLC31 (Perez-Silva L), SLC47 (Ortiz-Rivero S), other SLCs (Serrano MA), formatting and bibliographic aspects (Reviejo M, Marin JJG, Briz O)

Final revision: Marin JJG, Serrano MA, Herraez E, Lozano E, Ortiz-Rivero S, Perez-Silva L, Reviejo M, Briz O

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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