

Title Page

Emerging Roles of The Human Solute Carrier 22 Family (SLC22)

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Abbreviations:

DDI: Drug-drug Interaction

FLIPT: Fly-Like Putative Transporter

MFS: Major Facilitator Superfamily

OAT: Organic Anion Transporter

OCT: Organic Cation Transporter

OCTN: Organic Cation Transporter Novel (Organic Zwitterions/Cation Transporters)

SLC: Solute Carrier

SV: Synaptic Vesicle Proteins

SVOP: synaptic vesicle 2-related proteins

TMD: Transmembrane domain

URAT: Uric Acid Reabsorptive Transporter

Running Title:

SLC22 family

ABSTRACT

The human Solute Carrier 22 family (SLC22), also termed the organic ion transporter family, consists of 28 distinct multi-membrane spanning proteins, which phylogenetically cluster together according to their charge specificity for organic cations (OCTs), organic anions (OATs) and organic zwitterion/cations (OCTNs).

Some SLC22 family members are well characterized in terms of their substrates, transport mechanisms and expression patterns, as well as their roles in human physiology and pharmacology, whereas others remain orphans with no known ligands. Pharmacologically, SLC22 family members play major roles as determinants of the absorption and disposition of many prescription drugs, and several including the renal transporters, OCT2, OAT1 and OAT3 are targets for many clinically important drug-drug interactions. In addition, mutations in some of these transporters (SLC22A5 (OCTN2) and SLC22A12 (URAT1) lead to rare monogenic disorders. Genetic polymorphisms in SLC22 transporters have been associated with common human disease, drug response and various phenotypic traits. Three members in this family were deorphaned in very recently: SLC22A14, SLC22A15 and SLC22A24, and found to transport specific compounds such as riboflavin (SLC22A14), anti-oxidant zwitterions (SLC22A15) and steroid conjugates (SLC22A24). Their physiologic and pharmacological roles need further investigation. This review aims to summarize the substrates, expression patterns and transporter mechanisms of individual SLC22 family members and their roles in human disease and drug disposition and response. Gaps in our understanding of SLC22 family members are described.

SIGNIFICANCE STATEMENT

In recent years, three members of the SLC22 family of transporters have been deorphaned and found to play important roles in the transport of diverse solutes. New research has furthered our understanding of the mechanisms, pharmacological roles, and clinical impact of SLC22 transporters. This minireview provides overview of SLC22 family members of their physiologic and pharmacologic roles, the impact of genetic variants in the SLC22 family on disease and drug response, and summary of recent studies deorphaning SLC22 family members.

Introduction

The human Solute Carrier Superfamily (SLC) now consists of 465 genes encoding multi-membrane spanning proteins that cluster together into 65 distinct families based upon sequence homology (Meixner et al., 2020). Most of the proteins with known function serve as facilitated or secondary active membrane transporters. Of the 65 families, the SLC22 family, known as the Organic Ion Transporter Family, is among the largest, with 28 members that cluster together phylogenetically based on charge specificity (**Figure 1**). Pharmacologically, many members of the SLC22 family play key roles in pharmacokinetics and drug disposition, including organic anion transporters (OATs) and organic cation transporters (OCTs). In addition, mutations in several of the transporters lead to rare monogenic disorders. Though most of the transporters have known biological functions as is evident through cellular assays, studies in genetically engineered mice and human genetic studies (**Figure 2**), there remain 10 orphans in the family, that is, genes encoding proteins with no known function. In this minireview, following a description of the SLC22 family including phylogenetic relationships among family members, individual transporters in each of the charge specific groups (anion, cation and zwitterion) are briefly described including their substrate selectivity, transport mechanism and tissue distribution. A section on the role of SLC22 family members in pharmacogenomics and as targets of drug-drug interactions is included. Finally, following a brief description of monogenic disorders caused by mutations in two SLC22 family members (OCTN2 (SLC22A5) and URAT1 (SLC22A12)), a perspective on future research in the SLC22 family is provided.

Brief Historical Perspective

The SLC22 family belongs to the major facilitator superfamily (MFS). In the human genome, the SLC22 family includes 28 members: 23 SLC22A family members and five atypical SLC22B, which are designated synaptic vesicle proteins (SV2A-C) and synaptic vesicle 2-related proteins (SVOP and SVOPL) (**Figure 1**) (Perland et al., 2017; Meixner et al., 2020). In 2004, the phylogenetic tree of the human SLC22 family only included 18 members (Koepsell and Endou, 2004). However, in 2007, the family was expanded to include

vesicular proteins, SV2 and SVOP, the unknown substrate transporters on chromosome 11q12.3 and others (Jacobsson et al., 2007; Fredriksson et al., 2008; Wu et al., 2009). Recently, a member MFSD10 was annotated as SLC22A32 resulting in the current 28 members in the human SLC22 family (Meixner et al., 2020). All share a predicted 12-transmembrane domain structure with a large extracellular loop between TMD1 and TMD2 (Fredriksson et al., 2008). With the exception of MFSD10, which was crystallized in an outward-facing state at 2.6 Å resolution by X-ray crystallography (Pascoa et al., 2021) no other SLC22 family member has been crystallized or structurally resolved.

In 1994, the rat organic cation transporter (Oct1), Slc22a1, was the first member in the SLC22 family to be molecularly identified through expression cloning (Grundemann et al., 1994). Subsequently in 1997, the human ortholog, SLC22A1 (OCT1) and a paralog, SLC22A2 (OCT2) were identified (Gorboulev et al., 1997; Zhang et al., 1997). Soon after the identification of OCT1 and OCT2, two zwitterion transporters, OCTN1 (SLC22A4) and OCTN2 (SLC22A5) were cloned and characterized (Tamai et al., 1997; Wu et al., 1998). OCTN1 was at first thought to be a weak carnitine transporter and was later found to be an excellent transporter of ergothioneine (Grundemann et al., 2005). OCTN2 was immediately recognized as an important carnitine transporter in the intestine and kidney and was later discovered to be responsible for Carnitine Transporter Deficiency (Nezu et al., 1999), a life-threatening autosomal recessive human disorder. Although it was reported that a novel kidney transporter (NKT) in mouse exist in 1997 (Lopez-Nieto et al., 1997), the human organic anion transporters were identified and functionally characterized in 1999 (SLC22A6 (OAT1) and SLC22A8 (OAT3)) (Race et al., 1999) and in 2001 (SLC22A7 (OAT2)) (Sun et al., 2001) (**Figure 2, Supplemental Table 1**).

After publication of the sequence of the human genome in 2001, many more organic ion transporters in the SLC22 family were cloned and characterized. In 2003, the HapMap Consortium developed the first human genomewide maps of common variation in three major ancestral populations (International HapMap, 2003; Claussnitzer et al., 2020). From 2000 to 2015, investigators associated with the Pharmacogenomics of Membrane Transporters project, funded by the National Institutes of Health (NIH) identified and functionally characterized genetic variants in membrane transporter genes including many members of the SLC22

family (**Figure 2**) (Shu et al., 2006; Kroetz et al., 2010). Variants were identified in DNA samples from four major ethnic groups (**Figure 2, Supplemental Table 1**).

Direct species orthologs of most of the genes in the human SLC22A and SLC22B family exist; however, some of the genes have no direct species orthologs (**Figure 1 and 2**). For example, the genes in the human chromosomal region 11q12.3 (hg38, chr11:63,079,940-63,410,294), which includes SLC22A9, SLC22A10, SLC22A24 and SLC22A25 have low sequence identity to the parallel mouse syntenic region localized on mouse chromosome 19. Notably, the genes in mouse chromosome 19 (chr19:7,643,247-8,392,204, mm39) are designated as Slc22a19, Slc22a26, Slc22a27, Slc22a28, Slc22a29 and Slc22a30 (Wu et al., 2009), and lack direct human orthologs. In addition, the orphan transporter SLC22A31 has no mouse ortholog. Conversely, the mouse transporters, Slc22a21 (*Octn3*) and Slc22a20 (*Oat6*) (Wu et al., 2015a) have no human orthologs. In fact, the human SLC22A20 is annotated as a pseudogene by NCBI (https://www.ncbi.nlm.nih.gov/nucore/NR_033396.1).

The major events that involved the discovery and characterization of members of the human SLC22 family are shown in **Figure 2**, which begins with discovery of the molecular identities of members of the SLC22 family and includes functional characterization of their polymorphisms, knockout mice and recent deorphaning studies.

Key Recent Advances

In this section, we summarize the function, tissue distribution and transport mechanisms of individual transporters in the SLC22 family. Further, we describe recent advances in deorphaning members of the SLC22 family, and present new information on genomics, pharmacogenomics and disease genetics of members of the SLC22 family.

Organic Cation Transporters: Function; Tissue Distribution and Transport Mechanism

Three transporters with known preference for organic cations are members of the SLC22 family: OCT1 (SLC22A1), OCT2 (SLC22A2) and OCT3 (SLC22A3). In the human genome, the genes encoding these

transporters are located on chromosome 6 and are about 70% identical to one another. Localized primarily to the plasma membrane, OCT1, OCT2 and OCT3 are facilitated transporters that are independent of sodium or proton gradients. These transporters have been extensively studied and excellent review articles have been recently published (Lai et al., 2018; Koepsell, 2020; Samodelov et al., 2020; Koepsell, 2021b; Koepsell, 2021a). Their function, tissue distribution and substrate selectivity are briefly summarized below.

OCT1 (SLC22A1): As the first member of the human SLC22 family to be cloned and functionally characterized (**Figure 2**), OCT1 is among the most highly expressed SLC transporter in the human liver (**Figure 3, Supplemental Table 2**). Studies have shown significant correlation of OCT1 transcript and protein levels in liver tissues or hepatocytes (Nies et al., 2009; Fattah et al., 2017) and OCT1 protein expression is lower in neonates and significantly higher in adults (Prasad et al., 2016). In contrast, OCT1 has extremely low expression levels in all other tissues except whole blood, where its expression levels are detectable and higher than its two paralogs, OCT2 and OCT3. Proteomic studies showed protein expression levels of OCT1 in small intestine although much lower levels than other known transporters, such as OATP2B1 (Drozdik et al., 2019; Kiss et al., 2021). OCT1 promiscuously transports structurally diverse organic cations including naturally occurring compounds such as thiamine (vitamin B1) and histamine and many synthetic drugs (e.g., metformin and sumatriptan) (**Table 1**). The transport mechanism is bidirectional and is driven by the substrate concentration and potential difference across the plasma membrane (**Figure 4**). Inhibitors of the transporter include a diverse array of prescription drugs (Ahlin et al., 2011; Chen et al., 2017; Meyer et al., 2019; Koepsell, 2021b). Canonical substrates of OCT1 used in functional assays in cells are TEA (tetraethylammonium) and MPP⁺ (N-methylpyridinium). ASP⁺ (4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide) has been used as a fluorescent substrate of the transporter and its paralogs (Gorboulev et al., 1997; Zhang et al., 1997; Ciarimboli et al., 2004). Canonical Inhibitors of OCT1, which can be used in cellular assays, include verapamil and quinidine.

OCT2 (SLC22A2): In contrast to OCT1 with its primary expression in the liver, OCT2 is highly expressed in the kidney, where it is localized to the basolateral membrane of the renal tubule. OCT2 expression in the kidney is largely in the proximal tubule (**Figure 3**), but it is also present in the Loop of Henle and distal

tubule (Humphreys, 2021). Targeted proteomic studies showed high abundance of OCT2 in human kidney and a strong correlation between transcript and protein levels of OCT2 in kidney (Cheung et al., 2019). Similarly, to OCT1, OCT2 protein levels are lower in neonates (Cheung et al., 2019) but similar across children, adolescents and adults (Li et al., 2019). It works in concert with apical membrane transporters, e.g., multi-drug and toxin extrusion proteins (MATEs, SLC47) to mediate secretory flux from blood to urine of many basic drugs. The substrate selectivity of OCT2 overlaps extensively with OCT1. That is, the transporter interacts with structurally diverse basic drugs and naturally occurring amines. Canonical substrates of OCT2 include the anti-diabetic drug, metformin, and the anti-cancer drug, cisplatin. OCT2 is thought to play major roles in the renal elimination of basic drugs and the renal toxicity of cisplatin. Canonical inhibitors include cimetidine, trimethoprim and pyrimethamine (Koepsell, 2020); however, these compounds also inhibit MATEs albeit with different kinetic properties. Thus, in a clinical situation or *in vivo* in animals it is often difficult to pinpoint the transporter implicated in a renal drug-drug interaction.

OCT3 (SLC22A3): In contrast to both OCT1 and OCT2, which are highly expressed in a single tissue, OCT3 is expressed in many tissues including arterial tissues, tibial nerve, prostate, ovaries and uterus (**Figure 3**). It is also expressed in tissues important in drug absorption and elimination including the liver, kidney and intestine, both at transcript and proteomic studies (Nies et al., 2009; Drozdziak et al., 2019; Oswald et al., 2019). In the intestine, OCT3 appears to be localized to the apical membrane and to play a role in drug absorption (Chen et al., 2015) whereas in the liver and kidney, the transporter appears to co-localize with its paralogs, OCT1 and OCT2 on the basolateral membrane. In organs of elimination, OCT3 is expressed at substantially lower levels than its paralogs, suggesting that it plays a lesser role in the elimination of most drugs. Like OCT1 and OCT2 the transport mechanism for OCT3 is facilitated and based on the electrochemical gradient across the plasma membrane. The substrate selectivity of OCT3 overlaps substantially with OCT1 and OCT2. Endogenously the transporter appears to be involved in the reuptake of catecholamines thus regulating local concentrations of neurotransmitters in the vicinity of their receptors (Song et al., 2019). In cancer, inhibition of OCT3 transport has been shown to be protective against doxorubicin-induced cardiac injury (Huang et al., 2021). In addition, loss of OCT3 appears to play a role in promoting hepatic fibrosis, where *Oct3^{-/-}* mice showed increasing expression levels of Tgfβ1 (both protein

and mRNA), as well as upregulation of transforming growth factor (TGF) β -dependent genes (Vollmar et al., 2019).

Organic Anion Transporters: Function; Tissue Distribution and Transport Mechanism

The human organic anion transporter subfamily of the SLC22 family consists of eight transporters: OAT1 (SLC22A6), OAT2 (SLC22A7), OAT3 (SLC22A8), OAT4 (SLC22A11), OAT7 (SLC22A9), OAT10 (SLC22A13), SLC22A24 and URAT1 (SLC22A12). SLC22A24, which was recently deorphaned, will be described in the section *Recent Deorphaning Studies of Transporters in the SLC22A Family*. Localized primarily to the plasma membrane, these transporters have distinct mechanisms to mediate transmembrane flux of their substrates. Below, their function, specificity, tissue distribution and other molecular characteristics are described. Excellent reviews, which describes most of these transporters, have been recently published (Nigam, 2015; Nigam, 2018; Kuang et al., 2021; Zhang et al., 2021).

OAT1 (SLC22A6): The first member of the organic anion transporter subfamily, OAT1 is highly and predominantly expressed in the human kidney (**Figure 3**). To handle the high plasma levels of organic anions, the transporter is exclusively localized to the basolateral membrane of the proximal tubule (Breljak et al., 2016; Humphreys, 2021). Proteomic studies showed significant correlation with transcript levels and high abundance in the kidney (Nakamura et al., 2016; Cheung et al., 2019; Li et al., 2019; Oswald et al., 2019). The mechanism by which OAT1 transports its solutes across the plasma membrane is through exchange with the dicarboxylic acid, alpha-ketoglutarate, which is transported into the renal epithelia by sodium-dependent transporters in the SLC13 family. Thus, the transport mechanism is considered to be tertiary active. That is, the primary active transporter, sodium-potassium ATPase, creates an inwardly-directed sodium gradient, which in turn, drives the intracellular accumulation of alpha-ketoglutarate. Alpha-ketoglutarate then flows down its concentration gradient in the efflux direction via OAT1 in exchange for an OAT1 substrate (in the influx direction) (Lu et al., 1999; Uwai et al., 2017). Typical substrates of OAT1 include drugs (e.g., penicillins, cephalosporins, non-steroidal inflammatory drugs, and anti-viral drugs), toxins (ochratoxin) and a range of compounds derived from gut bacterial or human metabolism such as uric acid, para-amino hippuric acid, and indoxyl sulfate (**Table 1**). Like OCT2, the transporter is a target for

renal drug-drug interactions, and therefore is studied extensively during drug development (International Transporter et al., 2010; Zamek-Gliszczyński et al., 2018).

OAT3 (SLC22A8): Similar to OAT1, OAT3 is highly and predominantly expressed in the human kidney, with much lower levels of expression in other tissues (**Figure 3**). Proteomic studies showed similar abundance of OAT1 and OAT3 in the kidney, with lower expression levels in the neonates (Cheung et al., 2019; Li et al., 2019; Oswald et al., 2019). Its high levels of expression in the kidney is consistent with the transporter's role in eliminating many naturally occurring and synthetic compounds (Nigam, 2015; Nigam, 2018; Kuang et al., 2021; Zhang et al., 2021). Single cell RNA-seq data place OAT3 in all three segments of the proximal tubule (S1, S2 and S3) (Humphreys, 2021) and along with OAT1, OAT3 has been localized to the basolateral membrane serving in the secretion of its substrates (Breljak et al., 2016). In the choroid plexus, the transporter appears to move its substrates from the CSF back to the blood (Uchida et al., 2020). Like OAT1, OAT3 is a tertiary active transporter moving its substrates into the proximal tubule cells in exchange for alpha-ketoglutarate (Burckhardt et al., 2005; Burckhardt, 2012; Uwai et al., 2017) (**Figure 4**).

Pharmacologically, OAT3 interacts with structurally diverse organic anions and has overlapping but broader substrate specificity compared to OAT1 (**Table 1**). Recent studies suggest that both OAT1 and OAT3 potently interact with drug metabolites, including sulfate and glucuronide conjugates as well as oxidized metabolites (Wu et al., 2017; Zou et al., 2021); however, OAT3 has a broader selectivity for metabolites than OAT1 (Astorga et al., 2011). Consistently, OAT3, in contrast to OAT1, can interact potently with certain non-anionic compounds including some basic drugs such as cimetidine, where it may play a role in their renal elimination (Tahara et al., 2005).

OAT2 (SLC22A7): In contrast to OAT1 and OAT3, which have a predominant localization to the kidney, OAT2 is expressed abundantly in both the kidney and liver with lower levels of expression in other tissues and organs (**Figure 3**). This is similar to proteomic studies of the liver and kidney (Nakamura et al., 2016; Oswald et al., 2019). The transporter interacts with many organic anions such as para-aminohippuric acid, and various anti-viral drugs, as well as other compounds. For example, OAT2 is also capable of transporting various nucleobases, nucleosides and nucleotides including the cyclic nucleotide, cGMP as

well as nucleoside analog drugs (e.g., ganciclovir, warfarin) (Bi et al., 2018; Mathialagan et al., 2018). Recent studies suggest that the transporter works with other hepatic uptake transporters to mediate drug disposition (Zamek-Gliszczynski et al., 2018). Its role can be distinguished from other liver organic anion transporters with the use of a specific inhibitor, ketoprofen (Bi et al., 2019), and penciclovir has been proposed as a specific substrate for use in human hepatocytes (Mathialagan et al., 2018).

OAT4 (SLC22A11): Most highly homologous to URAT1 (*SLC22A12*) in the SLC22 family (**Figure 1**), OAT4 is highly and selectively expressed in the kidney; however, its transcript and proteomic levels are more akin to OCT2 than to the much higher levels of OAT1 or OAT3 (**Figure 3**) (Li et al., 2019). Unlike OAT1, OAT2 and OAT3, OAT4 has an apical localization in the proximal tubule where it plays a role in renal reabsorption (Miyazaki et al., 2005). It appears to be localized to segments 1 and 3 of proximal tubule epithelial cells and at lower levels in other cell types in the kidney (Humphreys, 2021). The transporter is also found in human placenta where it appears to be responsible for the removal of sulfated conjugates of steroids from the fetus (Ugele et al., 2003). OAT4 also exhibits a diverse substrate specificity with a preference for organic anions. Typical substrates include uric acid, the toxin ochratoxin A, and estrone sulfate (**Table 1**). Studies showed that substitution of chloride in the uptake buffer enhanced uptake of estrone sulfate in cells expressing OAT4 (Hagos et al., 2007). Recent studies showed that OAT4 efflux glutamate and aspartate, similar to OAT10 (Skwara et al., 2017). There is no mouse ortholog for this gene.

OAT7 (SLC22A9): OAT7 has not been well-studied. It is expressed in the liver at approximately 6% of the transcript levels of OAT2 according to GTEx portal, with lower expression levels in the brain and negligible expression levels in other tissues (**Figure 3**). Protein levels of OAT7 in the human liver showed similar abundance as OAT2 (Vildhede et al., 2018). Specific substrates for the transporter have been difficult to identify. Recent studies have demonstrated that estrone 3-O-sulfate and dehydroepiandrosterone 3-O-sulfate (DHEAS) are excellent substrates but not specific as OATPs are known to take up sulfated steroids (Mathialagan et al., 2018). Orthologs of OAT7 are found in primates, but not rodents.

OAT10 (SLC22A13): With its highest expression levels in the kidney according to GTEx (**Figure 3**), OAT10 has been the subject of recent studies of uric acid disposition (Wang et al., 2020a). The transporter has been recognized as a uric acid reabsorptive transporter localized to the apical membrane of the renal tubule (Burckhardt, 2012; Otani et al., 2020). Single cell RNA-seq data however suggest that in comparison to URAT1 (SLC22A12), OAT10 is expressed at much lower levels in the proximal tubule (Humphreys, 2021). The transporter has a high affinity for nicotinic acid and a lower affinity for uric acid (Bahn et al., 2008). It also takes up the typical OAT substrate, para-amino hippuric acid, with optimal uptake at pH 5 suggesting that it may act as a proton-organic anion symporter.

URAT1 (SLC22A12): With higher transcript and protein expression levels in the kidney and much lower levels in other tissues, URAT1 is a selective uric acid transporter (**Figure 3**) (Nakamura et al., 2016; Cheung et al., 2019). Expressed on the apical membrane of the renal proximal tubule, URAT1, together with other transporters, serves in the reabsorption of uric acid. The transporter acts as an anion exchanger taking up uric acid in exchange for inorganic (e.g., Cl⁻) and organic anions (e.g., lactate, nicotinate). It is the target of many uricosuric drugs including lesinurad and newer drugs (Bardin and Richette, 2018). URAT1 has been extensively discussed in many review articles on gout and uric acid disposition (see (Koepsell, 2013; Nigam and Bhatnagar, 2018; Dong et al., 2019)) and therefore will not be further reviewed here.

Zwitterion Transporters: Function; Tissue Distribution and Transport Mechanism

Four family members, which primarily transport zwitterions cluster together phylogenetically in the human SLC22 family. These include OCTN1 (SLC22A4), OCTN2 (SLC22A5), SLC22A15 and SLC22A16 (FLIPT2). SLC22A15 was recently deorphaned (see section *Recent Deorphaning Studies of Transporters in the SLC22A Family*). As with other SLC22 family members, the transporters all contain 12 transmembrane domains and a large extracellular loop between the first and second transmembrane domain. A few review articles about OCTNs have been recently published (Pochini et al., 2019; Betterton et al., 2021; Sweet, 2021). Below we briefly describe OCTN1, OCTN2 and SLC22A16.

OCTN1 (SLC22A4): Expressed in a variety of tissues throughout the body and in particular, in whole blood (**Figure 3**). Protein expression levels of OCTN1 in the kidney is lower than OCT2 and OATs (Li et al., 2019) and its protein is also expressed in the small intestine (Nakamura et al., 2016). OCTN1 is sometimes termed the ergothioneine transporter (Grundemann et al., 2005). Ergothioneine is a naturally occurring zwitterion, which is derived from fungi and some bacterial species. Its levels in whole blood are dependent on OCTN1 expression, consistent with a major role of OCTN1 in ergothioneine disposition. Ergothioneine is thought to function as an important anti-oxidant in the body. Though not a true vitamin with a deficiency syndrome, ergothioneine has been proposed to be a “longevity” vitamin (Ames, 2018) because of its potent anti-oxidant activity and high levels in the human body. OCTN1 transports ergothioneine in a sodium-dependent fashion, thus promoting the intracellular accumulation of ergothioneine in tissues in which it is expressed. In addition, OCTN1 transports various organic cations including choline and acetylcholine, and tetraethylammonium (Pochini et al., 2019). There are some data suggesting that the transporter may function biologically in the release of acetylcholine. OCTN1 appears to have a complex transport mechanism that depends on both the direction of transport (influx or efflux) as well as the charge of its substrates. In particular, though influx of ergothioneine is sodium dependent, influx of acetylcholine, a cation, is inhibited by sodium. In contrast, acetylcholine efflux is not sodium sensitive. Proteoliposomes have been used to characterize OCTN1 function, which provides excellent support for its transport mechanism as well as its substrate selectivity (Pochini et al., 2019). Drugs that have been identified as substrates of OCTN1 include metformin, sulpiride, gabapentin and cytarabine, although these substrates are controversial (Tschirka et al., 2018) (**Table 1**).

OCTN2 (SLC22A5): In contrast to OCTN1, OCTN2 is primarily a carnitine transporter. The transporter gene is located together with OCTN1 in a locus on chromosome 5. With ubiquitous expression in most tissues in the body, including the proximal tubule and intestine (Kato et al., 2006), OCTN2 serves in carnitine homeostasis providing 70 to 80% of the body’s supply of carnitine through intestinal dietary absorption and renal reabsorption mechanisms. In humans, transport of carnitine across the intestinal basolateral membrane transporter is not well-established. Studies suggest that the rodent ortholog of OCTN3, which is localized to the basolateral membrane in intestinal epithelia may play a role in carnitine

absorption (Duran et al., 2005; Garcia-Miranda et al., 2005). The remainder of the body's carnitine is synthesized. Essential in fatty acid oxidation, carnitine is needed by virtually all tissues. Carnitine Transporter Deficiency (CTD) is an autosomal recessive disease caused by mutations in OCTN2 (see section *Rare Diseases Involving Mutations in SLC22 Family*). OCTN2 is a sodium co-transporter and serves in carnitine influx. It also interacts with carnitine acyl esters as well as various synthetic molecules. The transporter can serve in a sodium-independent fashion in efflux of its substrates and in particular, acyl-carnitine esters when their intracellular concentrations exceed their extracellular concentrations. Drugs that are substrates of OCTN2 include mildronate and sulpiride (Grigat et al., 2009; Li et al., 2017) (**Table 1**). OCTN2 and CTD have been the subject of many review articles (Longo, 2016; Almannai et al., 2019; Pochini et al., 2019).

FLIPT2 (SLC22A16): Sometimes termed CT2 or FLIPT2, SLC22A16 is a high affinity carnitine transporter (Enomoto et al., 2002b). Only a few studies characterizing the function of SLC22A16 have been published (**Table 1**). The transporter is highly expressed in human testes with much lower levels of expression in other tissues. It appears to be localized to Sertoli cells within the testis and to the luminal membrane of epididymal epithelium. Carnitine is essential in the regulation of motility of spermatozoa as well as to their maturation. Because of its polarity, carnitine clearly needs a transporter to foster its intracellular accumulation. In the testes, SLC22A16 is a highly specialized transporter. SLC22A16-mediated carnitine uptake is inhibited by acyl-carnitine derivatives as well as betaine. SLC22A16 is over-expressed in some cancers such as AML (Wu et al., 2015b), and its over-expression is tied to the growth and viability of the tumor cells suggesting that it may be a viable target for the treatment of cancers.

SLC22B Synaptic Vesicular Glycoprotein 2

The SLC22B subfamily is comprised of three synaptic vesicle glycoprotein 2 members (SV2A (SLC22B1), SV2B (SLC22B2) and SV2C (SLC22B3)) and SVOPL and SVOP. These proteins are most closely aligned with SLC22A18 and MFSD10 in the SLC22 family. Multiple sequence alignments of the five SLC22B family members with MFSD10 and SLC22A18 result in approximately ~13 to 19% identity, suggesting that SLC22A and SLC22B are related but do not meet the 25% criteria for sequence homology of family

members. The SV2 family has recently been reviewed (Janz et al., 1998; Bartholome et al., 2017; Stout et al., 2019) and is briefly described here. Consistent with other SLC22 family members, SV2 family members are 12-transmembrane proteins, which have about 65% sequence homology with one another. These proteins are expressed in secretory vesicles, such as synaptic vesicles, and seem to be important in neurotransmission, yet their exact function remains unknown (Bajjalieh et al., 1993; Crowder et al., 1999). Nevertheless, the proteins, and in particular SV2A, have been targeted by small molecules. For example, levetiracetam targets SV2A to treat epilepsy. The drug was approved for clinical use before its target was identified. Within the brain, the three proteins have distinct expression patterns with SV2A being the most ubiquitous followed by SV2B which is found primarily in the trigeminal and motor nuclei followed by SV2C, which is found in the striatum, midbrain, and ventral pallidum. Despite extensive experimentation, the precise function of these proteins is unknown. The proteins have been thought to function in vesicular transport similar to the monoamine transporters in the SLC18 family; however, to date evidence for vesicular transport function has not been found. SV2A has been shown to transport galactose when vesicles are fused with the plasma membrane (Madeo et al., 2014). SV2 proteins in vesicles that are fused to the plasma membrane may interact with botulinum and tetanus neurotoxins (Dong et al., 2006; Stout et al., 2019). The three proteins are implicated in Alzheimer's disease and Parkinson's disease⁶⁷ though until their precise functions are identified, the mechanisms for their roles in neurodegeneration will remain elusive. SVOP (SLC22B4) and SVOPL (SLC22B5) are more distantly related to SV2, but nevertheless in the SLC22B family. The proteins are both vesicular. SVOP has been studied in knockout mice and is clearly not essential for the fertility or viability of the mice, which have no obvious phenotypes (Yao et al., 2013). Like SV2A, SVOP is ubiquitously expressed in all brain regions. SVOPL is a paralog of SVOP (Jacobsson et al., 2007). Little is known about the gene and protein; however, the gene appears to be maternally imprinted with the paternal allele inactivated through DNA methylation (Yao et al., 2013). Expressed earlier in development, SVOPL expression levels in the brain decline with aging.

Recent Deorphaning Studies of Transporters in the SLC22A Family

Among the 28 members of the SLC22 family, ten are orphans. Six of the orphans are SLC22A members and four are atypical SLC22B members. These ten orphan transporters have no known substrates. Three

of the 28 SLC22 members were deorphaned in the last few years (**Figure 2**). These are SLC22A24 (Yee et al., 2019), SLC22A15 (Yee et al., 2020) and SLC22A14 (Kuang et al., 2021). Notably, untargeted metabolomic approaches were used as the primary method to identify substrates of these recently deorphaned transporters. Other methods were used in the deorphaning studies, for example, microscopy methods to localize the transporter as well as structural method to detect the charge specificity of the transporters.

SLC22A24: In the phylogeny tree, SLC22A24 clusters with the organic anion transporters, SLC22A6, SLC22A8, SLC22A11 and SLC22A12. SLC22A24 substrates were discovered using a combination of genomewide association-metabolomic studies (GWAS-metabolomic) and untargeted metabolomic methods in HEK293 cells overexpressing SLC22A24 (Yee et al., 2019). In the GWAS-metabolomic studies, a common nonsense mutation in SLC22A24, p.Tyr501Ter was found to be associated at genomewide levels of significance with lower plasma levels of three steroid metabolites, progesterone, etiocholanolone glucuronide and androsterone glucuronide. In the untargeted metabolomic studies, cells recombinantly expressing SLC22A24 were exposed to media containing fetal bovine serum and found to take up several steroid sulfate and glucuronide conjugates, bile acids and dicarboxylic acids. The transport mechanism was determined to be independent of sodium and involve exchange with glutaric acid. Because the variant, p.Tyr501Ter is common, transcript levels of SLC22A24 are difficult to detect presumably because of nonsense mediated decay. However, according to data from single cell RNAseq (Humphreys, 2021), SLC22A24 is expressed in segment 3 of the renal proximal tubule. Further, because the p.Tyr501Ter, which was found to be non-functional, was associated with reduced plasma levels of steroid conjugates, the transporter was presumed to function in the reabsorption of its substrates and play a role in steroid homeostatic mechanisms. Sequencing studies have revealed that approximately 50-80% of individuals in all populations have at least one allele of SLC22A24 containing the nonsense polymorphism (rs11231341), suggesting the transporter is disappearing from the human genome. In fact, SLC22A24 was also found to have interesting evolutionary pattern, with great apes having a direct ortholog of SLC22A24 but old and new world monkeys lacking a direct ortholog. Further, the gene was not found in many mammals, but was found in mouse lemur, horse and rat. However, species differences in the substrate specificity of the SLC22A24

orthologs were notable suggesting that the transporter is under evolution pressure. Future studies are needed to determine the membrane localization of SLC22A24 and its pharmacological role in drug disposition.

SLC22A15: In the phylogenetic tree, SLC22A15 clusters together with zwitterion transporters, SLC22A4, SLC22A5 and SLC22A16. To deorphan this transporter, untargeted metabolomic approaches were used in cells recombinantly expressing SLC22A15. These approaches showed that SLC22A15 transports zwitterions such as ergothioneine, carnitine, betaine, as well as to a lesser extent cations including MPP⁺ and neurotransmitters. Prior to characterization of SLC22A15 (Yee et al., 2020), only SLC22A4 was a known specific ergothioneine transporter (Grundemann et al., 2005); however, questions remained about how ergothioneine, a hydrophilic zwitterion found in abundance in the brain, entered brain parenchyma. The deorphaning studies show that SLC22A15 transports ergothioneine, but with a higher *K_m* (affinity) than SLC22A4. Like SLC22A4, SLC22A15 transports its substrates in a sodium dependent fashion, and is thus able to concentrate its substrates intracellularly. Though both transporters are expressed in multiple tissues, SLC22A15 is expressed more abundantly in various regions of the brain (**Figure 3**) suggesting it may play a role in the CNS disposition of ergothioneine and carnosine, two important anti-oxidants. SLC22A15 has been shown to play a role in cell proliferation (Zhu et al., 2019; Fang et al., 2021).

SLC22A14: SLC22A14 is a specific transporter in the testes. Male *Slc22a14* knockout mice and also male mice with a deletion on chromosome 9 which includes *Slc22a14* along with several other genes are phenotypically infertile (Runkel et al., 2008; Maruyama et al., 2016). However, the mechanism for the infertility remained unclear until a recently published deorphaning study revealed the substrate of SLC22A14 (Kuang et al., 2021). Unlike SLC22A15 and SLC22A24, which are expressed on the plasma membrane, SLC22A14 and its mouse ortholog *Slc22a14* are expressed in the mitochondria. Therefore, mitochondrial lysates from HEK293 cells overexpressing empty vector, and human and mouse SLC22A14 were isolated and subject to untargeted metabolomic analyses (Kuang et al., 2021). Riboflavin was the top metabolite and was present at significantly higher levels in the mitochondrial lysate from HEK293 cells overexpressing human or mouse SLC22A14 compared to empty vector. Other metabolites relevant to the

role of riboflavin in energy metabolism were also modulated. These include fatty acids and triacylglycerides. In further elegant studies, the mechanisms by which riboflavin deficiency in Slc22a14 knockout mice caused infertility were revealed and included reduced sperm motility leading to infertility. It is not known whether SLC22A14 transports other anions that may overlap with SLC22A13 since they cluster together phylogenetically (**Figure 1**).

Pharmacogenetics of SLC22 Transporters

Genetic polymorphisms in the coding and non-coding regions of 10 members in the SLC22 family have been discovered and functionally characterized (**Figure 2, Supplemental Table 1**). At about the same time as the publication of the draft human genome sequence, common genetic variants in SLC22A1 and SLC22A2 were discovered through sequencing approximately 200 DNA samples from ethnically diverse populations. These variants were functionally characterized to determine their effects on transporter activity or expression levels (Kerb et al., 2002; Leabman et al., 2002; Leabman et al., 2003). Several of these coding variants have been significantly associated with drug disposition in candidate genes studies (**Supplemental Table 1**, (Yee et al., 2018)). The first candidate gene study of a SLC22 family member was performed by the Giacomini laboratory to determine the effect of OCT1 reduced function variants (p.R61C, p.G401S, p.M420Del, p.G465R) on metformin disposition and response (Shu et al., 2007; Shu et al., 2008). Since then, many other studies have documented the impact of reduced function variants in OCT1 on the disposition, toxicity, and response of a wide range of basic drugs. These include metformin (Song et al., 2008), morphine (Tzvetkov et al., 2013; Balyan et al., 2017), ondansetron (Tzvetkov et al., 2012), sumatriptan (Matthaei et al., 2016) and more recently amitriptyline (Matthaei et al., 2021). Importantly, these reduced function variants are common in individuals of European ancestry, which range from 2% (OCT1 p.G401S) to 18% (OCT1 p.M420Del). Though absent in East Asians, OCT1 p.M420Del is present other ethnic groups, albeit at variable allele frequencies (African ancestry 5%, Latino 29%, South Asians 15%, Central Asia 20%, Middle East 10%) (Seitz et al., 2015). The common missense variant in East Asian is OCT1 p.P341, although predicted to be deleterious, but did not show any functional differences among the substrates screened (Shu et al., 2007; Seitz et al., 2015). This growing body of literature led the International Transporter Consortium to designate polymorphisms in OCT1, along with OATP1B1

(SLCO1B1) and BCRP (ABCG2) as important determinants of drug disposition and response (Yee et al., 2018).

Unlike OCT1 which has many common missense polymorphisms, other members of the SLC22 family have fewer common missense variants and only a few of these have shown significant associations with drug disposition or response. Although the missense variant OCT2 p.A270S (rs316019) has been widely studied, the effect of this variant is inconsistent across different ethnic groups with respect to metformin disposition (Wang et al., 2008; Chen et al., 2009; Tzvetkov et al., 2009; Zolk et al., 2009; Yoon et al., 2013; Moon et al., 2018; Kuhlmann et al., 2021) and is weakly or not associated with the disposition of other drugs (Borghetti et al., 2019; Yamamoto et al., 2019; Costa et al., 2021). The allele frequency of OCT2 p.A270S ranges from 5% in Latino to 15% in African American (<https://gnomad.broadinstitute.org/>). However, SLC22A2 polymorphisms, including rs316019 have shown significant associations with serum creatinine and estimated glomerular filtration rate in genomewide association studies perhaps due to larger sample sizes, usually of at least 5000 individuals (Shin et al., 2014; Pattaro et al., 2016; Gorski et al., 2017; Kanai et al., 2018). The impact of genetic variations in organic cation transporters on drug disposition has been recently reviewed (Koepsell, 2020; Zazuli et al., 2020; Kolz et al., 2021). Genetic variants in other SLC22 family have also been studied (see **Table 1**).

Drug-Drug Interactions Involving SLC22 Family Members

The SLC22 family is among the most important families in mediating clinically relevant drug-drug interactions. In particular, three transporters in the family, all expressed in the kidney, are studied extensively as targets for drug-drug interactions during drug development: OCT2 (SLC22A2), OAT1 (SLC22A6) and OAT3 (SLC22A8) (International Transporter et al., 2010; Zamek-Gliszczynski et al., 2018) (**Table 2**). Another transporter in the family, OCT1 (SLC22A1) is considered a potential target for hepatic drug-drug interactions and is increasingly being studied during drug development (Zamek-Gliszczynski et al., 2018). Guidance from regulatory authorities include methods for performing standardized cellular uptake assays to assess the interaction and inhibition potency of a new drug with the three transporters (OAT1, OAT3 and OCT2). The inhibition potency (IC_{50}) is compared to clinical plasma concentrations of the

unbound drug to predict the liability of the drug to cause a clinical drug-drug interaction. If the expected unbound plasma concentrations exceed $0.1 \times IC_{50}$, a clinical drug-drug interaction study should be considered (International Transporter et al., 2010). For both in vitro and clinical studies, appropriate assay conditions, and probe substrates and inhibitors should be used (Sudsakorn et al., 2020). In addition to these renal transporters, OCT1 is being increasingly recognized as a potential target for clinical drug-drug interactions (Zamek-Gliszczynski et al., 2018), and as noted in the previous section, the transporter has several polymorphisms that may affect drug disposition and response (Matthaei et al., 2016; Tzvetkov et al., 2018; Yee et al., 2018). Hypothetically prescription drug inhibitors of the transporter, which would phenocopy the reduced function polymorphisms, may also lead to drug-drug interactions.

Rare Diseases Involving Mutations in SLC22 Family

Common and rare genetic variants in membrane transporters influence various traits as well as the onset and progression of human disease (Lin et al., 2015; Huizing and Gahl, 2020; Juan-Carlos et al., 2021; Kabra and Singh, 2021). Here we focus on members in the SLC22 family, which are associated with human disease. In particular, rare mutations in SLC22A5 (OCTN2) and SLC22A12 (URAT1) are causal for carnitine transporter deficiency (CTD) and renal hypouricemia, respectively (Nezu et al., 1999; Enomoto et al., 2002a). Both disorders are inherited in an autosomal recessive manner, where two alleles containing reduced function variants are needed to cause the disease. Currently, several databases annotate the mutations found in sequencing: LOVD (<https://www.lovd.nl/>) and ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>).

CTD is tested for biochemically as part of newborn screening in California and other states and countries (Gallant et al., 2017). One of the more common mutations among individual with CTD is p.Pro46Ser (Frigeni et al., 2017). Patients with untreated CTD present with various clinical symptoms including cardiomyopathy, fatty liver, and hypoglycemia (Magoulas and El-Hattab, 2012). Over 90 mutations in SLC22A5 have been functionally characterized for their effects on carnitine uptake (Frigeni et al., 2017). Most mutations that are causal for the disease are associated with reduced function and many are complete loss of function variants. Methods to characterize the effect of OCTN2 mutations include isotopic uptake

studies of carnitine in cells recombinantly expressing OCTN2 (e.g. HEK293, CHO cells), uptake studies in fibroblasts from individual patients with CTD (Urban et al., 2006; Frigeni et al., 2017), and microscopy studies in cells expressing GFP-tagged OCTN2 (Lamhonwah and Tein, 1999; Wang et al., 1999; Ferdinandusse et al., 2019).

Renal hypouricemia occurs as a result of rare mutations in SLC22A12. Hypouricemia is not considered deleterious to individuals and in fact, is often beneficial. Notably, SLC22A12 (URAT1) is a target for the treatment of hyperuricemia (gout) (Reginato et al., 2012). Individuals with two alleles containing reduced function variants of SLC22A12 have renal hypouricemia. Hypouricemia is characterized by low levels of uric acid in the plasma but high levels of uric acid in the urine which can cause urolithiasis, and potentially lead to acute kidney injury (Chung and Kim, 2021). The most common mutations found in patients with renal hypouricemia are SLC22A12 p.Trp258Ter and p.Arg90His, which are found in East Asians (Cha et al., 2019). Other mutations associated with renal hypouricemia found in other ethnic groups have been identified in various case studies (Claverie-Martin et al., 2018; Vidanapathirana et al., 2018). Functional studies to characterize the missense variants have been conducted and in general, show reduced uptake of uric acid in cells expressing the variant transporters and poor localization of the mutant transporters to the plasma membrane (Tasic et al., 2011; Claverie-Martin et al., 2018).

In addition to rare mutations in the transporters in the SLC22 family that are causal for human disease, common variants in several SLC22 transporters have been associated with more common disease (**Table 1**). For example, common polymorphisms in SLC22A5 and SLC22A12 are significantly associated with carnitine and uric acid levels respectively in multiple metabolomic genomewide association studies (Rhee et al., 2013; Shin et al., 2014; Chen et al., 2020). These polymorphisms have also been associated with common diseases relevant to carnitine (e.g. body mass) (Hubel et al., 2019) and uric acid (i.e., gout) (Tin et al., 2011). Furthermore, low-frequency damaging variants in SLC22A12 have been significantly associated with reduced gout risk (Tin et al., 2018). In **Table 1**, we provide references and information about associations of polymorphisms in SLC22 family members with human traits and diseases as well as information from knockout mice.

Current Challenges, Knowledge Gaps and Future Directions

The SLC22 family is increasingly recognized for its critical roles in human pharmacology and biology. As mediators of drug-drug interactions and pharmacogenomic phenotypes, transporters in this family have been highly studied. Nevertheless, there remain important gaps in our understanding of this transporter family. In particular, structural information of mammalian SLC22 orthologs are lacking, making it difficult to understand the precise mechanisms of substrate binding and release and rendering docking studies for drug discovery purposes not possible. Further, there remain 10 orphan transporters in the human SLC22 family, in which no substrates or transport mechanisms have been identified. These orphan transporters are SLC22A10, SLC22A17, SLC22A18, SLC22A23, SLC22A25, SLC22A31, SV2B, SV2C, SVOP and SVOPL. Some of these orphan transporters are associated with human disease, yet their mechanisms for association remain unresolved. For example, SLC22A17 is also known as lipocalin-2 receptor. In 2005, Devireddy et al. showed that Slc22a17 (a murine receptor for 24p3 (lipocalin)) is involved in endocytosis of iron which may represent its biological function (Devireddy et al., 2005). However, SLC22A17 has been studied in various systems in relation to its role in cancer prognosis (Miyamoto et al., 2016; Chi et al., 2020; Wang et al., 2020b; Wei et al., 2020), kidney disease (Langelueddecke et al., 2012) and obesity (Kim et al., 2019; Suzuki et al., 2021). It is not clear whether these traits are related to its role in endocytosis of iron. Other orphan transporters, in particular, SLC22A18 and SLC22A23 have been shown to play a role in cancer resistance (Chen et al., 2011; Ekizoglu et al., 2018; Ito et al., 2018; Yang et al., 2018). In addition, SLC22A18 plays a role in lipid metabolism, whereas genetic polymorphisms in SLC22A23 are associated with inflammatory bowel disease (Serrano Leon et al., 2014; Naito et al., 2018) and quetiapine-induced QT prolongation (Aberg et al., 2012). Efforts are needed to identify substrates of these orphan transporters to understand the mechanisms for these associations. Attempts to identify transporter ligands for SLC22A17 and SLC22A23 have not been successful perhaps because these transporters function primarily in endocytosis (Bennett et al., 2011). The mechanisms for many associations of polymorphisms in SLC22 family members with human traits and disease need to be identified, as many associations have been made in human genetic studies but mechanistic information is lacking. Finally, genetic polymorphisms and

mutations need functional annotation to understand and predict their impact in human disease and drug response.

Conclusions

The SLC22 family is of great pharmacological and physiological importance. Most members of the family are highly promiscuous transporting a diverse array of substrates, though having charge specificity for organic anions, cations and zwitterions. This promiscuity as well as their high expression levels in organs of elimination results in the critical roles of many of these transporters (e.g., OCT1, OCT2, OAT1 and OAT3) in pharmacokinetics, pharmacogenetics and as targets for drug-drug interactions. Some of the transporters, OCTN2 and URAT1, however have a narrow substrate selectivity transporting essential solutes such as carnitine and uric acid and leading to their roles in human disease. Future research should be focused on functional genomics of SLC22 transporters important in pharmacogenomics and human disease, deorphaning the many orphan transporters in both the SLC22A and SLC22B subfamilies, further understanding the biological and pharmacological roles of these transporters including their roles in remote sensing and signalling (Nigam and Bush, 2019; Nigam et al., 2020), developing tools for modulating their function, and elucidating structures to enable drug discovery as well as a complete understanding of their transport mechanisms.

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Footnote

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Figure Legends

Figure 1. Phylogeny tree analysis of the 28 members of the human SLC22A and SLC22B family using their amino acid sequences available from Uniprot (uniprot.org).

Figure 2. Timeline showing main key discoveries and events in research on the SLC22 family. See Supplemental Table 1 for references. Figure was created with Biorender.com.

Figure 3. Transcriptomic measurements of 28 members in the SLC22 family across 54 tissues. Transporters which have similar transcriptomic profiles are clustered closer together. For example, MFSD10 and SLC22A17 are expressed at high abundance (darker blue) across almost all tissues and thus are next to each other. See Supplemental Table 2 to obtain the median TPM (transcripts per kilobase million) values for each transporter and tissue. The data used in this figure were obtained from the Genotype-Tissue Expression (GTEx) Multi Gene Query page (<https://www.gtexportal.org/home/multiGeneQueryPage>) (GTEx Consortium, 2020). This visualization page allows user to enter a list of genes and to display the expression in a heat map across tissues. The heat map is generated using the hierarchical clustering method described in <https://gtexportal.org/home/home/news?id=360> (section 2018-04-04). GTEx Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS.

Figure 4. Classification of solute carrier transport mechanisms. Circles depict substrate. The arrows show the general direction of flux. Triangles represent sodium and hexagons represent anions, which may include organic anions such as glutaric acid. Sodium and anions are ions that provide a driving force for transport by moving down their concentration gradients. Examples of transporters in the SLC22 family that function to move substrates across the plasma membrane by one of the mechanisms (passive transport or secondary active transport) from high to low concentrations are shown in the figure. Secondary active SLC transport can be classified further into co-transport (symport) and antiport. Figure was created with Biorender.com.

Table 1. Substrates, membrane localization, genetic polymorphisms and associated phenotypes of transporters in the SLC22 family.

*SLC22 (membrane localization)	Selected Substrates	Drugs (Levels or Response) Associated with Genetic Polymorphisms	** Metabolite Levels Associated with Genetic Polymorphisms	**Common Disease or Traits Associated with Genetic Polymorphisms	Phenotypes of Knockout Mice
SLC22A1 (Plasma membrane)	thiamine, MPP+, metformin, oxaliplatin, TEA, sumatriptan, ondansetron, morphine	metformin, morphine, ondansetron, sumatriptan, amitriptyline, tramadol, fenoterol	Isobutyrylcarnitine, other acylcarnitine	lipid levels, cardiovascular disease	(i) altered pharmacokinetics of metformin in Oct1/Oct2 double knockout mice; (ii) Oct1 ^{-/-} showed reduced liver size, increased body weight and changes in lipids levels; (iii) increased plasma levels of several organic cation drugs in Oct1/Oct2 knockout mice
SLC22A2 (Plasma membrane)	thiamine, metformin, atenolol, propranolol, oxaliplatin, cisplatin, TEA, MPP+, dopamine, histamine, sulpiride	metformin, gabapentin, cisplatin	Unknown metabolite (X- 12798), creatinine, N1- methyadenosine	estimated GFR, serum creatinine	(i) Significantly reduced renal secretion of organic cations; (ii) Oct2 ^{-/-} mice showed significant reduction in brain tissue concentrations of norepinephrine and serotonin; (iii) protected from cisplatin-induced nephrotoxicity and ototoxicity; (iv) reduced metformin renal clearance, reduced volume of distribution in Oct1/Oct2 double knockout mice
SLC22A3 (Plasma membrane)	TEA, histamine, serotonin, norepinephrine, dopamine, metformin	Metformin	creatinine	Lipid levels, cardiovascular disease, prostate cancer, fat mass/body weight	(i) Upon norepinephrine administration, Oct3 ^{-/-} induces higher body temperature, thermogenesis, and lipolysis; (ii) Upon induction of middle cerebral artery, Oct3 ^{-/-} showed significant increased histamine content in ischemic cortex; (iii) Oct3 ^{-/-} mice and Oct3 ^{-/-} pregnant mice showed significant differences in metformin pharmacokinetic; (iv) Upon bile duct ligation and carbon tetrachloride induced cirrhosis, Oct3 ^{-/-} developed more fibrosis; (v) Catecholamine uptake by Oct3 is important in activation of beta1 adrenergic receptor stimulation; (vi) Oct3 ^{-/-} is protected from doxorubicin-induced cardiotoxicity; (vii) https://www.mousephenotype.org/data/genes/MGI:1333817
SLC22A4 (Plasma membrane and mitochondria)	ergothioneine, gabapentin, cytarabine, betaine, TEA, homostachydrine, sulpiride	gabapentin	Acylcarnitine, carnitine, ergothioneine	Crohn's disease, hematological traits	(i) Upon epileptic seizures induced, Octn1 ^{-/-} has lower seizure score; (ii) Oxidative stress indicators were increased in Octn1 ^{-/-} mice; (iii) reduced absorption of 5-aminosalicylic acid in Octn1 ^{-/-} upon oral administration to mice; (iv) LPS-stimulation increase interleukin in

					microglia cultured from Octn1 ^{-/-} ; (v) https://www.mousephenotype.org/data/genes/MGI:1353479#phenotypesTab
SLC22A5 (Plasma membrane)	carnitine, pyrilamine, TEA, betaine, 3-(18)F-l- α -methyl-tyrosine, sulpiride, mildronate, oxaliplatin	Unknown	Acylcarnitine, carnitine, acetylcarnitine, ergothioneine	asthma, hematological traits, body mass	(i) Homozygous knockout (preweaning lethality), carnitine deficiency; (ii) Octn2 ^{-/-} mice altered pyrilamine disposition (iii) https://www.mousephenotype.org/data/genes/MGI:1329012#phenotypesTab
SLC22A6 (Plasma membrane)	PAH, indoxyl sulfate, alpha ketoglutaric acid, uric acid, tenofovir, 3-(18)F-l- α -methyl-tyrosine, acamprosate, adefovir, cidofovir	Unknown	Uric acid	Unknown	(i) Reduced renal clearance of organic anions (e.g. para-amino hippuric acid, furosemide) in Oat1 ^{-/-} mice; (ii) Differentiated levels of metabolites, including uremic solutes in different tissues, plasma and urine of Oat1 ^{-/-} .
SLC22A7 (Plasma membrane)	cGMP, cAMP, estrone sulfate, tenofovir, orotic acid, creatinine, uric acid, warfarin	anthracycline-induced cardiotoxicity	Uric acid, creatinine	Glomerular filtration rate, blood pressure, pulse pressure, stroke	No data
SLC22A8 (Plasma membrane)	estrone sulfate, estradiol glucuronide, indoxyl sulfate, uric acid, tetradecanedioic acid, cefotaxime, 17alpha-Ethinylestradiol-3-O-Sulfate, sitagliptin, enalaprilat	Cefotaxime	Pregnanediol-3-glucuronide	Unknown	(i) Differentiated levels of metabolites in plasma and urine of Oat3 ^{-/-} mice; (ii) https://www.mousephenotype.org/data/genes/MGI:1336187#phenotypesTab
SLC22A9 (Plasma membrane)	estrone sulfate, DHEAS, ochratoxin A, pravastatin	Unknown	Uric acid, thyroxine	Unknown	No ortholog in mouse
SLC22A11 (Plasma membrane)	estrone sulfate, DHEAS, ochratoxin A, uric acid, levocetirizine, perfluorooctanoate, 17alpha-Ethinylestradiol-3-O-Sulfate, enalaprilat	Unknown	Uric acid	Gout	No ortholog in mouse
SLC22A12 (Plasma membrane)	estrone sulfate, uric acid, perfluorooctanoate	Unknown	Uric acid	Gout	(i) Double knockout mice Urat1 and uricase (Uox) is a suitable mouse model of renal hypouricemia Type 1.
SLC22A13	nicotinic acid, uric	Unknown	Unknown	Unknown	No data

(Plasma membrane)	acid, 3-(18)F-l- α -methyl-tyrosine, glutamate, aspartate				
SLC22A14 (mitochondrial)	riboflavin	Unknown	Unknown	Unknown	(i) Defective fatty acid oxidation in Slc22a14 ^{-/-} spermatozoa; (ii) Lower intracellular pH of Slc22a14 ^{-/-} sperm and no changed increased in pH upon addition of bicarbonate. https://www.mousephenotype.org/data/genes/MGI:3607704#phenotypesTab
SLC22A15 (Plasma membrane)	ergothioneine, carnitine, MPP+, carnosine, creatine, betaine, dimethylglycine gabapentin	Unknown	Triacylglycerol	Unknown	
SLC22A16 (Plasma membrane)	carnitine, dimethylglycine, betaine, doxorubicin	(i) platinum-based chemotherapy; (ii) 5-fluorouracil, doxorubicin, cyclophosphamide; (iii) doxorubicin and cyclophosphamide	Acylcarnitine	Hematological traits	Not available
SLC22A17 (Plasma membrane)	Substrates unknown, it is known as a receptor for lipocalin-2, an adipocytokine.	anthracycline-induced cardiotoxicity	Unknown	Obese/overweight	Homozygous knockout (preweaning lethality); https://www.mousephenotype.org/data/genes/MGI:1926225#phenotypesTab
SLC22A24 (Plasma membrane)	estrone sulfate, estradiol glucuronide, taurocholic acid, methotrexate	Unknown	progesterone, steroid glucuronide	Conotruncal heart defect	No ortholog in mouse
SLC22A32 (MFSD10) (Plasma membrane)	diclofenac	Unknown	Unknown	Unknown	https://www.mousephenotype.org/data/genes/MGI:1915544#phenotypesTab

Data not available or not known is noted as unknown. *Membrane localization information is from <https://opendata.cemmm.at/gslab/slcontology/>. **Genetic polymorphisms of these transporters that are associated with metabolites levels and with common diseases or human traits are obtained from GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) and from the list of published GWAS with metabolomics (<http://www.metabolomix.com/list-of-all-published-gwas-with-metabolomics/>). Among the members in the SLC22A family, SLC22A10, SLC22A18, SLC22A23, SLC22A25 and SLC22A31 have no information about their interactions with any substrates or phenotypes in knockout mouse, therefore are not included in this table. The references supporting information for each of the transporters are listed below.

SLC22A1: (Tzvetkov et al., 2011; Higgins et al., 2012; Tzvetkov et al., 2012; Tzvetkov et al., 2013; Chen et al., 2014; Matthaei et al., 2016; Balyan et al., 2017; Kim et al., 2017; Liang et al., 2018; Tzvetkov et al., 2018; Morse et al., 2020; Matthaei et al., 2021)

SLC22A2: (Jonker et al., 2003; Song et al., 2008; Chen et al., 2009; Filipinski et al., 2009; Zolk et al., 2009; Ciarimboli et al., 2010; Bacq et al., 2012; Higgins et al., 2012; Shin et al., 2014; Yin et al., 2016; Gorski et al., 2017; Li et al., 2017; Miyake et al., 2019; Clemens et al., 2020; Costa et al., 2021)

SLC22A3: (Zhu et al., 2012; Lee et al., 2014; Chen et al., 2015; Shirasaka et al., 2016; Wang et al., 2016; Lee et al., 2018; Song et al., 2019; Vollmar et al., 2019; Huang et al., 2021; Wang et al., 2021)

SLC22A4: (Grundemann et al., 2005; Taubert et al., 2005; Urban et al., 2008; Shimizu et al., 2015; Li et al., 2017; Shinozaki et al., 2017; Ishimoto et al., 2018; Tschirka et al., 2018; Nishiyama et al., 2020)

SLC22A5: (Grigat et al., 2009; Kato et al., 2009; Jong et al., 2011; Wei et al., 2016; Li et al., 2017)

SLC22A6: (Ho et al., 2000; Eraly et al., 2006; Wikoff et al., 2011; Zou et al., 2018; Antonescu et al., 2020; Bush et al., 2020)

SLC22A7: (Cropp et al., 2008; Lepist et al., 2014; Shen et al., 2015; Visscher et al., 2015; Bi et al., 2018)

SLC22A8: (Chu et al., 2007; Han et al., 2010; Vallon et al., 2012; Yee et al., 2013; Bush et al., 2017; Bush et al., 2020; Smeets et al., 2020)

SLC22A9: (Shin et al., 2007; Emami Riedmaier et al., 2016; Mathialagan et al., 2018; Gunjaca et al., 2019; Boocock et al., 2020)

SLC22A11: (Ugele et al., 2008; Nakagawa et al., 2009; Han et al., 2010; Yang et al., 2010; Noguchi et al., 2017; Skwara et al., 2017; Smeets et al., 2020)

SLC22A12: (Yang et al., 2010; Hosoyamada et al., 2016; Tin et al., 2018; Cha et al., 2019; Chung and Kim, 2021)

SLC22A13: (Schulz et al., 2014; Wei et al., 2016)

SLC22A14: (Maruyama et al., 2016; Ito et al., 2021; Kuang et al., 2021)

SLC22A15: (Zhu et al., 2019; Yee et al., 2020; Fang et al., 2021)

SLC22A16: (Enomoto et al., 2002b; Okabe et al., 2005; Bray et al., 2010; Tecza et al., 2018; Takeuchi et al., 2020; Cui et al., 2021)

SLC22A17: (Visscher et al., 2015; Lee et al., 2016; Kim et al., 2019; Jaber et al., 2021)

SLC22A24: (Ruth et al., 2016; Long et al., 2017; Yee et al., 2019)

SLC22A32: (Ushijima et al., 2008)

Table 2. Substrates, inhibitors and biomarkers of SLC22 transporters that are potential targets for drug-drug interactions. Table 2 lists the canonical in vitro substrates and inhibitors of the three SLC22 family members that are targets for drug-drug interactions, along with clinical substrates and inhibitors that have been recommended by the U.S. Food and Drug Administration (see <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2>). In addition, the International Transporter Consortium has recommended a set of biomarkers for each of these transporters (Chu et al., 2018). These biomarkers are endogenous substrates of the transporters and can be measured during clinical studies to assess the effect of candidate drugs on the transporter. Changes in the levels of the biomarkers in the presence of a new drug indicates that the drug may potentially inhibit the transporter and cause a transporter-mediated clinical drug-drug interaction.

Transporter	<i>In vitro</i> Substrates	<i>In vitro</i> Inhibitors	Clinical Substrates	*Clinical Inhibitors	**Biomarkers	References [#]
OAT1	Adefovir, PAH, Cidofovir, Tenofovir	Benzylpenicillin , Probenecid	Adefovir, Cefaclor, Ceftizoxime,	PAH, Probenecid, Teriflunomide	Taurine, kynurenic acid	(Honari et al., 1977; Aherne et al., 1978;
OAT3	Benzylpenicillin , Estrone-3- sulfate, Methotrexate, Pravastatin	Benzylpenicillin , Probenecid	Famotidine, Furosemide, Ganciclovir, Methotrexate , Oseltamivir Carboxylate, Penicillin G		6βHC, GCDCA-S, kynurenic acid	Laskin et al., 1982; Inotsume et al., 1990; Cimoch et al., 1998; Wattanagoo n et al., 2009; Wiebe et al., 2020; Tang et al., 2021)
OCT2	Metformin,	Cimetidine	Metformin	Cimetidine,	N1-	(Somogyi et

	MPP+, TEA			Dolutegravir, Isavuconazole , Ranolazine, Trimethoprim, Vandetanib	methylnicotinamid e (NMN), creatinine,	al., 1987; Kusuhara et al., 2011; Grun et al., 2013; Johansson et al., 2014; Muller et al., 2015; Zack et al., 2015; Song et al., 2016; Yamazaki et al., 2017; Wiebe et al., 2020)
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MPP⁺: 1-methyl-4phenypyridinium, TEA: Tetraethylammonium, PAH: p-aminohippurate, 6βHC:6β-hydroxycortisol;

GCDCA-S: glycochenodeoxycholate- 3-O-sulfate

*Clinical Inhibitors of OCT2 are generally more potent inhibitors of MATE1 and MATE2-K and likely act via inhibition of those transporters rather than OCT2. Data from: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2>

**Including recommendations from the International Transporter Consortium (ITC)(Chu et al., 2018)

#References: *In vivo* clinical studies in humans demonstrating the drug-drug interaction involving the transporter substrate and inhibitors.

Figure 1.

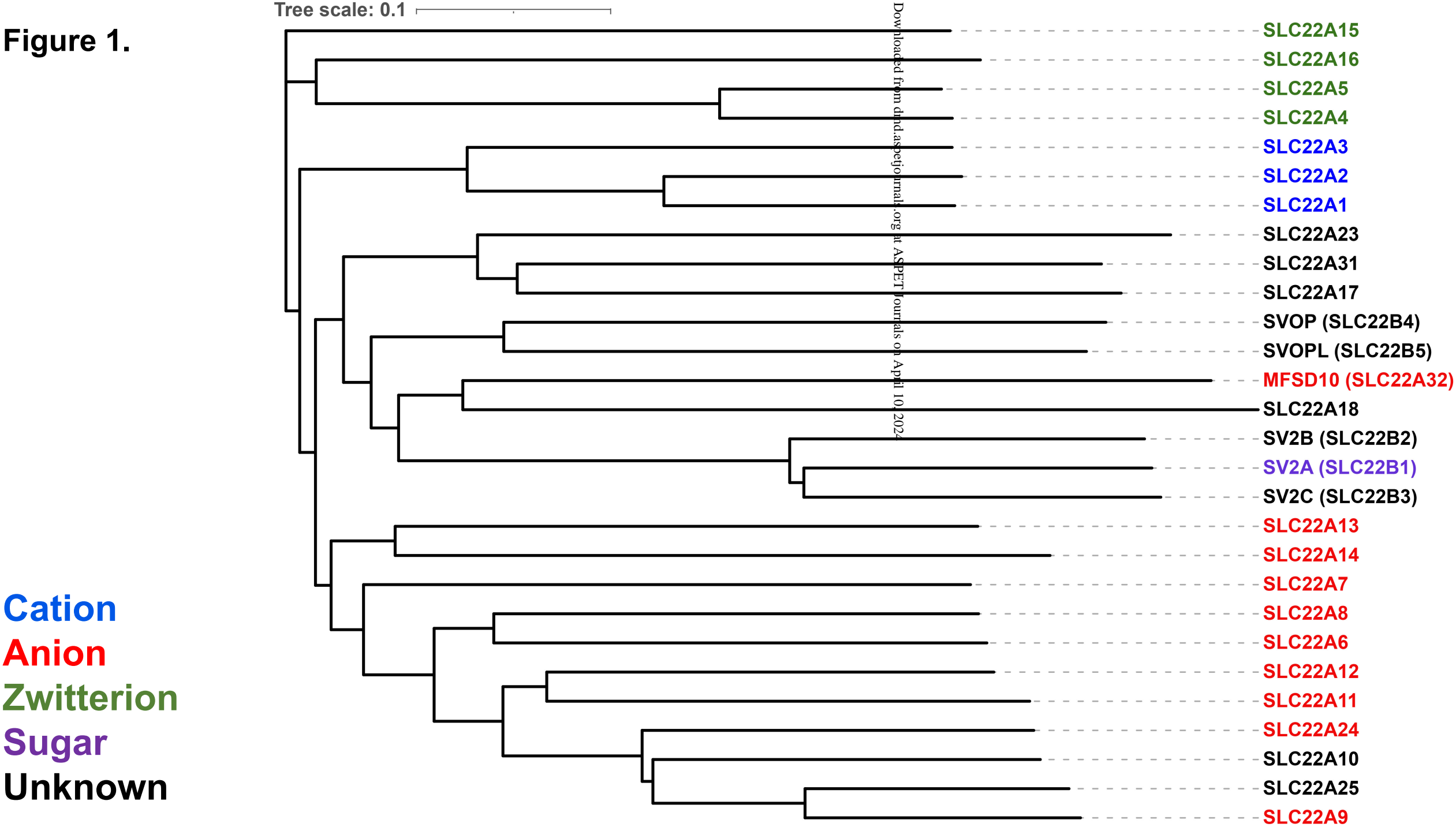


Figure 2. Events in SLC22 research: From molecular identification through mouse models and functional genomics

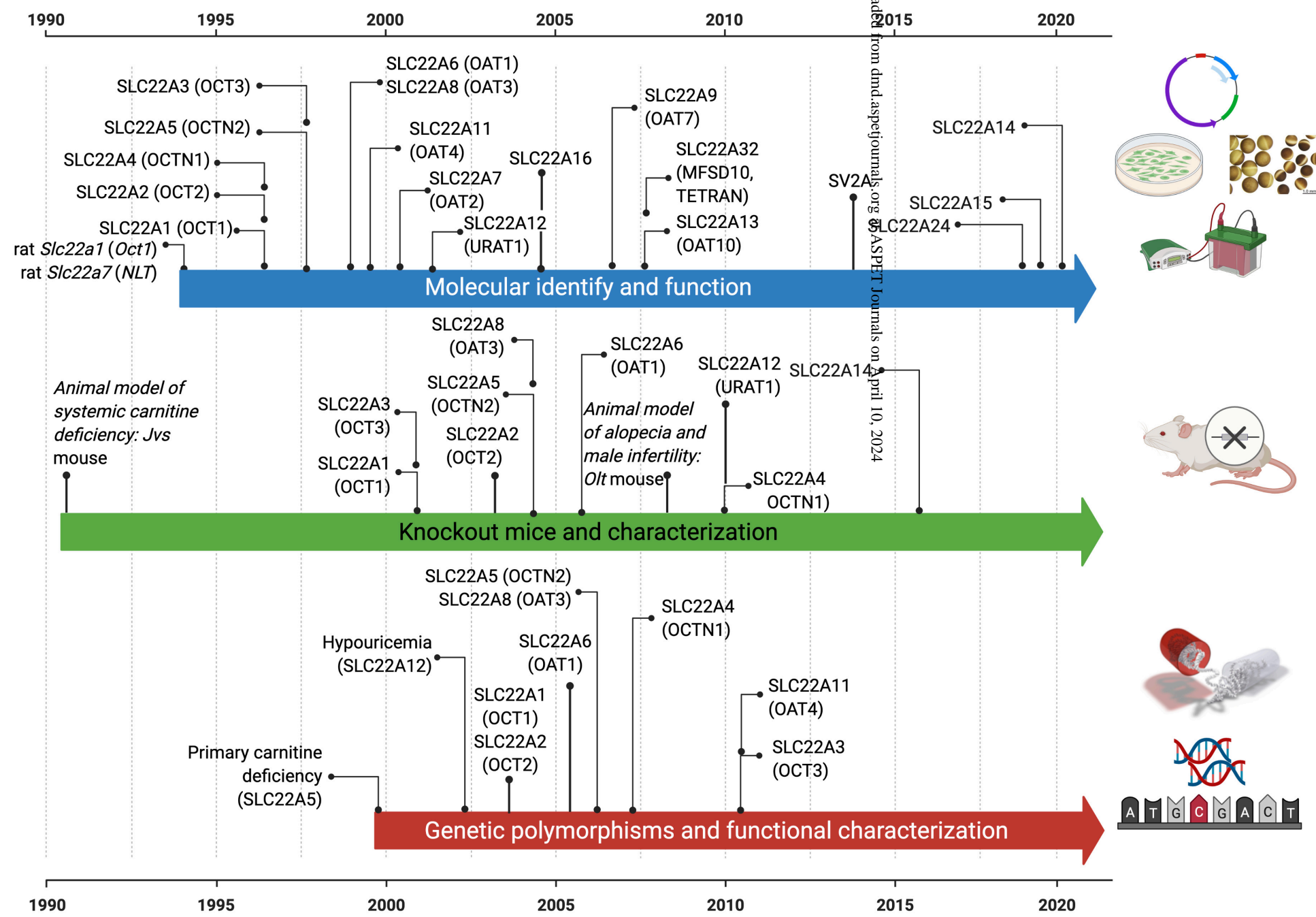


Figure 3.

