Databases 101 for Clinical Pharmacologists: What You Need to Know

Tools and Resources for Membrane Transporters

2017

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Hypothetical Example

Group Leader

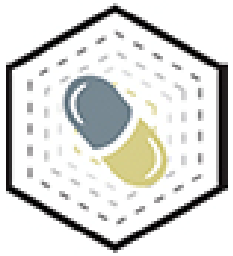
“We have a problem with one of our drug in Phase 3 clinical trial.”

Clinical Pharmacologist Team

Hypothetical Example

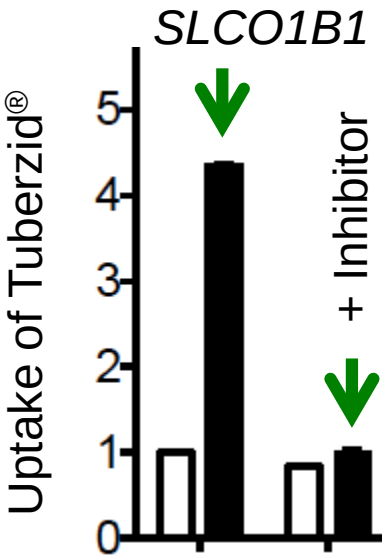
Phase 3 Trial in Africa

Anti-Tuberculosis

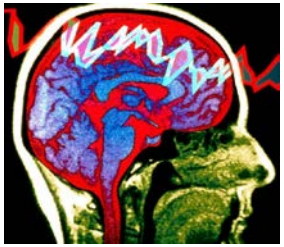


Tuberzid®

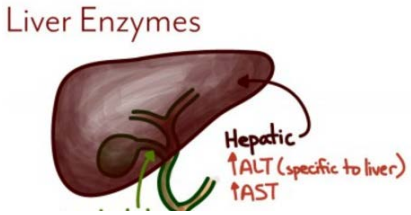
Substrate of *SLCO1B1*



Reported Side Effects



Seizures



↑Bilirubin

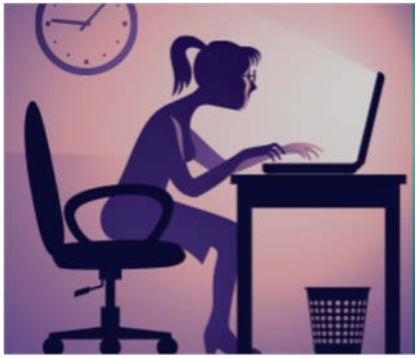
What could cause this serious side effects?

Clinical Pharmacologist Team

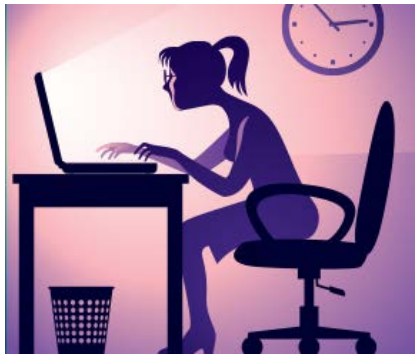
Where can we find these information about *SLCO1B1*?

SLCO1B1
SNPs and Allele
Frequency in Africans ?

Clinical Pharmacologist Team



Drugs that Inhibit *SLCO1B1*?



SLCO1B1
Expression
Levels in Tissues?

Phenotypes
Associated with *SLCO1B1* variants?

1. *SLCO1B1* SNPs and Allele Frequencies in Africans ?

- ✓ **Pharmacogenetics of Membrane Transporter Database** http://pharmacogenetics.ucsf.edu/
- ✓ PharmGKB
- ✓ dbSNP
- ✓ 1000 Genomes Browser
- ✓ ExAC
- ✓ Exome Variant Server
- ✓ DiscovEHR
- ✓ SPHINX

Obtain SNP Information for Transporter Gene and in Different Ethnic Populations

http://pharmacogenetics.ucsf.edu/

Pharmacogenetics.UCSF.edu

1 SLCO1B1

Information | Data Access | Policies | Reviewer Access | Intranet

Find gene: Examples: ABCA1, rs2246298, 2987

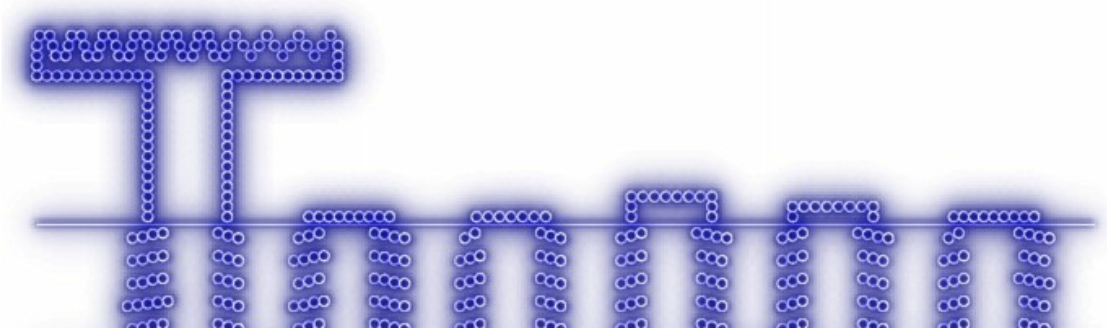
Pharmacogenetics of Membrane Transporters Database

You are in: **Pharmacogenetics of Membrane Transporters Database**

The UCSF Pharmacogenetics of Membrane Transporters (PMT) Project is sponsored by the National Institutes of Health's National Institute of General Medical Sciences (grant U01 GM61390). The Project is part of the Pharmacogenetics Research Network and Knowledgebase. Information about the entire Network can be found at NIH Pharmacogenomics Research Network. Pharmacogenetics is the study of the genetic basis for variation in response to drugs. Membrane transporters play a major role in drug response in two ways. First, many drugs work by affecting function of transporters. Second, transporters determine the level of drugs within the body by mediating drug absorption, distribution and elimination. Transporters are also determinants of drug resistance. The goal of the UCSF PMT Project is to understand the genetic basis for variation in response for drugs that interact with membrane transporters. Support for the bioinformatics activities of the PMT project also comes from the NIH/NIGMS Biomedical Technology Research Center (grant P41 GM103311).

The PMT project began in 2000. Our current research focuses on two major superfamilies, the Solute Carrier Superfamily (SLC) and the ATP Binding Cassette (ABC) Superfamily. Our SNP discovery studies include coding and non-coding regions of transporter genes. These studies focus on identifying genetic variants in membrane transporters in ethnically diverse populations. A fairly complete list of SLC and ABC transporters in the human genome is available. If you are a researcher in the Pharmacogenetics Research Network, please let us know if you are studying drug response pathways in these two superfamilies, as it may be possible to place the relevant transporters involved in these pathways in our high priority group for SNP discovery.

This database provides information on genetic variants (including single nucleotide polymorphisms (SNPs) and insertions/deletions) in membrane transporter genes that have been discovered by the PMT project. Positions of the SNPs and allele frequencies in major racial and ethnic populations are provided. All variants are mapped to the gene structure, and variants that alter the protein sequences of the transporters are mapped to the secondary structure of the transporters. Links to information on each transporter on NCBI databases are provided.



Example of SNP Information for *SLCO1B1* in Different Ethnic Populations

http://pharmacogenetics.ucsf.edu/

Pharmacogenetics.UCSF.edu

Information | Data Access | Policies | Reviewer Access | Intranet | Find gene: Examples: ABCA1, rs2246298, 2987

Gene View

You are in: PMT » Data Access » Transporter List » **SLCO1B1**

SLCO1B1

Common Name:	OATP1B1
HGNC Symbol:	SLCO1B1
HGNC Description:	solute carrier organic anion transporter family, member 1B1
HGNC ID:	10959
Superfamily:	SLC
Chromosome:	Chr.12(+): 21284128-21392730 GRCh37
Location:	12p
OMIM:	604843
OMIM Phenotype:	None
Accessions:	NM_006446
Nucleotide RefSeq:	NM_006446
Protein RefSeq:	NP_006437
Entrez:	10599
Ensembl:	ENSG00000134538
Isoforms:	1
Evidence:	Substrate In Vitro Evidence: Substrate System Reference Bile salts: cholate NA [3] glycocholate NA [3] taurocholate X oocytes [1] Hormones and their conjugates: dehydroepiandrosterone-sulfate (DHEAS) X oocytes [1] estradiol-17?-glucuronide X oocytes [1] estrone-3-sulfate X oocytes [1] T3 X oocytes [1] T4 X oocytes [1] Eicosanoids: Leukotriene C4 X oocytes [1] Leukotriene E4 X oocytes [1] prostaglandine E2 X oocytes [1] thromboxane B2 X oocytes [1] Drugs: benzylpenicillin HEK-293 cells [6] pravastatin HEK-293 cells [4] rifampicin X oocytes [7] Other organic anions: bilirubin HEK-293 cells [2] monoglucuronosyl bilirubin HEK-293 cells [5] HEK-293 cells [2] bisglucuronosyl bilirubin HEK-293 cells [2] sulfobromophthalein (BSP) HEK-293 cells [2] Tissue Distribution Evidence: liver Northern [1] References: 1. Abe, T., et al., Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1. J Biol Chem, 1999. 274(24): p. 17159-63. 2. Cui, Y., et al., Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. J Biol Chem, 2001. 276(13): p. 9626-30. 3. Hagenbuch, B. and P.J. Meier, The superfamily of organic anion transporting polypeptides. Biochim Biophys Acta, 2003. 1609(1): p. 1-18. 4. Hsiang, B., et al., A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. J Biol Chem, 1999. 274(52): p. 37161-8. 5. Konig, J., et al., A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. Am J Physiol Gastrointest Liver Physiol, 2000. 278(1): p. G156-64. 6. Tamai, I., et al., Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. Biochem Biophys Res Commun, 2000. 273(1): p. 251-60. 7. Vavricka, S.R., et al., Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver.

SNP Information for *SLCO1B1* in Different Ethnic Populations

Variant Data

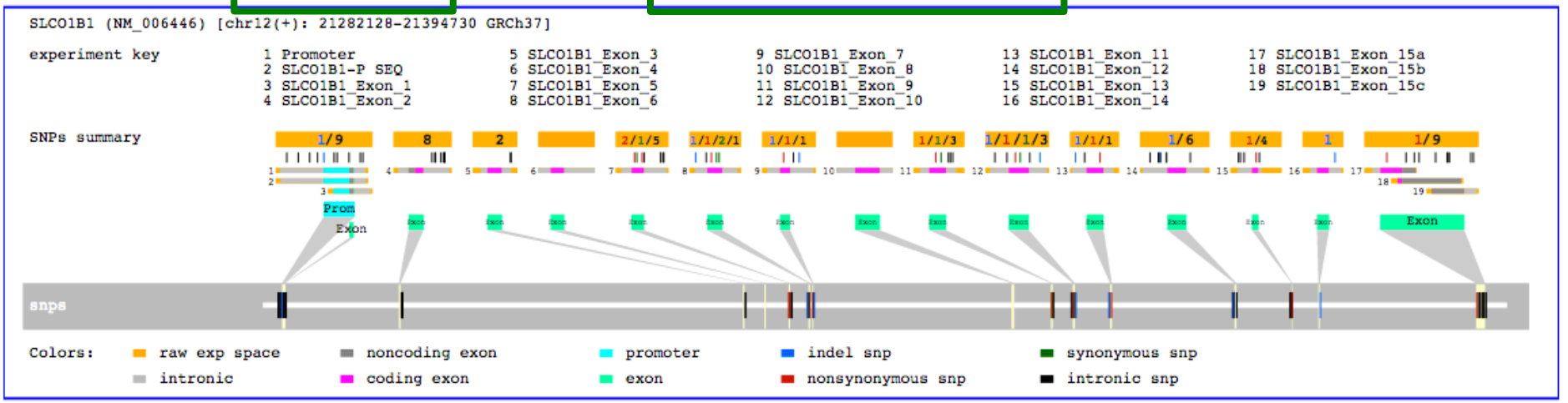
Variant Data

View all PMT variants for SLCO1B1 on UCSC Genome Browser

Showing SNP features for transcript: NM_006446

SLCO1B1 Resequencing | 1000 Genomes

1000 Genomes



Study Name: SLCO1B1 Resequencing

Experiments:

Promoter	SLCO1B1-P SEQ	SLCO1B1_Exon_1	SLCO1B1_Exon_2	SLCO1B1_Exon_3
SLCO1B1_Exon_4	SLCO1B1_Exon_5	SLCO1B1_Exon_6	SLCO1B1_Exon_7	SLCO1B1_Exon_8
SLCO1B1_Exon_9	SLCO1B1_Exon_10	SLCO1B1_Exon_11	SLCO1B1_Exon_12	SLCO1B1_Exon_13
SLCO1B1_Exon_14	SLCO1B1_Exon_15a	SLCO1B1_Exon_15b	SLCO1B1_Exon_15c	

PMT impact: P - Public D - Discovered E - Exclusive (dbSNP build 142)

Array availability: I - found on Illumina Human1M-Duo BeadChip (2011-04-21) A - found on Affymetrix Genome-Wide SNP Array 6.0 (2011-06-21)

Download the SNP table data as a tab-delimited file.

SNP Information for *SLCO1B1* in Different Ethnic Populations

1000 Genomes

Gene region, rsID, Position, Transcript and Coding position, Nucleotide change

26 Populations across 5 Subpopulations (African, Ad Mixed American, East Asian, European, South Asian)

Feature	PMT ID	dbSNP	Array Availability	Genomic Position	Transcript Position	Coding Position	Nucleotide Change	Strand	Amino Acid Position	Amino Acid Change	Statistics	ACB Freq	ASW Freq	BEB Freq	CDX Freq	CEU Freq	CHB Freq	CHS Freq	CLM Freq	ESN Freq	FIN Freq	GBR Freq	GIH Freq	GWD Freq	IBS Freq	ITU Freq	JPT Freq	KHV Freq	LWK Freq	MSL Freq	MXL Freq	PEL Freq	PJL Freq	PUR Freq	STU Freq	TSI Freq	YRI Freq
		rs398088125		21329915			G → C	+			C=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		rs540931079		21329973			G → C	+			C=	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000
		rs542138054		21329986			C → T	+			T=	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.005	0.000	0.000	0.000
	2961	rs11045820	I	21329991			C → T	+			T=	0.031	0.041	0.035	0.000	0.207	0.005	0.000	0.144	0.005	0.076	0.154	0.034	0.004	0.159	0.039	0.000	0.010	0.000	0.000	0.047	0.024	0.047	0.125	0.000	0.131	0.005
	2962	rs4149044		21329996			A → T	+			T=	0.526	0.549	0.215	0.591	0.177	0.505	0.510	0.250	0.616	0.328	0.181	0.107	0.531	0.192	0.201	0.375	0.525	0.576	0.500	0.125	0.194	0.125	0.269	0.176	0.234	0.606
	2963	rs4149045		21330020			G → A	+			A=	0.526	0.541	0.215	0.591	0.177	0.505	0.510	0.250	0.616	0.328	0.181	0.107	0.531	0.192	0.201	0.375	0.525	0.576	0.500	0.125	0.194	0.125	0.269	0.176	0.234	0.606
	2964	rs4149046	I	21330022			G → A	+			A=	0.078	0.139	0.407	0.194	0.495	0.223	0.205	0.415	0.015	0.460	0.500	0.427	0.053	0.477	0.382	0.341	0.222	0.015	0.035	0.531	0.400	0.510	0.365	0.412	0.514	0.037
		rs541915392		21331360			A → G	+			G=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		rs561808252		21331386			A → G	+			G=	0.000	0.000	0.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.019	0.000	0.000	0.025	0.000	0.000	0.000	0.000	0.000	0.000	0.016	0.000	0.015	0.000	0.000
				21331389			TTACTTG → T	+			T=	0.589	0.598	0.267	0.618	0.399	0.515	0.514	0.431	0.657	0.439	0.352	0.141	0.540	0.364	0.260	0.375	0.540	0.540	0.547	0.195	0.229	0.167	0.413	0.176	0.425	0.639
		rs528079154		21331407			T → TA	+			TA=	0.000	0.008	0.000	0.005	0.000	0.015	0.000	0.011	0.000	0.000	0.000	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		rs527424621		21331437			T → C	+			C=	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		rs541218539		21331441			A → G	+			G=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		rs374904388		21331486			T → C	+			C=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	2966	rs74541382		21331499			T → C	+			C=	0.026	0.016	0.000	0.000	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.027	0.000	0.000	0.000	0.000	0.010	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.019
Exon 6: Coding		rs549667377		21331512	588	484	T → A	+	162	Cys → Ser (D=112)	A=	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Exon 6: Coding		rs141467543		21331546	622	518	A → G	+	173	Tyr → Cys (D=194)	G=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Exon 6: Coding	2967	rs4149056	I A	21331549	625	521	T → C	+	174	Val → Ala (D=64)	C=	0.021	0.066	0.052	0.140	0.146	0.136	0.119	0.181	0.000	0.182	0.143	0.019	0.000	0.117	0.064	0.120	0.101	0.020	0.000	0.078	0.141	0.036	0.120	0.044	0.215	0.009
Exon 6: Coding		rs548326440		21331555	631	527	T → G	+	176	Met → Arg (D=91)	G=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000
Exon 6: Coding		rs200331427		21331587	663	559	C → G	+	187	Pro → Ala (D=27)	G=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

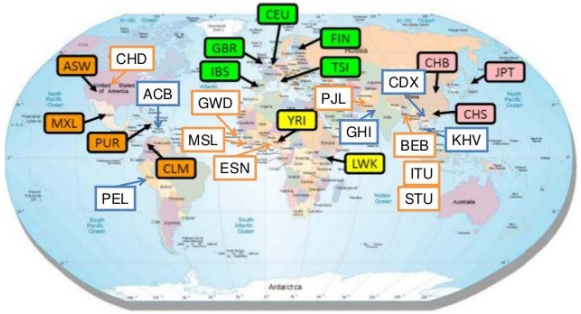
Who are these 26 Populations?

1000 Genomes Populations: 5 Subpopulations

African	Description
ACB	African-Caribbean
ASW	African American
ESN	Nigeria
GWD	Gambia
LWK	**Luhya in Webuye, Kenya**
MSL	Mende in Sierra Leone
YRI	Yoruba

Asian	Description
CHB	Han Chinese
JPT	Japanese
CHS	Southern Han Chinese
CDX	Chinese Dai
KHV	Vietnamese

American	Description
MXL	Mexican
PUR	Puerto Ricans
CLM	Colombians
PEL	Peruvians



European	Description
CEU	Utah residents
TSI	Toscani in Italia
FIN	Finnish
GBR	British
IBS	Iberian in Spain

South Asian	Description
ITU	Indian Telugu
GIH	Gujarati Indian
PJL	Punjabi
BEB	Bengali
STU	Sri Lankan

SLCO1B1 SNPs Allele Frequency in Africans ?

African	rs4149056
ACB	2.1%
ASW	6.6%
ESN	**0.0%**
GWD	**0.0%**
LWK	**2.0%**
MSL	**0.0%**
YRI	0.9%

Feature	PMT ID	dbSNP	Array Availability	Genomic Position	Transcript Position	Coding Position	Nucleotide Change	Strand	Amino Acid Position
		rs398088125		21329915			G → C	+	
		rs540931079		21329973			G → C	+	
		rs542138054		21329986			C → T	+	
	2961	rs11045820	I	21329991			C → T	+	
	2962	rs4149044		21329996			A → T	+	
	2963	rs4149045		21330020			G → A	+	
	2964	rs4149046	I	21330022			G → A	+	
		rs541915392		21331360			A → G	+	
		rs561808252		21331386			A → G	+	
				21331389			TTACTTG → T	+	
		rs528079154		21331407			T → TA	+	
		rs527424621		21331437			T → C	+	
		rs541218539		21331441			A → G	+	
		rs374904388		21331486			T → C	+	
	2966	rs74541382		21331499			T → C	+	
Exon 6: Coding		rs549667377		21331512	588	484	T → A	+	162
Exon 6: Coding		rs141467543		21331546	622	518	A → G	+	173
Exon 6: Coding	2967	rs4149056	I A	21331549	625	521	T → C	+	174
Exon 6: Coding		rs548326440		21331555	631	527	T → G	+	176
Exon 6: Coding		rs200331427		21331587	663	559	C → G	+	187

dbSNP	(partly hidden)	BS Freq	ITU Freq	JPT Freq	KHV Freq	LWK Freq	MSL Freq	MXL Freq	PEL Freq	PJL Freq	PUR Freq	STU Freq	TSI Freq	YRI Freq
rs398088125		.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs540931079		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000
rs542138054		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.005	0.000	0.000	0.000
rs11045820		.159	0.039	0.000	0.010	0.000	0.000	0.047	0.024	0.047	0.125	0.000	0.131	0.005
rs4149044		.192	0.201	0.375	0.525	0.576	0.500	0.125	0.194	0.125	0.269	0.176	0.234	0.606
rs4149045		.192	0.201	0.375	0.525	0.576	0.500	0.125	0.194	0.125	0.269	0.176	0.234	0.606
rs4149046		.477	0.382	0.341	0.222	0.015	0.035	0.531	0.400	0.510	0.365	0.412	0.514	0.037
rs541915392		.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs561808252		.000	0.025	0.000	0.000	0.000	0.000	0.000	0.000	0.016	0.000	0.015	0.000	0.000
(21331389)		.364	0.260	0.375	0.540	0.540	0.547	0.195	0.229	0.167	0.413	0.176	0.425	0.639
rs528079154		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs527424621		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs541218539		.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs374904388		.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs74541382		.000	0.000	0.000	0.000	0.010	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.019
rs549667377		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs141467543		.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rs4149056		.117	0.064	0.120	0.101	0.020	0.000	0.078	0.141	0.036	0.120	0.044	0.215	0.009
rs548326440	(D=91)	.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000
rs200331427	Pro → Ala (D=27) G= 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.000	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

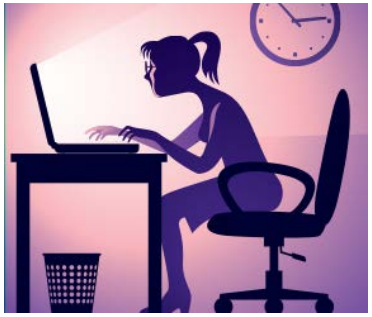
Allele Freq.
rs4149056
OATP1B1
Val174Ala

Pop.	rs4149056
CEU	14.6%
ASW	6.6%
CHB	13.6%
GIH	1.9%
MXL	7.8%

SNPs and Allele Frequencies in Different Populations

- Transporters and pharmacogenes focused:
  - http://pharmacogenetics.ucsf.edu/
  - PharmGKB
- Other databases:
  - ✓ dbSNP
  - ✓ 1000 Genomes Browser
  - ✓ ExAC
  - ✓ Exome Variant Server
  - ✓ DiscovEHR
  - ✓ SPHINX

- All genes
- SNPs Allele Frequency
- Other ethnic groups (European, Asian, African American)
- Larger populations
- Disease populations

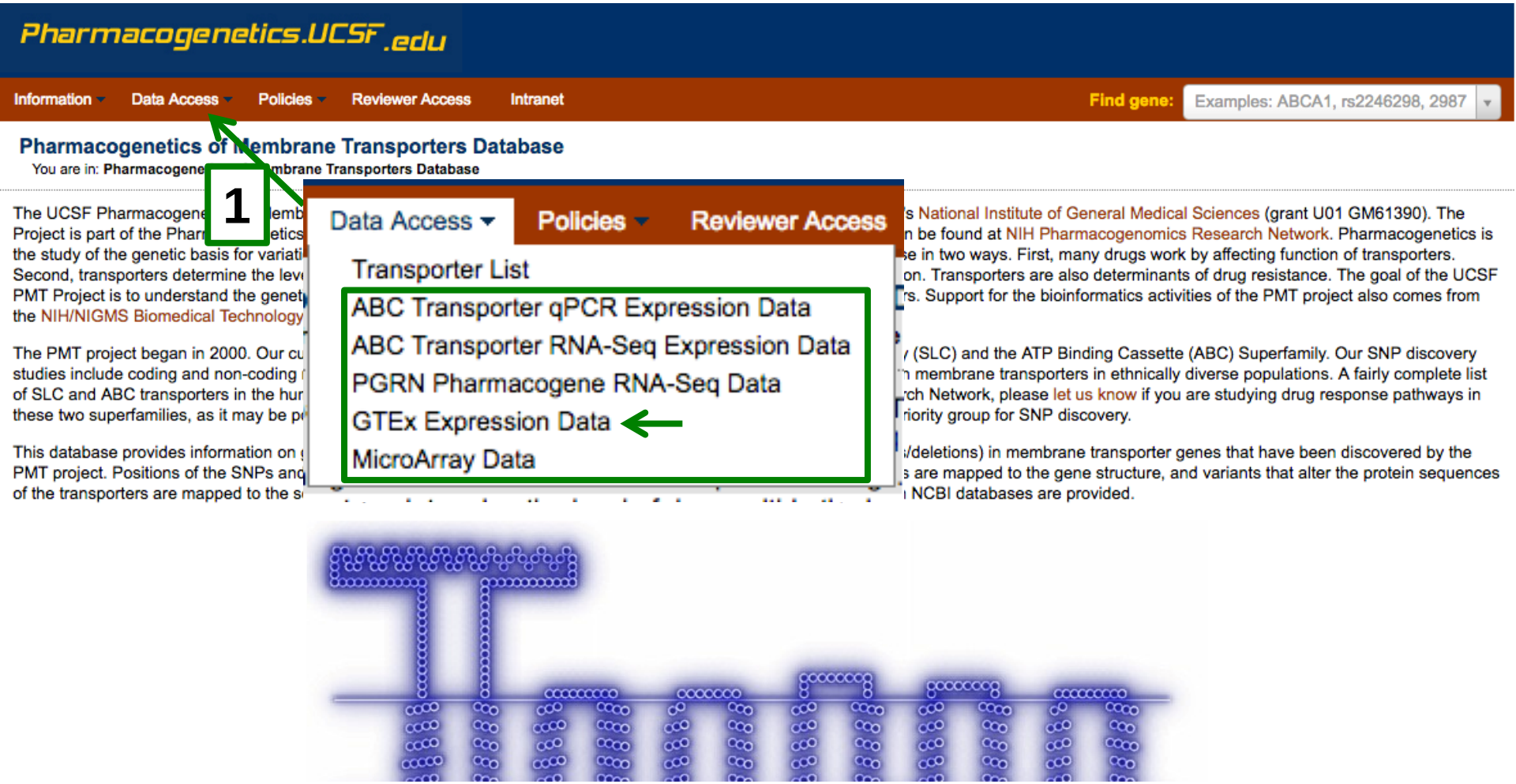


2. Where Is *SLCO1B1* Expressed?

- ✓ **Pharmacogenetics of Membrane Transporter Database** http://pharmacogenetics.ucsf.edu/
- ✓ GTEx Portal
- ✓ UCSF FDA Transportal
- ✓ Protein Atlas
- ✓ RNASeq Atlas
- ✓ Gene Expression across Normal and Tumor tissue (GENT)
- ✓ CCLE (>500 Cancer Cell-Lines)

Obtain Expression Levels of Transporter Genes in Different Tissues

http://pharmacogenetics.ucsf.edu/



Obtain Expression Levels of Transporter Genes in Different Tissues

http://pharmacogenetics.ucsf.edu/gtex/index.html

GTEx Portal

GTEx Expression Data

You are in: PMT » Data Access » **GTEx Expression Data**

PMT GTEx Expression Plotting

1. Select the Options: ABC, SLC, Both

nclude gene and transcript expression values by tissue sample in the form of

es relative expression of PMT genes by tissue type at two levels of tissue detail, e.g., 'Brain' and 'Brain - Amygdala'. Choose among four calculated expression values, including mean and median RPKM values, and quantile normalized (QN) distributions of these values. (Note that differences between some distributions are subtle.) The coloring is relative to the mean of all displayed values. All values are log base 2. ***Click on a gene or tissue to sort the data by expression level.***

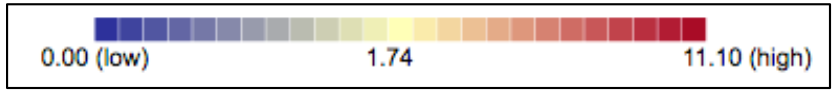
Genes: ○ All ◉ ABC ○ SLC ○ Other | Tissues: ○ Major ◉ Detail | Expression values: ○ Mean RPKM ○ Median RPKM ○ Mean QN RPKM ◉ Median QN RPKM

2. Select the Options: Mean, Median

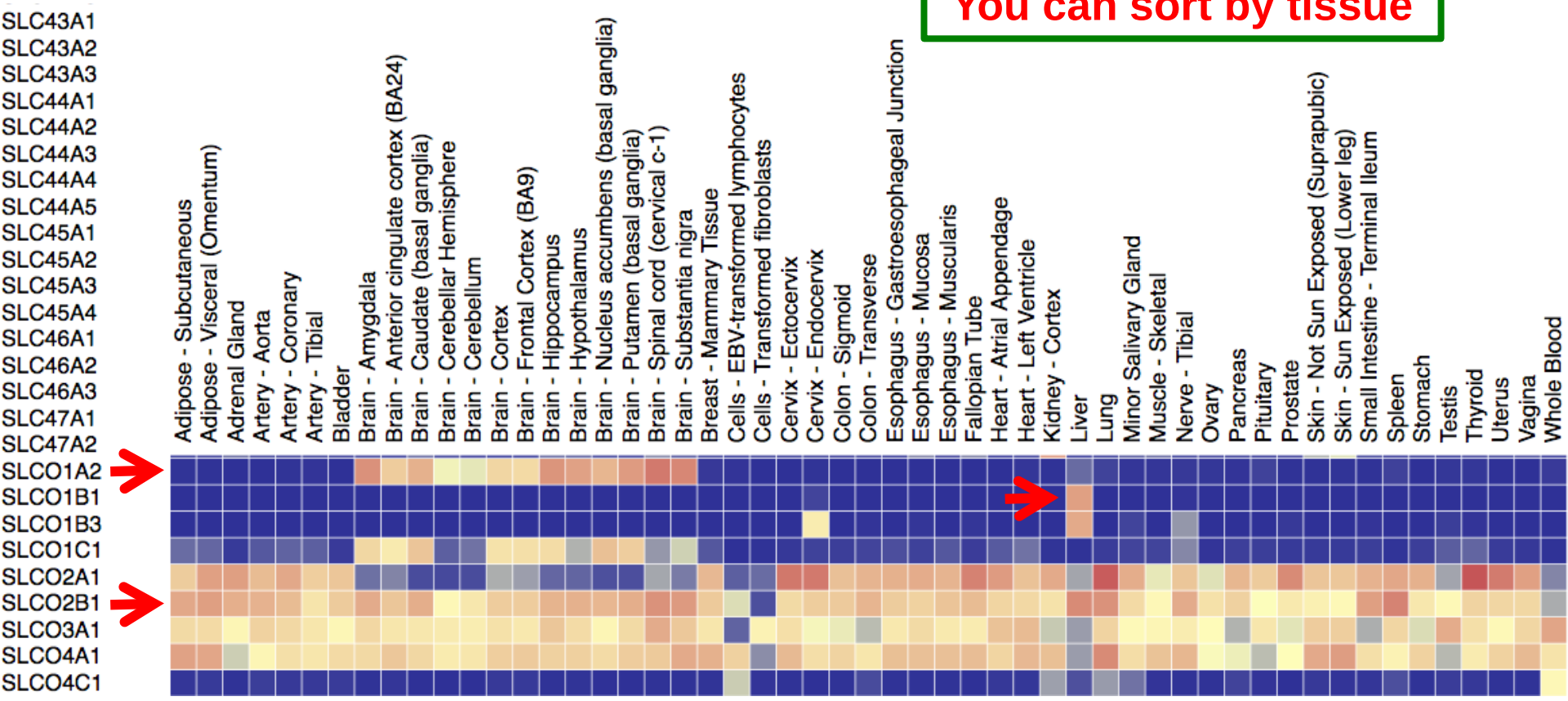
Comparison of the Transporter Genes Across Different Tissues

1. Select: SLC

2. Select: Median RPKM



You can sort by tissue

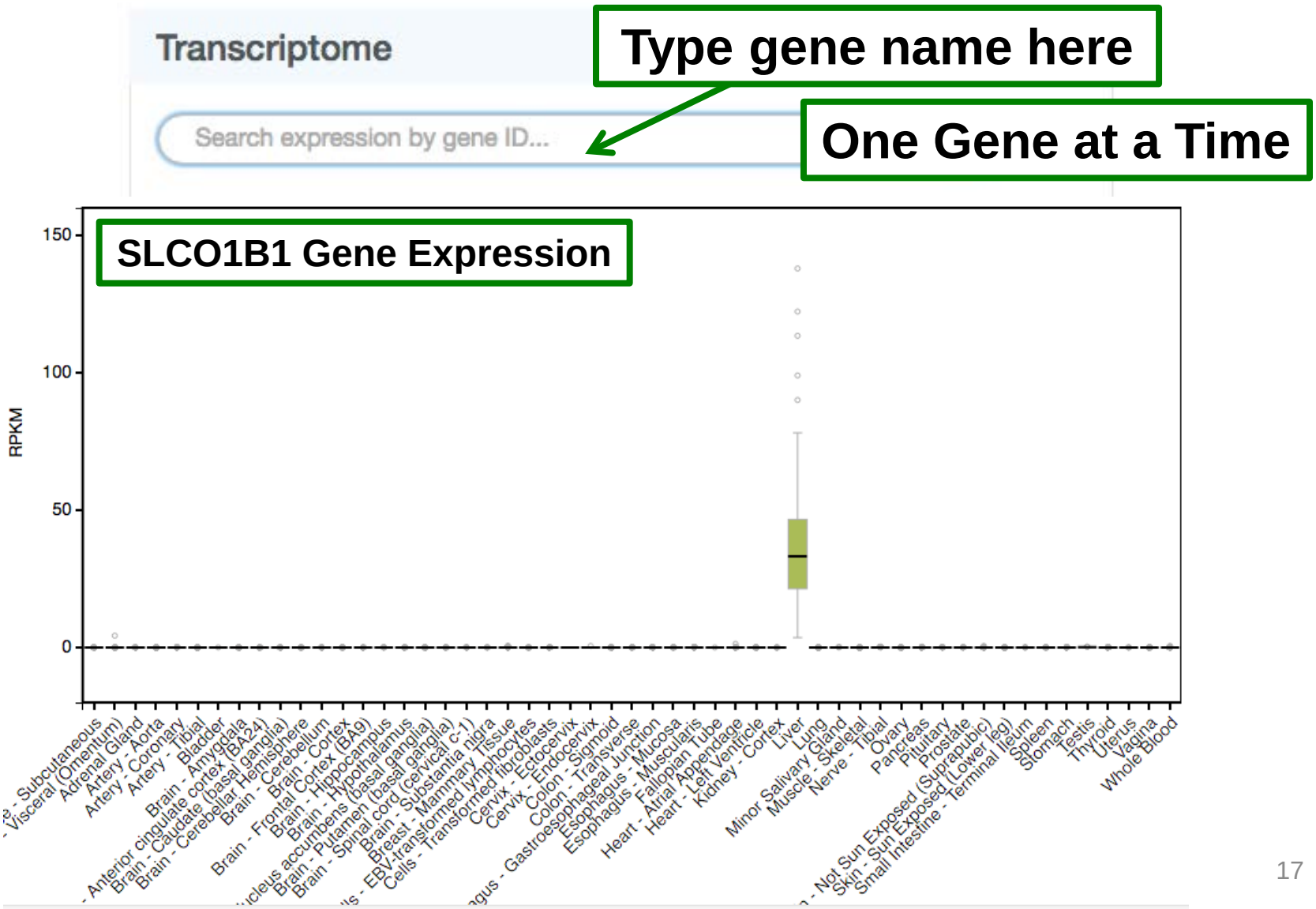


Specific vs Ubiquitous

Scroll your pointer to the square box for RPKM value

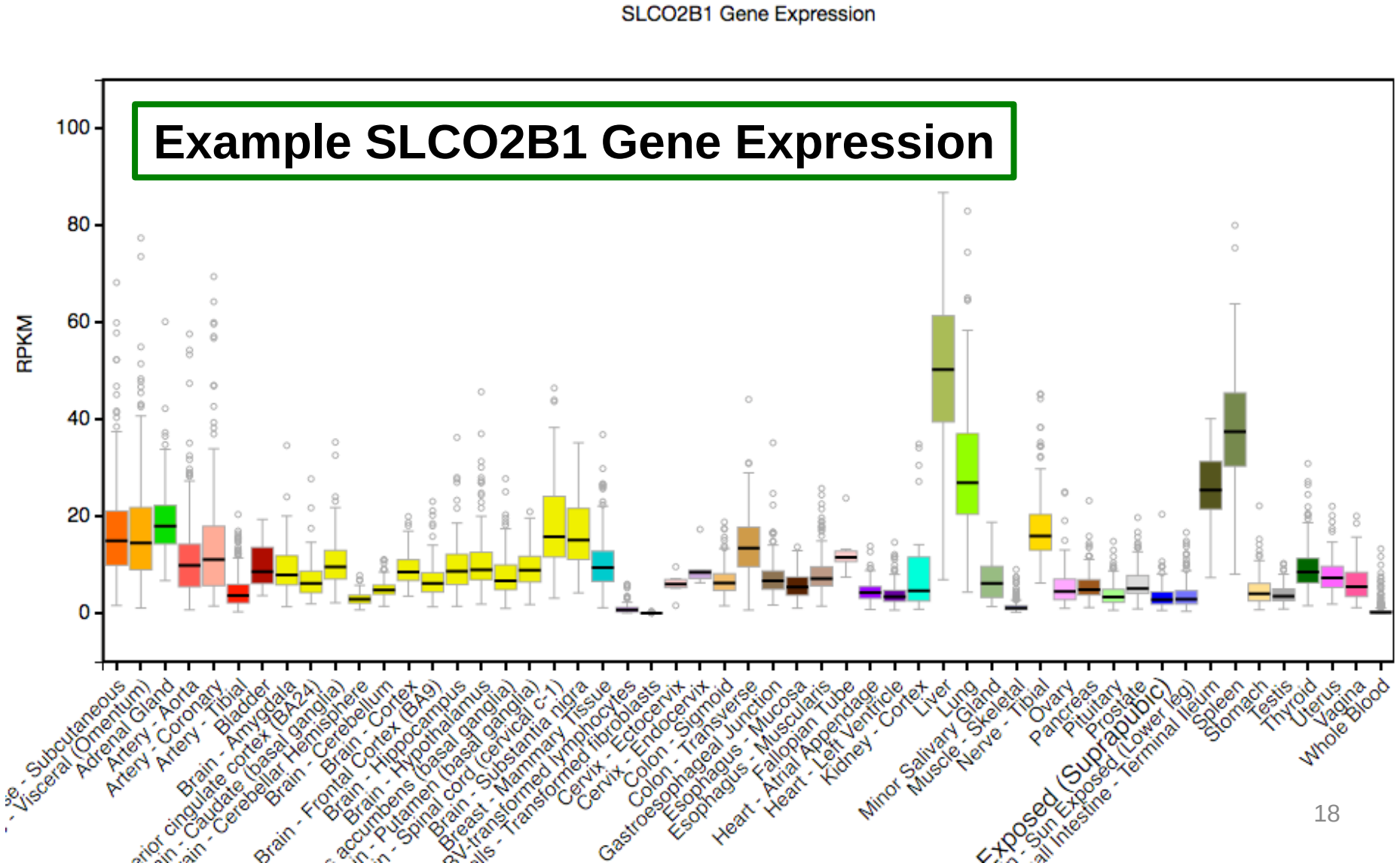
GTEx Portal

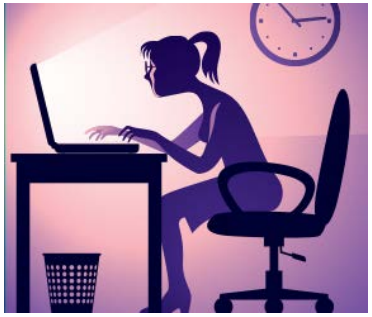
http://gtexportal.org/home/



GTEx Portal

http://gtexportal.org/home/





Expression Levels in Different Tissues and Cell Lines

- Transporters focused:
  - **Pharmacogenetics of Membrane Transporter Database**
  - ✓ UCSF FDA Transportal
- All other genes:
  - ✓ GTEx Portal
  - ✓ RNASeq Atlas
  - ✓ Protein Atlas
  - ✓ Gene Expression across Normal and Tumor tissue (GENT)
  - ✓ CCLE (>500 Cancer Cell-Lines)

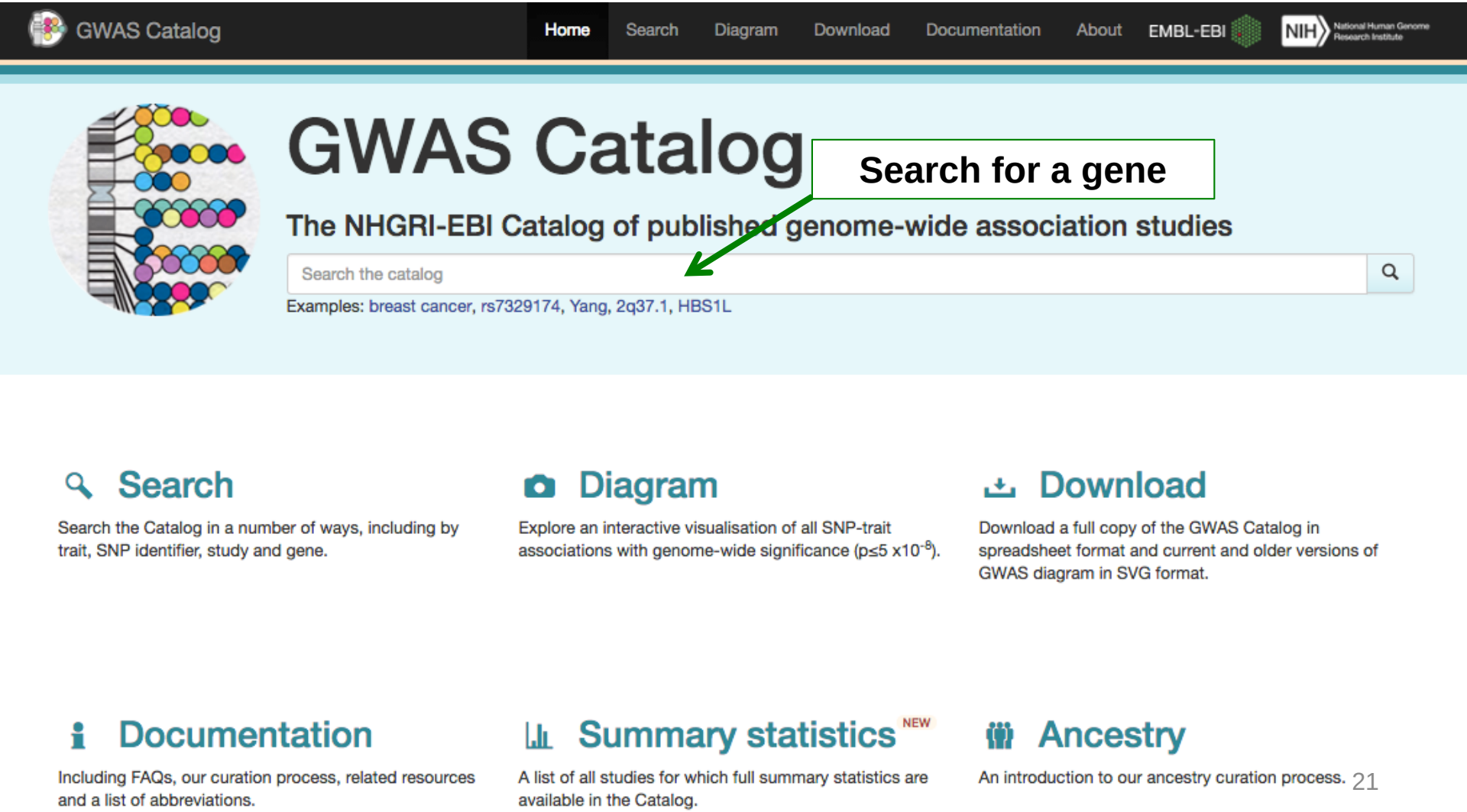
} • Normal and tumor tissues

3. Phenotypes Associated with *SLCO1B1* variants?

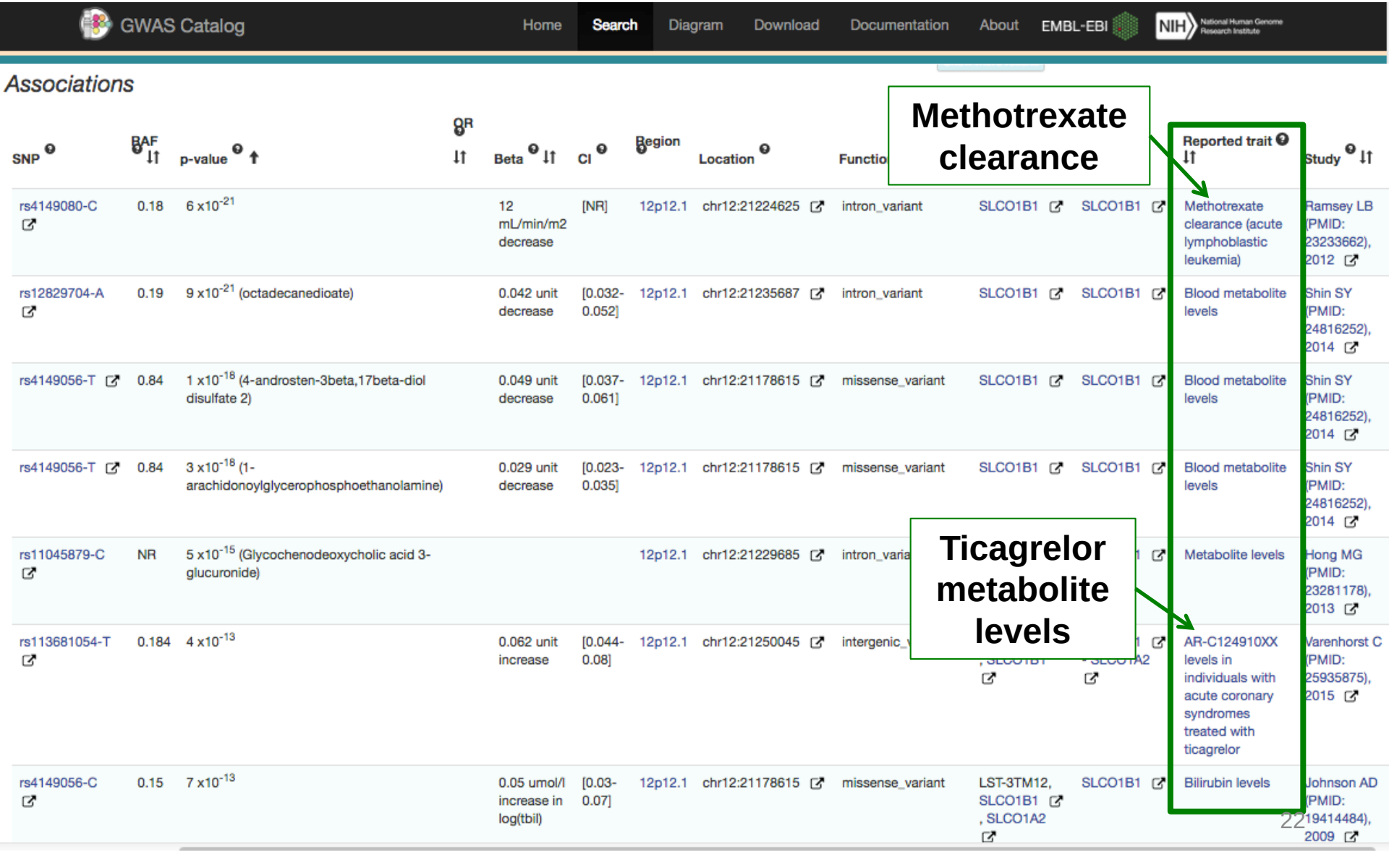
- Databases which you can find genetic association of the genes with phenotypes.
  - ✓PharmGKB
  - ✓ClinGen
  - ✓ClinVar
  - ✓GWAS Catalog

Searching Phenotypes/Traits Associated with a Gene (Transporter) or a Variant

https://www.ebi.ac.uk/gwas/



Phenotypes/Traits Associated with Variants in SLCO1B1



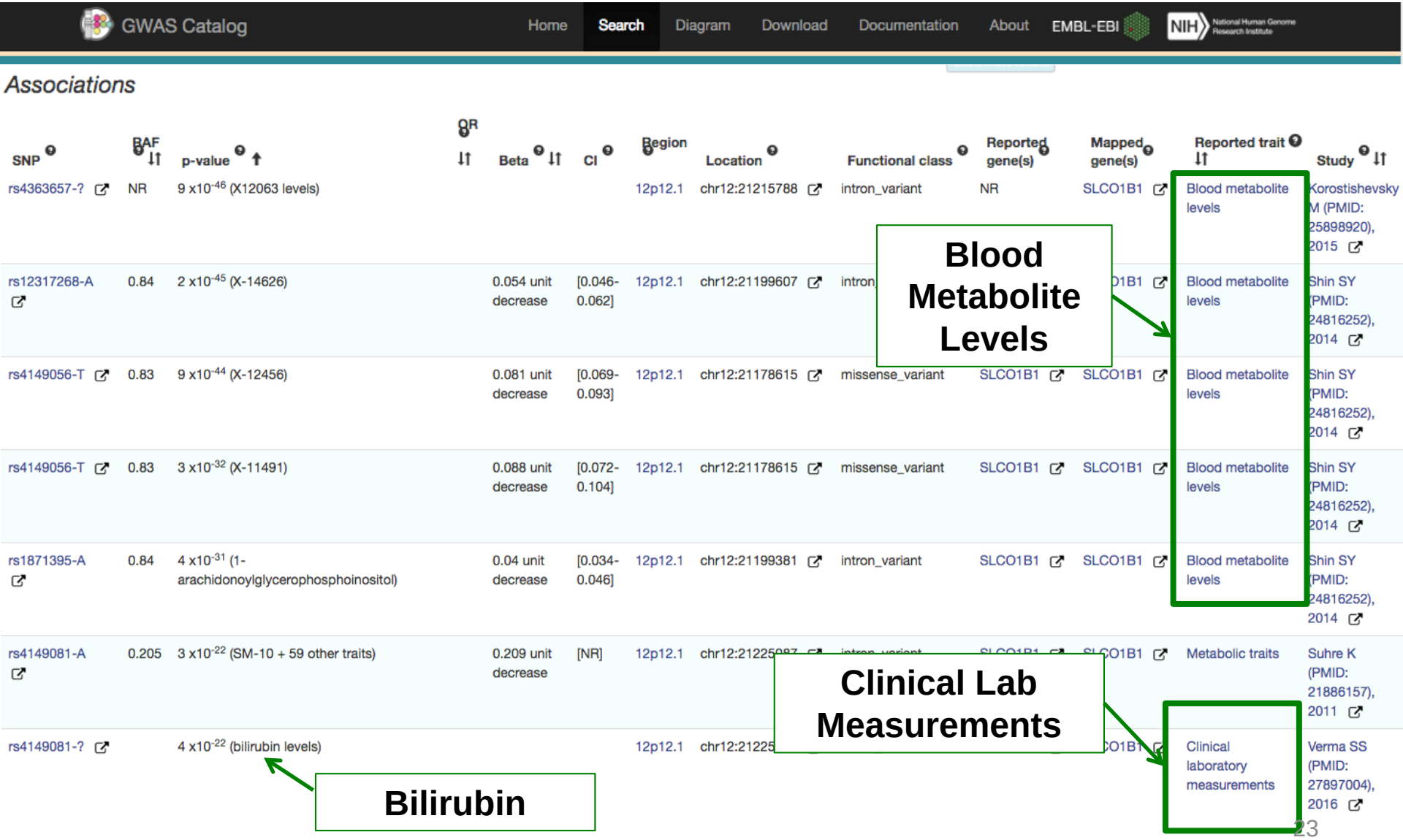
Associations

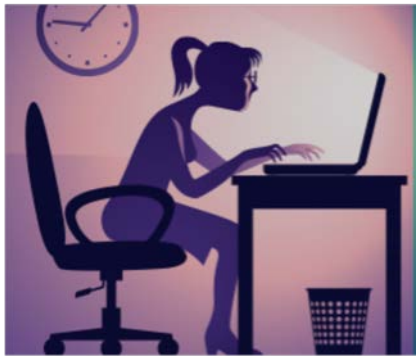
SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functio			Reported trait	Study
rs4149080-C	0.18	6 x10^{-21}		12 mL/min/m2 decrease	[NR]	12p12.1	chr12:21224625	intron_variant	SLCO1B1	SLCO1B1	Methotrexate clearance (acute lymphoblastic leukemia)	Ramsey LB (PMID: 23233662), 2012
rs12829704-A	0.19	9 x10^{-21} (octadecanedioate)		0.042 unit decrease	[0.032-0.052]	12p12.1	chr12:21235687	intron_variant	SLCO1B1	SLCO1B1	Blood metabolite levels	Shin SY (PMID: 24816252), 2014
rs4149056-T	0.84	1 x10^{-18} (4-androsten-3beta,17beta-diol disulfate 2)		0.049 unit decrease	[0.037-0.061]	12p12.1	chr12:21178615	missense_variant	SLCO1B1	SLCO1B1	Blood metabolite levels	Shin SY (PMID: 24816252), 2014
rs4149056-T	0.84	3 x10^{-18} (1-arachidonoylglycerophosphoethanolamine)		0.029 unit decrease	[0.023-0.035]	12p12.1	chr12:21178615	missense_variant	SLCO1B1	SLCO1B1	Blood metabolite levels	Shin SY (PMID: 24816252), 2014
rs11045879-C	NR	5 x10^{-15} (Glycochenodeoxycholic acid 3-glucuronide)				12p12.1	chr12:21229685	intron_varia			Metabolite levels	Hong MG (PMID: 23281178), 2013
rs113681054-T	0.184	4 x10^{-13}		0.062 unit increase	[0.044-0.08]	12p12.1	chr12:21250045	intergenic_v	, SLCO1B1	, SLCO1A2	AR-C124910XX levels in individuals with acute coronary syndromes treated with ticagrelor	Varenhorst C (PMID: 25935875), 2015
rs4149056-C	0.15	7 x10^{-13}		0.05 umol/l increase in log(tbil)	[0.03-0.07]	12p12.1	chr12:21178615	missense_variant	LST-3TM12, SLCO1B1, SLCO1A2	SLCO1B1	Bilirubin levels	Johnson AD (PMID: 19414484), 2009

Methotrexate clearance

Ticagrelor metabolite levels

Phenotypes/Traits Associated with Variants in SLCO1B1



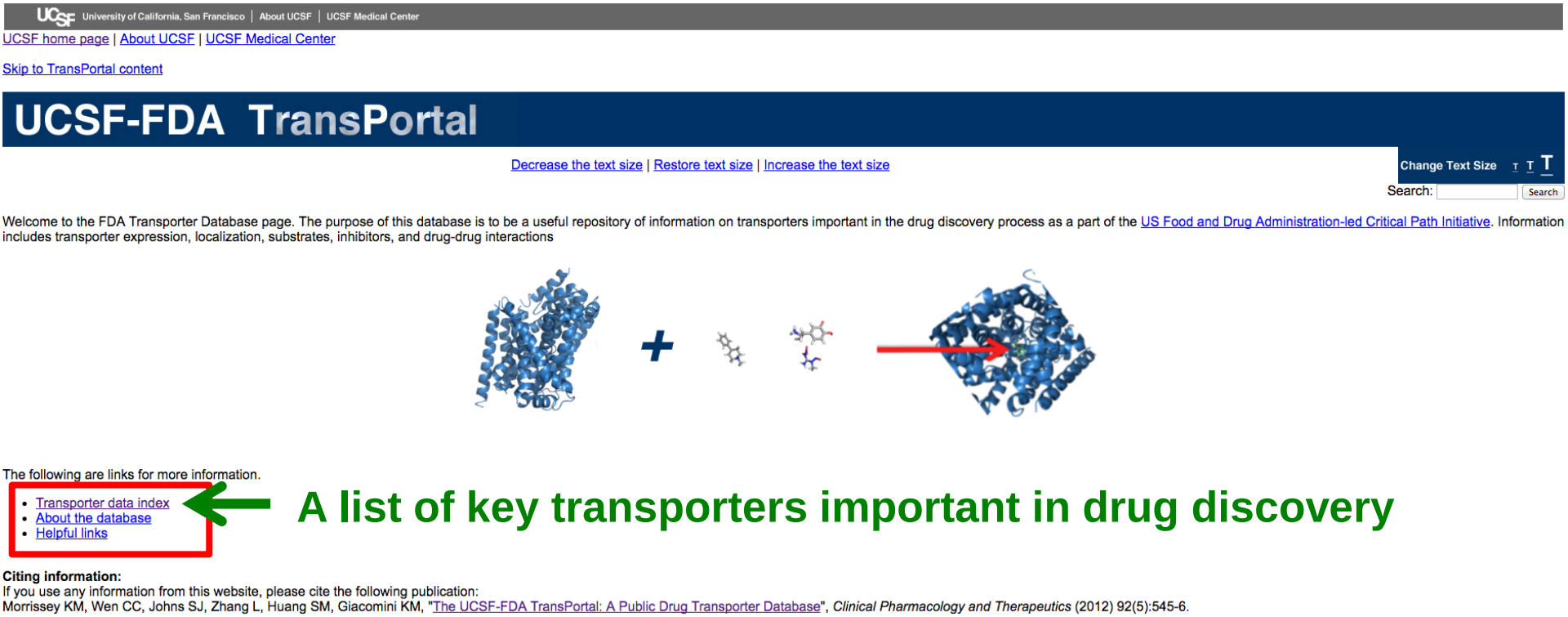


4. Drugs that Inhibit *SLCO1B1*?

- Manually curated databases which provide information about drug- interaction.
  - **UCSF-FDA TransPortal**
  - P450 Drug Interaction Table (Flockhart Table™)
  - Drug Interaction Database

UCSF-FDA TransPortal

http://transportal.compbio.ucsf.edu/



A list of key transporters important in drug discovery

UCSF-FDA TransPortal

http://transportal.compbio.ucsf.edu/

Are those patients with severe side-effects on another drug that inhibit OATP1B1?

Clinical Drug-Drug Interactions

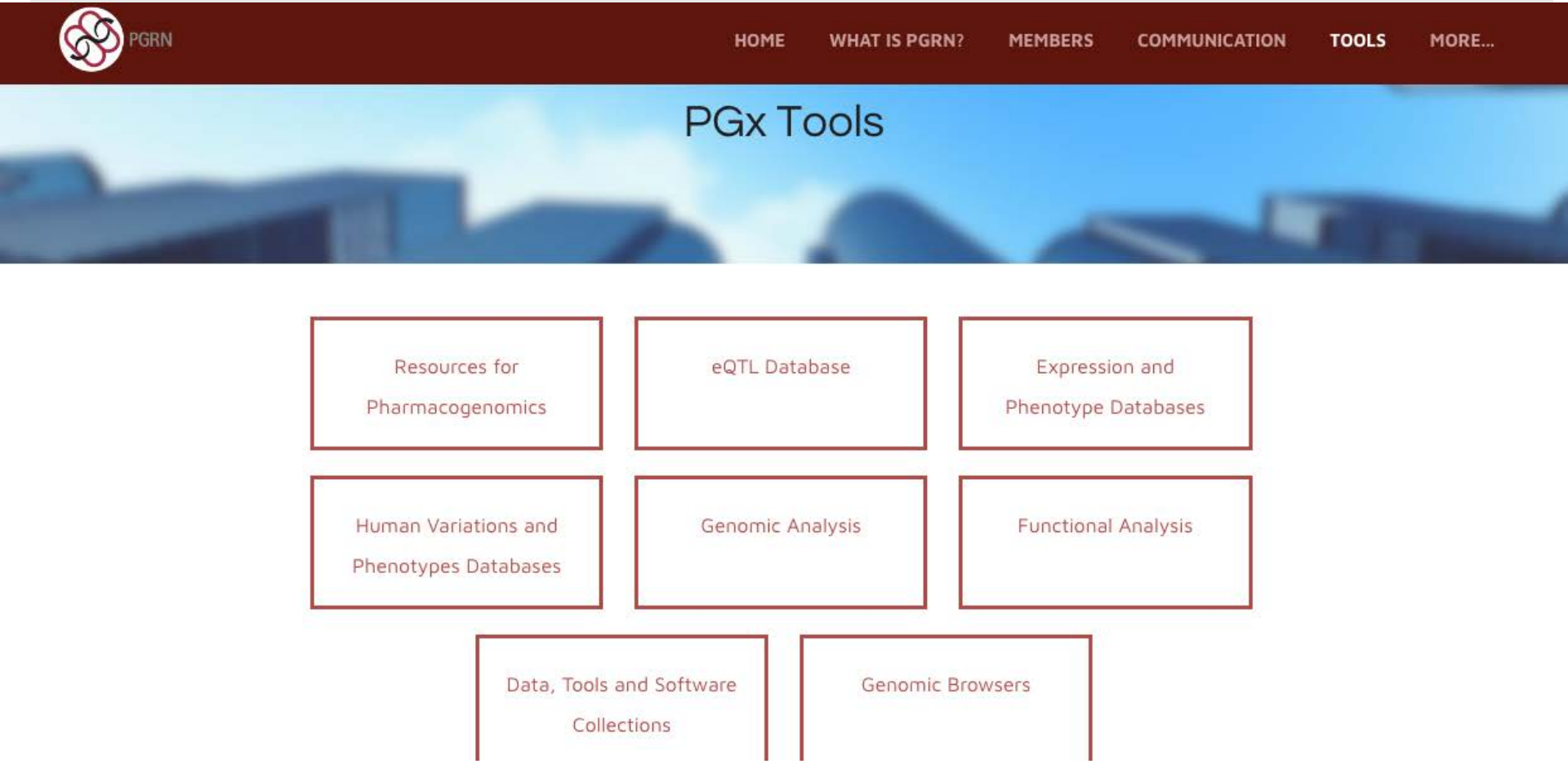
DDI	Implicated Transporter	Interacting Drug	Affected Drug	AUC	Cmax	CLR	CL/F	t1/2	Effect on PD	Reference	More Details
				Clinical PK Impact(fold change)							
1	ABCG2/OATPs	Atazanavir / Ritonavir	Rosuvastatin	3.1	7.0	ND	ND	ND	ND	Busti, 2008	DDI 1
2	ABCB1/OATPs	Cyclosporine	Docetaxel	7.3	5.7	ND	ND	ND	ND	Malingre, 2001	DDI 2
3	ABCB1/OATPs	Cyclosporine	Paclitaxel	8.5	2.0	ND	ND	ND	ND	Meerum, 1999	DDI 3
4	ABCG2/OATPs	Cyclosporine	Pitavastatin	4.6	6.6	ND	ND	ND	ND	Livalo Drug Label	DDI 4
5	ABCG2/OATPs	Cyclosporine	Rosuvastatin	5.0	10.6	ND	ND	ND	ND	Simonson, 2004	DDI 5
6	ABCG2/OATPs	Cyclosporine	Rosuvastatin	6.4	18.2	ND	ND	ND	ND	Simonson, 2004	DDI 6
7	ABCB1/OATPs	Erythromycin	Simvastatin	6.2	3.5	ND	ND	NS	ND	Kantola, 1998	DDI 7
8	ABCB1/OATPs	Indinavir / Ritonavir	Fexofenadine	4.8	2.5	ND	0.2	0.7	ND	Kharasch, 2009	DDI 8
9	OATPs	Lopinavir / Ritonavir	Rosuvastatin	2.1	4.7	ND	0.5	NS	yes	Kiser, 2008	DDI 9
10	OATPs	Rifampicin	Glyburide	2.2	1.8	NS	0.5	ND	yes	Zheng, 2009	DDI 10
11	ABCB1/OATPs	Ritonavir	Digoxin	1.9	ND	0.6	0.6	2.6	ND	Ding, 2004	DDI 11
12	ABCB1/OATPs	Ritonavir	Saquinavir	29.9	22.5	ND	ND	ND	ND	la, 2007	DDI 12
13	ABCB1/OATPs	Verapamil	Simvastatin	4.6	2.6	ND	ND	NS	ND	Kantola, 1998	DDI 13

The transporters are implicated by in vitro data and/or studies in humans with genetic polymorphisms of the transporter
DDI = Drug Drug Interaction
PK = pharmacokinetic
PD = pharmacodynamic
ND = not determined
NS = not significant
N/A = information not available
Calculation of Fold Change: fold change in the presence of the interacting drug = (value with interacting drug)/(value without interacting drug)
fold change > 1: increase in pharmacokinetic value
fold change < 1: decrease in pharmacokinetic value

Click “Rifampicin” to find out what other transporter(s) it inhibits

Summary

http://www.pgrn.org/tools.html



Acknowledgements

Pharmacogenetics of Membrane Transporters (PMT)

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UCSF-FDA TransPortal


Kathy Giacomini


Kari Morrissey


Chris Wen

Lei Zhang

Susan Johns

Shiew-Mei Huang

Funding of TransPortal: FDA

Thank You

Questions About

sookwah.yee@ucsf.edu

UCSF-FDA TransPortal

http://dbts.ucsf.edu/fdatransportal

If you know what other drugs that were used by patients with the severe side-effects, you can search the drug name in the portal.

TRIMETHOPRIM

In Vitro Inhibitors

* denotes drugs that can potentially be used for in vivo (clinical) studies of the designated transporter

Transporter	Synonyms	Inhibitor	IC50 (μM)	Ki (μM)	Substrate used	Cell System	Reference
SLC22A2	OCT2	Trimethoprim		13.2	Lamivudine	HEK-OCT2	Muller, 2013
SLC47A2	MATE2K	Trimethoprim		0.66	Lamivudine	HEK-MATE2-K	Muller, 2013
SLC22A2	OCT2	Trimethoprim	1318		N-methylpyridinium	HEK293-OCT2	Zolk, 2009

Back to top

Clinical Drug-Drug Interactions

DDI	Implicated Transporter*	Interacting Drug	Affected Drug	AUC	Cmax	CLR	CL/F	t1/2	Effect on PD	Reference	More Details
				Clinical PK Impact(fold change)							
1	SLC47A1	Trimethoprim	Metformin	1.295	ND	0.736	ND	ND	ND	Muller, 2015	DDI 1
2	OCTs	Trimethoprim	Zidovudine	NS	ND	0.5	NS	NS	ND	Chatton, 1992	DDI 2

PK = pharmacokinetic
The transporters are implicated by in vitro data and/or studies in humans with genetic polymorphisms of the transporter
DDI = Drug Drug Interaction
PD = pharmacodynamic
ND = not determined
NS = not significant
N/A = information not available
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fold change > 1: increase in pharmacokinetic value
fold change < 1: decrease in pharmacokinetic value

GTEx Portal

http://gtexportal.org/home/