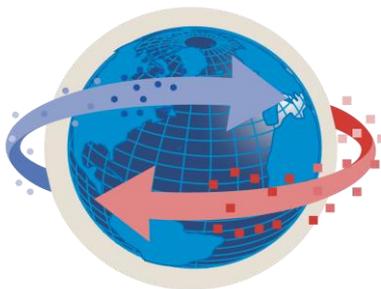


# GWA Studies Reveal Important Transporter Polymorphisms As Biomarkers for Pharmacokinetics and Pharmacodynamics

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INTERNATIONAL  
TRANSPORTER  
CONSORTIUM

ASCPT 2016 ANNUAL MEETING

MARCH 8-12, 2016

HILTON BAYFRONT, SAN DIEGO, CA

# Transporter Databases

Databases and Web Address	Content
<p><b>SLC Tables</b> <a href="http://www.bioparadigms.org/slc/intro.htm">http://www.bioparadigms.org/slc/intro.htm</a></p>	<p>Brief information about all genes in the SLC superfamily: substrates, link to review article.</p>
<p><b>Transporter Classification Database</b> <a href="http://www.tcdb.org">http://www.tcdb.org</a></p>	<p>Structure, sequence and annotation about the transporters</p>
<p><b>UCSF-FDA Transportal</b> <a href="http://dbts.ucsf.edu/fdatransportal">http://dbts.ucsf.edu/fdatransportal</a></p>	<p>Transporter-mediated Drug-Drug Interaction database</p>
<p><b>UCSF-PMT Pharmacogenomics of Membrane Transporter</b> <a href="http://pharmacogenetics.ucsf.edu">http://pharmacogenetics.ucsf.edu</a></p>	<p>Genetic variation of ABC and SLC transporters from PMT sequencing and 1000 Genome. Also expression data from GTEx</p>
<p><b>Human Transporter Database</b> <a href="http://htd.cbi.pku.edu.cn/index.php">http://htd.cbi.pku.edu.cn/index.php</a></p>	<p>Collected data from various databases including SNPs: NCBI, HapMap, PharmGKB etc.</p>

# Scenario 1: You have a new drug X in Phase I Clinical Trial

- It is a substrate of OCT1 and its drug concentrations were affected by OCT1 inhibitor in drug-drug interaction study.
- Consider doing a genetic study in Phase I clinical trial.
- Which SNP(s) should you genotype?
- Are there clinical association of the SNPs with phenotype?

<http://pharmacogenetics.ucsf.edu>

*Pharmacogenetics.UCSF.edu*

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Reviewer Access Intranet



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	
Exon 1: Coding		rs187313078		160542973	111	6	C → T	+	2	Pro = Pro	T=	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
Exon 1: Coding	3932	rs34447885		160543008	146	41	C → T	+	14	Ser → Phe (D=155)	T=	0.026	0.008	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000
Exon 1: Coding	3933	rs34570655		160543034	172	67	C → G	+	23	Leu → Val (D=32)	G=	0.000	0.008	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000



Feature	PMT ID	dbSNP	Array	Genomic Position	Transcript Position	Coding Position	Nucleotide Change	Strand	Amino Acid Position	Amino Acid Change
Exon 1: Coding		rs187313078	Colombian in Medellin, Colombia (94 subjects)	160542973	111		T	+	2	Pro = Pro
Exon 1: Coding	3932	rs34447885	Bengali in Bangladesh (86 subjects)	160543008	146		T	+	14	Ser → Phe (D=155)
				160543034	172		G	+	23	Leu → Val (D=32)

Kinh in Ho Chi Minh City, Vietnam (99 subjects)

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	
T=	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	0.000	0.000	0.000	0.000	0.000	0.000	0.000
T=	0.026	0.008	0.000	0.000	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.018	0.005	0.000	0.000	0.000	0.020	0.018	0.008	0.006	0.000	0.005	0.000	0.000	0.000	0.014
G=	0.000	0.008	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
T=	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	0.000
A=	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	0.009	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
A=	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.016	0.000	0.000	0.005	0.005	0.000	0.009	0.000	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.024	0.000	0.009	0.000	
T=	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	0.000	0.000
C=	0.391	0.295	0.186	0.312	0.197	0.408	0.410	0.245	0.348	0.172	0.148	0.228	0.283	0.196	0.186	0.466	0.348	0.328	0.376	0.391	0.341	0.161	0.221	0.240	0.206	0.269	

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

**Find gene:** Examples: ABCA1, rs2246298, 2987

SLC22A1

SLC22A1

**Variant Data**

Showing SNPs for transcript:  View all PMT variants for SLC22A1 on [UCSC Genome Browser](#)

SLC22A1 Resequencing 1000 Genomes



Feature	PMT ID	dbSNP/ PubMed	Array Availability	Genomic Position	Transcript Position	Coding Position	Nucleotide Change	Strand	Amino Acid Position	Amino Acid Change	Statistics	AA Freq	CA Freq	AS Freq	ME Freq	PA Freq
Promoter	3160	rs60541448		160542739 GRCh37 160462729 NCBI36	-124	-229	GCTTAGACCCCACTGACTCGTCCC G → A GGCAAAGCAAACGATTTGATCAGAT	+			n= 134 G/G= 67 G/A= 0 A/A= 0 A= 0.000	134 67 0 0 0.000	130 65 0 0 0.000	136 67 0 0 0.007		n/a 0.000
Promoter	3161	rs58812592		160542767 GRCh37 160462757 NCBI36	-96	-201	CAAAGCAAACGATTTGATCAGATGG C → G CACGTGCATTTCTCTTTTCTGAA	+			n= 134 C/C= 66 C/G= 1 G/G= 0 G= 0.007	134 67 0 0 0.000	130 65 0 0 0.000	136 68 0 0 0.000		n/a 0.000
Promoter	3162	rs6899549	I	160542819 GRCh37 160462809 NCBI36	-44	-149	CCAGCACCATAGGGTAAAGATTAT T → C TCTACTTGGTTGCCTCCAGATGTT	+			n= 134 T/T= 61 T/C= 5 C/C= 1 C= 0.052	134 67 0 0 0.000	130 65 0 0 0.000	136 68 0 0 0.000		n/a 0.000
Exon 1: Coding	3932	rs34447885 5 pubs		160543008 GRCh37 160462998 NCBI36	146	41	GACATTCTGGAGCAGGTTGGGGAGT C → T TGGCTGGTTCCAGAAGCAAGCCTTC	+	14	Ser → Phe (D=155)	n= 196 C/C= 93 C/T= 4 T/T= 1 T= 0.031	192 96 0 0 0.000	60 30 0 0 0.000	18 9 0 0 0.000	14 7 0 0 0.000	
Exon 1: Coding	3933	rs34570655		160543034 GRCh37 160463024 NCBI36	172	67	TGGCTGGTTCCAGAAGCAAGCCTTC C → G TCATCTTATGCCTGCTGCGCTGC	+	23	Leu → Val (D=32)	n= 198 C/C= 98 C/G= 1 G= 0.005	194 97 0 0.000	60 30 0 0.000	18 9 0 0.000	14 7 0 0.000	

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

Exon 1: Coding	3936 rs12208357 19 pubs	160543148 GRCh37 160463138 NCBI36	286	181	TCCTGGGGTGGCTGAGCTGAGCCAG C → T GCTGTGGCTGGAGCCCTGCCGAGGA Reduced metformin and MPP+ uptake in transfected cells. PMID: 846.	+	61	Arg → Cys (D=180)	n= 198 C/C= 99 C/T= 0 T/T= 0 T= 0.000	194 83 14 0	60 30 0 0	18 8 1 0	14 7 0 0
Exon 1: Coding	3936 rs12208357 19 pubs		61	Arg → Cys (D=180)	GCCCCGGGGCGAGGCCTTC C → T TTGGCCAGTGCAGGCGCTATGAAGT	+	85	Leu → Phe (D=22)	n= 198 C/C= 97 C/T= 2 T/T= 0 T= 0.010	194 97 0 0	60 30 0 0	18 9 0 0	14 7 0 0

Exon 1: Coding	3937 rs35546288				TCCTGGGGTGGCTGAGCTGAGCCAG C → T GCTGTGGCTGGAGCCCTGCCGAGGA Reduced metformin and MPP+ uptake in transfected cells. PMID: 19940846.	+	61	Arg → Cys (D=180)					
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Exon 2: Coding	3938 rs683369 9 pubs				CCTGGGGCCCCGCGGGCGAGGCCTTC C → T TTGGCCAGTGCAGGCGCTATGAAGT	+	85	Leu → Phe (D=22)					
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Statistics	AA Freq	CA Freq	AS Freq	ME Freq	PA Freq
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AGTCCTGTTTGAATGCGGGCTTCTT	61	Arg → Cys (D=180)	n= 198 C/C= 99 C/T= 0 T/T= 0 T= 0.000	194 83 14 0	60 30 0 0	18 8 1 0	14 7 0 0
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	85	Leu → Phe (D=22)	n= 198 C/C= 97 C/T= 2 T/T= 0 T= 0.010	194 97 0 0	60 30 0 0	18 9 0 0	14 7 0 0
--	----	------------------	---	---------------------	--------------------	-------------------	-------------------

	160	Phe → Leu (D=22)	n= 200 C/C= 99 C/G= 1 G/G= 0 G= 0.005	200 88 11 1	60 29 1 0	20 9 1 0	14 7 0 0
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# Scenario 2: You want to know other drug response phenotypes associated with *SLCO1B1* variant

## GRASP: Genome-Wide Repository of Associations Between SNPs and Phenotypes

<https://grasp.nhlbi.nih.gov/Overview.aspx>



[Accessible Search Form](#)

  
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Monday, March 07, 2016

### Genetics & Genomics Programs

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## GRASP: Genome-Wide Repository of Associations Between SNPs and Phenotypes

### Overview

GRASP includes all available genetic association results from papers, their supplements and web-based content meeting the following guidelines:

- All associations with  $P < 0.05$  from GWAS defined as  $\geq 25,000$  markers tested for 1 or more traits.
- Study exclusion criteria: CNV-only studies, replication/follow-up studies testing  $< 25K$  markers, non-human only studies, article not in English, gene-environment or gene-gene GWAS where single SNP main effects are not given, linkage only studies, aCGH/LOH only studies, heterozygosity/homozygosity (genome-wide or long run) studies, studies only presenting gene-based or pathway-based results, simulation-only studies, studies which we judge as redundant with prior studies since they do not provide significant inclusion of new samples or exposure of new results (e.g., many methodological papers on the WTCCC and FHS GWAS).
- More detailed methods and resources used in constructing the catalog are described at the "[Methods & Resources](#)" page.

### Now Accepting GWAS Results Submissions

[Subscribe to the GRASP-GWAS-L mailing list](#) to find out details on how to submit results in conjunction with your publications

# SEARCH

Genetics & Genomics Programs

## GRASP Search - v2.0.0.0

[GRASP Overview](#)

The GRASP search tool searches genome-wide association study (GWAS) catalog data housed at the National Center for Biotechnology Information (NCBI). By accessing and using this catalog you agree to comply with the [complete terms of use](#).

### Phenotype Selection

**Category:**

**Trait:**

**P-Value <**

### Genotype Selection

[Location](#)  [Gene](#)  [SNP](#)

**Gene names or IDs:**

SLCO1B1

\* Separate multiple values using Commas

### SNP Functional Class

exon  intron  neargene  UTR  ncRNA

# Export the file to excel to view the results

rsID

p-value

phenotypes

Snp Id	Pvalue	PMID	Phenotype	chr	pos	InGene	Journal
rs4149080	5.60E-21	2.3E+07	Methotrexate plasma clearance (24-hour infusion of a 1 g/m2 dose)	12	21224625	(SLCO1B1)	Blood
rs73063122	9.30E-21	2.3E+07	Methotrexate plasma clearance (24-hour infusion of a 1 g/m2 dose)	12	21208279	(SLCO1B1)	Blood
rs58258204	9.60E-21	2.3E+07	Methotrexate plasma clearance (24-hour infusion of a 1 g/m2 dose)	12	21215081	(SLCO1B1)	Blood
rs55695203	3.30E-20	2.3E+07	Methotrexate plasma clearance (24-hour infusion of a 1 g/m2 dose)	12	21204819	(SLCO1B1)	Blood
rs11045759	4.00E-03	2E+07	Triglycerides change with statins	12	21104489		PLoS One
rs11045758	4.10E-03	2E+07	Triglycerides change with statins	12	21104468		PLoS One
rs4363657	1.60E-05	2.1E+07	Cerivastatin-associated rhabdomyolysis	12	21215788	(SLCO1B1)	Pharmacogenet
rs4149056	3.10E-05	2.1E+07	Cerivastatin-associated rhabdomyolysis (No gemfibrozil use)	12	21178615	(SLCO1B1)	Pharmacogenet
rs3829306	2.00E-04	2.2E+07	Cognitive response to topiramate treatment as measured by the	12	21189346	(SLCO1B1)	Epilepsia
rs12317268	4.10E-06	2.2E+07	LDL cholesterol response to statins (fractional change in LDL ch	12	21189607	(SLCO1B1)	Circ Cardiovasc
rs12317268	2.90E-05	2.2E+07	LDL cholesterol response to statins (absolute change in LDL ch	12	21199607	(SLCO1B1)	Circ Cardiovasc
rs1120964	3.00E-05	2.3E+07	Blood pressure response to candesartan treatment	12	21186756	(SLCO1B1)	Hypertension
rs2417967	3.10E-05	2.3E+07	Blood pressure response to candesartan treatment	12	21207801	(SLCO1B1)	Hypertension
rs4149021	6.00E-04	2.3E+07	Drug-induced liver injury-all DILI cases with a macrolide antibiot	12	21141851	(SLCO1B1)	Pharmacogenet
rs4149021	1.00E-03	2.3E+07	Drug-induced liver injury-all DILI cases with age of onset greate	12	21141851	(SLCO1B1)	Pharmacogenet
rs4149056	5.00E-08	2.3E+07	LDL cholesterol response after 40mg daily simvastatin treatmer	12	21178615	(SLCO1B1)	Eur Heart J
rs4149056	1.00E-07	2.3E+07	APOB (apolipoprotein B) response after 40mg daily simvastatin	12	21178615	(SLCO1B1)	Eur Heart J
rs11045819	2.40E-05	2.3E+07	LDL cholesterol response after 40mg daily simvastatin treatmer	12	21176879	(SLCO1B1)	Eur Heart J
rs11045819	4.30E-04	2.3E+07	APOB (apolipoprotein B) response after 40mg daily simvastatin	12	21176879	(SLCO1B1)	Eur Heart J

Methotrexate plasma clearance

Response to statins (TG, LDL)

Blood pressure response  
Drug-induced liver injury

# Q & A

- What other information that you would like to know about transporter polymorphisms that are not covered here?
- What are the transporter databases that you use often and like to share with the group?