Review and Emerging Evidence on Transporter Polymorphisms

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International Transporter Consortium Criteria for Clinically Important Transporter Polymorphisms

- (i) genome-wide association studies have identified them to be significantly associated with the pharmacokinetics or pharmacodynamics of one or more drugs at genome-wide level significance
- (ii) multiple candidate gene studies have identified significant associations between these polymorphisms and drug disposition, efficacy, or toxicity
- (iii) the polymorphisms have exhibited functional changes in in vitro studies

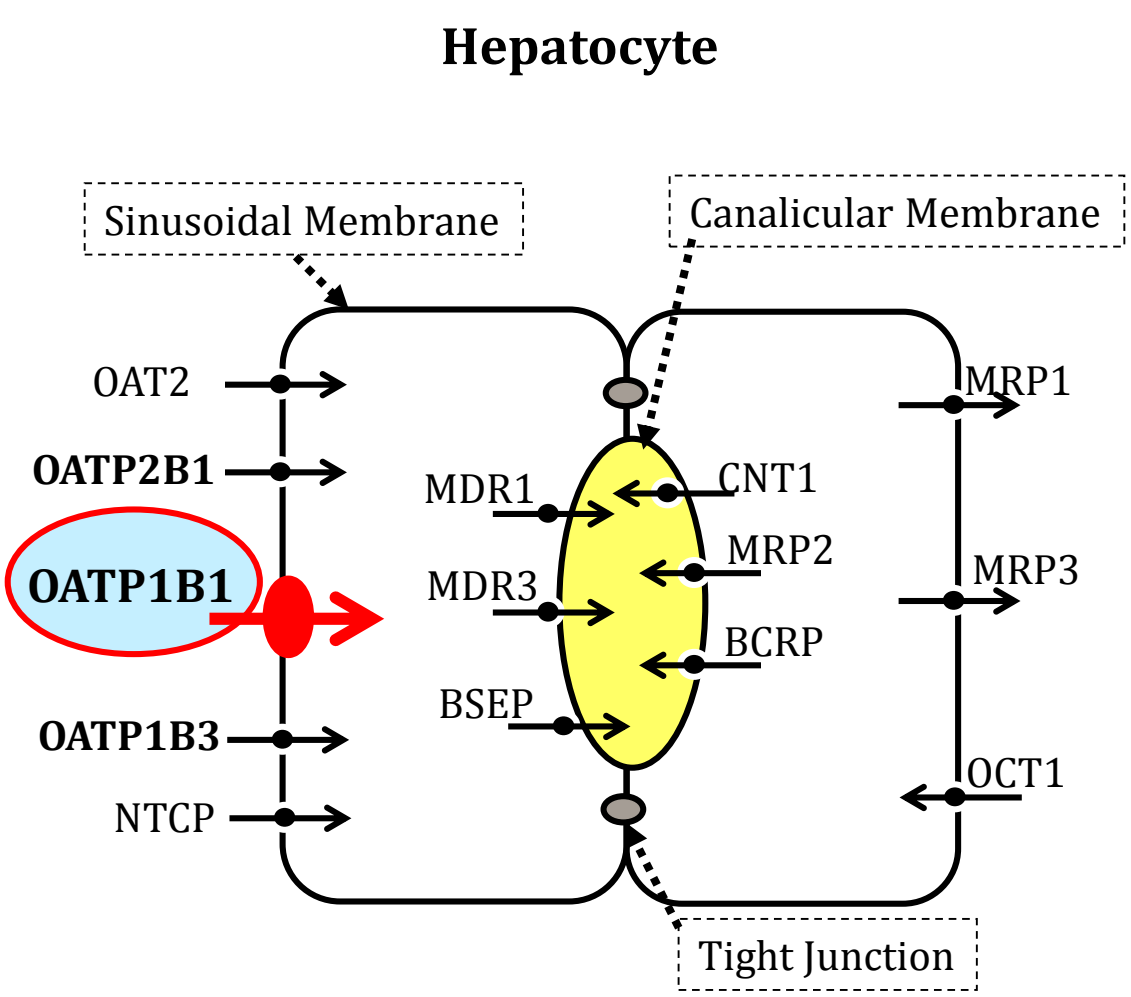
Giacomini et al, Clin Pharm & Ther, 94:23-26, 2013.

International Transporter Consortium Recommendations

- **SLCO1B1 encoding OATP1B1**
  - c.521T>C, p.V174A, rs4149056
- **BCRP (ABCG2)**
  - c.421C>A,p.Q141K, rs2231142

Giacomini et al, Clin Pharm & Ther, 94:23-26, 2013.

Importance of OATP1B1

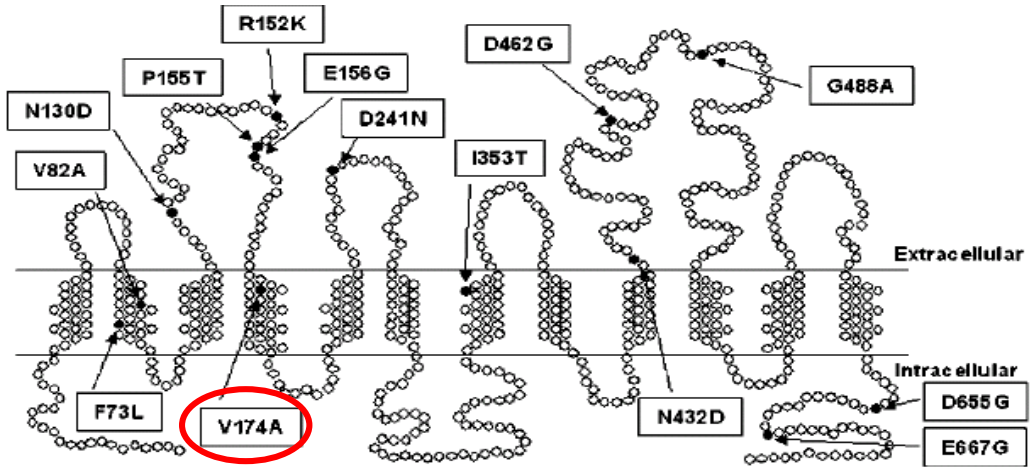


Drugs Interacting with OATP1B1

- Statins (S,I)
- Repaglinide (S, I)
- Atrasentan (S)
- Rosiglitazone (I)
- Fexofenadine (S)
- Bile Acids (S,I)
- Rifampin (S, I)
- Cyclosporin A (I)
- Gemfibrozil (I)

S- Substrate
I- Inhibitor

SLCO1B1 Variants Leading to Amino Acid Changes in OATP1B1



Tirono et al. (2001) JBC vol 276.

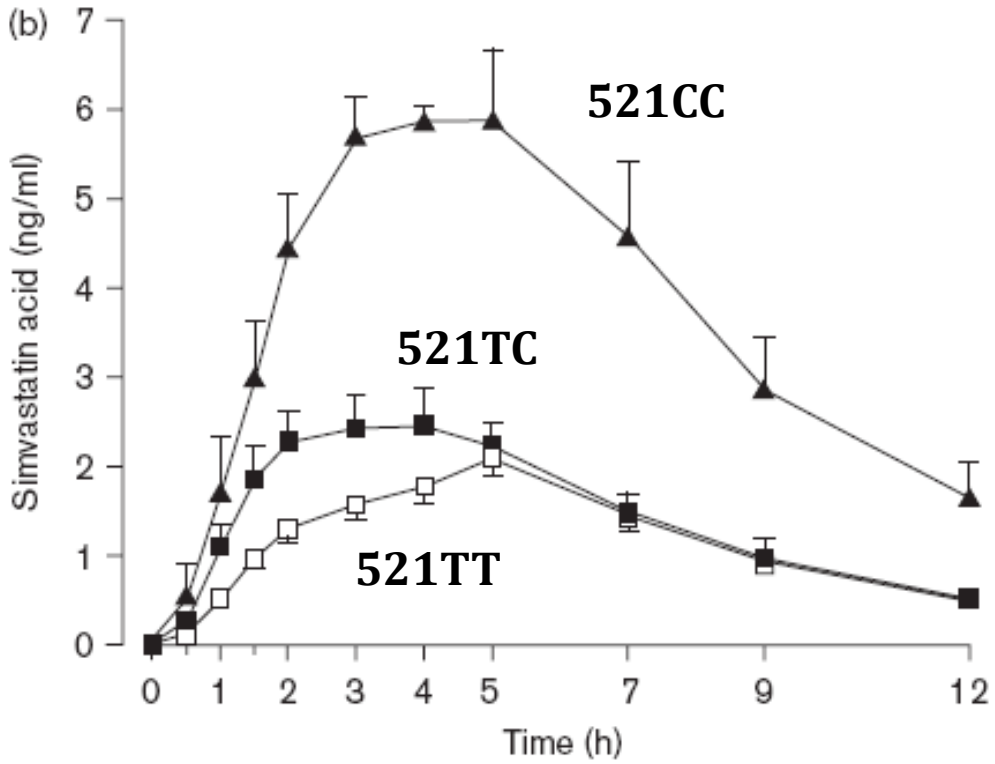
SLCO1B1 Allele	Polymorphisms	Protein Variation	Consequence	NA	EA	S/CA	ME	EU	AM	SA
***1a**	*1 Reference Allele, wt	NA		34	25	52	49	56	37	21
***1b**	388A>G	Asn130Asp	Increased activity?	48	63	39	31	26	39	77
***5**	521T>C	Val174Ala	Decreased Function	2	0	0	5	2	0	0
***15**	388A>G 521T>C	Asn130Asp Val174Ala	Decrease Function	16	12	9	15	16	24	2

NA – North Africa, EA – East Asia, S/CA – South or Central Asia, ME – Middle East, EU – Europe, AM – America, SA – Sub-Saharan Africa

Modified from: Pasanen et al. (2008) *Pharmacogenomics*. 9(1).

OATP1B1 521T>C Pharmacokinetic Impact

Individuals with Polymorphisms of OATP1B1 Have Higher Plasma Levels of Simvastatin Acid

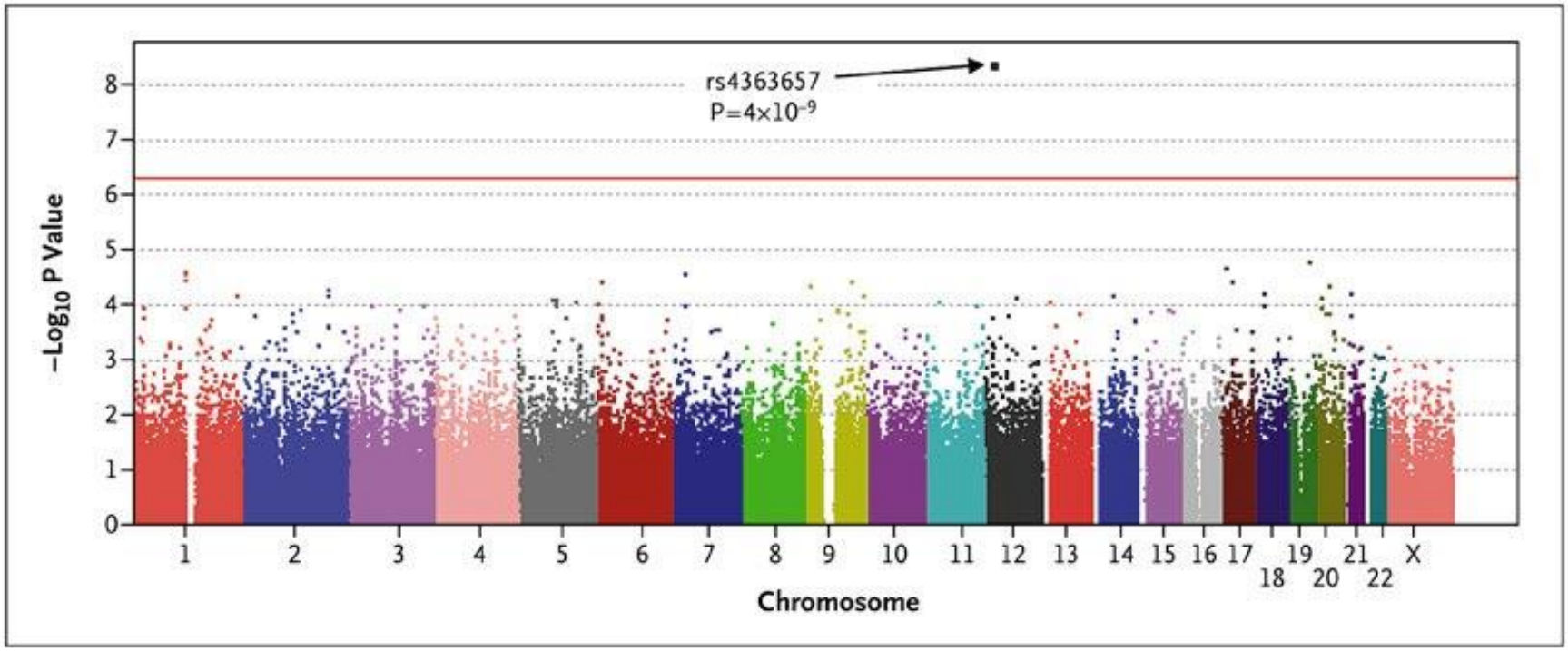


Drugs Effected by OATP1B1 Genetic Variants

Pravastatin
Repaglinide
Methotrexate
Maraviroc
Nateglinide
Pitavastatin
Simvastatin
Rosuvastatin
Lopinavir
Erythromycin
Flavopiridol
Enalapril
Atorvastatin

Pasanen et al (2006) Pharmacogenetics and Genomics16:873–879

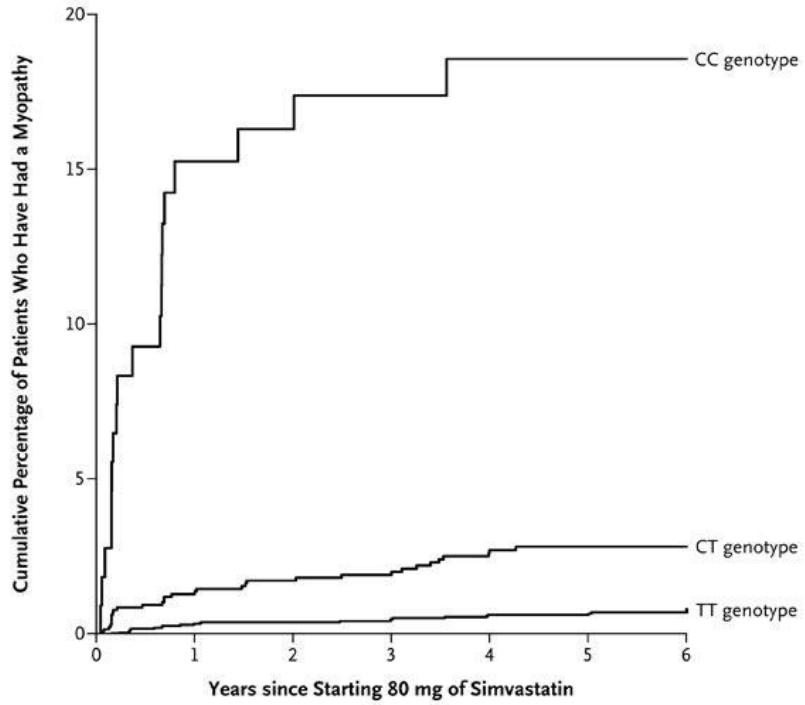
OATP1B1 Variants and Statin-induced Myopathy



- Genome Wide Association Study (GWAS) using approximately 300,000 markers
- 12,000 participants; all were taking simvastatin (80 mg) daily
- 85 subjects with definite or incipient myopathy and 90 controls
- No associations between myopathy and SNPs in any other region yielded an uncorrected P value of $< 10^{-5}$

NEJM (2008) 359(8):789-799

Cumulative Risk of Myopathy Associated with SLCO1B1 Minor C Allele



Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Subjects on 80 mg simvastatin

521CC homozygotes:
- 18% cumulative risk
- Myopathy occurred primarily during the first year

521CT heterozygotes:
- 3% cumulative risk

521TT homozygotes:
- 0.6% cumulative risk

Overall, more than 60% of myopathy cases could be attributed to the 521T>C variant in OATP1B1.

NEJM (2008) 359(8):789-799

Evidence from PharmGKB

Clinical PGx | PGx Research | Overview | VIP | Haplotypes | Pathways | Is Related To | Publications | LinkOuts

Dosing Guidelines (1) | **Drug Labels (0)** | **Clinical Annotations (43)**

Clinical Variants that meet the highest level of criteria, manually curated by PharmGKB, are shown below. Please follow the link in the "Position" column for more information about a particular variant. Each link in the "Position" column leads to the corresponding PharmGKB Variant Page. The Variant Page contains summary data, including PharmGKB manually curated information about variant-drug pairs based on individual PubMed publications. The PMIDs for these PubMed publications can be found on the Variant Page.

To see more Clinical Variants with lower levels of criteria, click the button at the bottom of the table.

rs4149056 related to simvastatin - toxicity/adr (1A)

Level of Evidence
Level 1A

Type
Toxicity/ADR

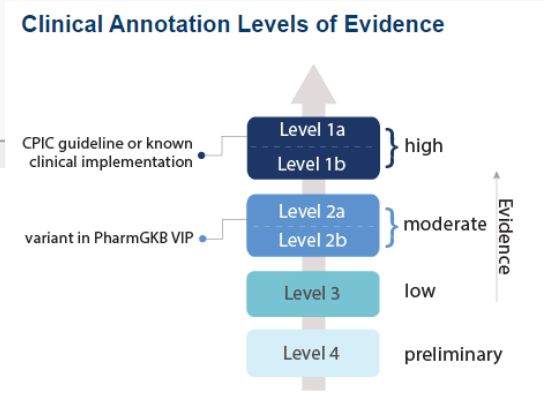
Genes
SLCO1B1

Phenotypes
Muscular Diseases, Myopathy, Central Core

OMB Race
Mixed Population

CC	Patients with the CC genotype may have a higher risk of simvastatin-related myopathy as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.
CT	Patients with the CT genotype may have a higher risk of simvastatin-related myopathy as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.
TT	Patients with the TT genotype may have a lower risk of simvastatin-related myopathy as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity.

View Evidence



from search: OATP1B1

GENE:
SLCO1B1
solute carrier organic anion transporter family, member 1B1

1. CPIC Guideline for simvastatin and SLCO1B1

last updated 01/28/2016

Table 1: Recommended dosing of simvastatin based on SLCO1B1 phenotype

Adapted from Table 1 and 2 of the 2014 guideline update manuscript.

Phenotype	Examples of diplotypes [a]	Genotype at rs4149056	Implications for simvastatin	Dosing recommendations for simvastatin [b,c]	Classification of recommendations [d]
Normal function, Homozygous wild-type (two normal function alleles)	*1a/*1a, *1a/*1b, *1b/*1b	TT	Normal myopathy risk	Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.	Strong
Intermediate function, Heterozygous (one normal function allele plus one decreased function allele)	*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17	TC	Intermediate myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); consider routine CK surveillance.	Strong
Low function, Homozygous variant or mutant (two decreased function alleles)	*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17	CC	High myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); consider routine CK surveillance.	Strong

CK, creatine kinase.
[a] SLCO1B1 alleles are often named using * allele nomenclature, representing various SNPs alone or in combination (http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=33) (2014 Update Supplemental Table S1) that are associated with low SLCO1B1 protein expression or function (2014 Update Supplemental Table S2). The minor C allele at rs4149056 is contained within SLCO1B1*5 (rs4149056 alone) as well as the *15 and *17 haplotypes and is associated with lower plasma clearance of simvastatin. The magnitude of this effect is similar for *5, *15, and *17 haplotypes.

GWAS Study on Low-Density Lipoprotein Cholesterol Response After Statin Treatment

Table 1 | Genome-wide significant associations in stage 1, stage 2 and combined meta-analysis.

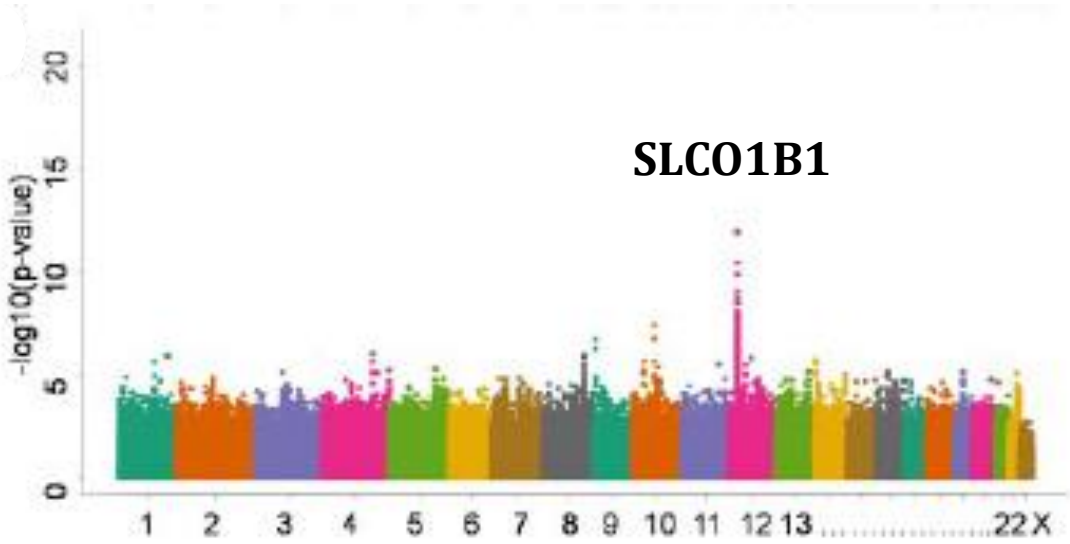
Chr	Position	Lead SNP	Gene	Coding allele	Noncoding allele	Phase	*N*	Frequency-coding allele	Beta*	s.e.	% Extra reduction†	*P* value
1	109620053	rs646776	*SORT1/CELSR2/PSRC1*	C	T	Stage 1	16,697	0.230	−0.015	0.003	1.5	6.70×10^{-7}
						Stage 2	21,902	0.216	−0.010	0.003	1.0	2.43×10^{-4}
						Combined	38,599		−0.013	0.002	1.3	1.05×10^{-9}
6	160930108	rs10455872	*LPA*	G	A	Stage 1	12,981	0.069	0.041	0.006	−4.1	1.95×10^{-11}
						Stage 2	18,075	0.087	0.059	0.005	−5.9	7.14×10^{-35}
						Combined	31,056		0.052	0.004	−5.2	7.41×10^{-44}
12	21260064	rs2900478	*SLCO1B1*	A	T	Stage 1	16,749	0.165	0.016	0.003	−1.6	2.26×10^{-6}
						Stage 2	7,504	0.164	0.017	0.006	−1.7	3.54×10^{-3}
						Combined	24,253		0.016	0.003	−1.6	1.22×10^{-9}
19	50107480	rs445925	*APOE*	A	G	Stage 1	13,909	0.098	−0.043	0.005	4.3	1.58×10^{-18}
						Stage 2	3,613	0.157	−0.088	0.011	8.8	1.41×10^{-15}
						Combined	17,522		−0.051	0.005	5.1	8.52×10^{-29}

Chr, chromosome; SNP, single nucleotide polymorphism.
*Beta for difference between the natural log-transformed on- and off-treatment low-density lipoprotein cholesterol (LDL-C) levels adjusted for natural log-transformed off-treatment LDL-C-, age-, sex- and study-specific covariates. The beta reflects the fraction of differential LDL-C lowering in carriers versus non-carriers of the SNP; a negative beta indicates a better statin response (stronger LDL-C reduction), a positive beta a worse statin response. Betas and *P* values were generated using linear regression analysis.
†This percentage reflects the % extra LDL-C lowering in carriers versus non-carriers of the SNP.

Genomic Investigation of Statin Therapy (GIST) consortium
Combination of multiple statins dose adjusted.

Postmus et al., Nat Commun. 28;5:5068, 2014.

SLCO1B1 Minor C Allele Associated with Methotrexate Clearance



Meta-analysis of St Jude (n=699) and COG (n=1279) patients, after we adjusted for rs4149056.

Methotrexate clearance is adjusted for age, sex, race, and treatment arm

Table 1. Covariates related to methotrexate clearance in a multivariate general linear model

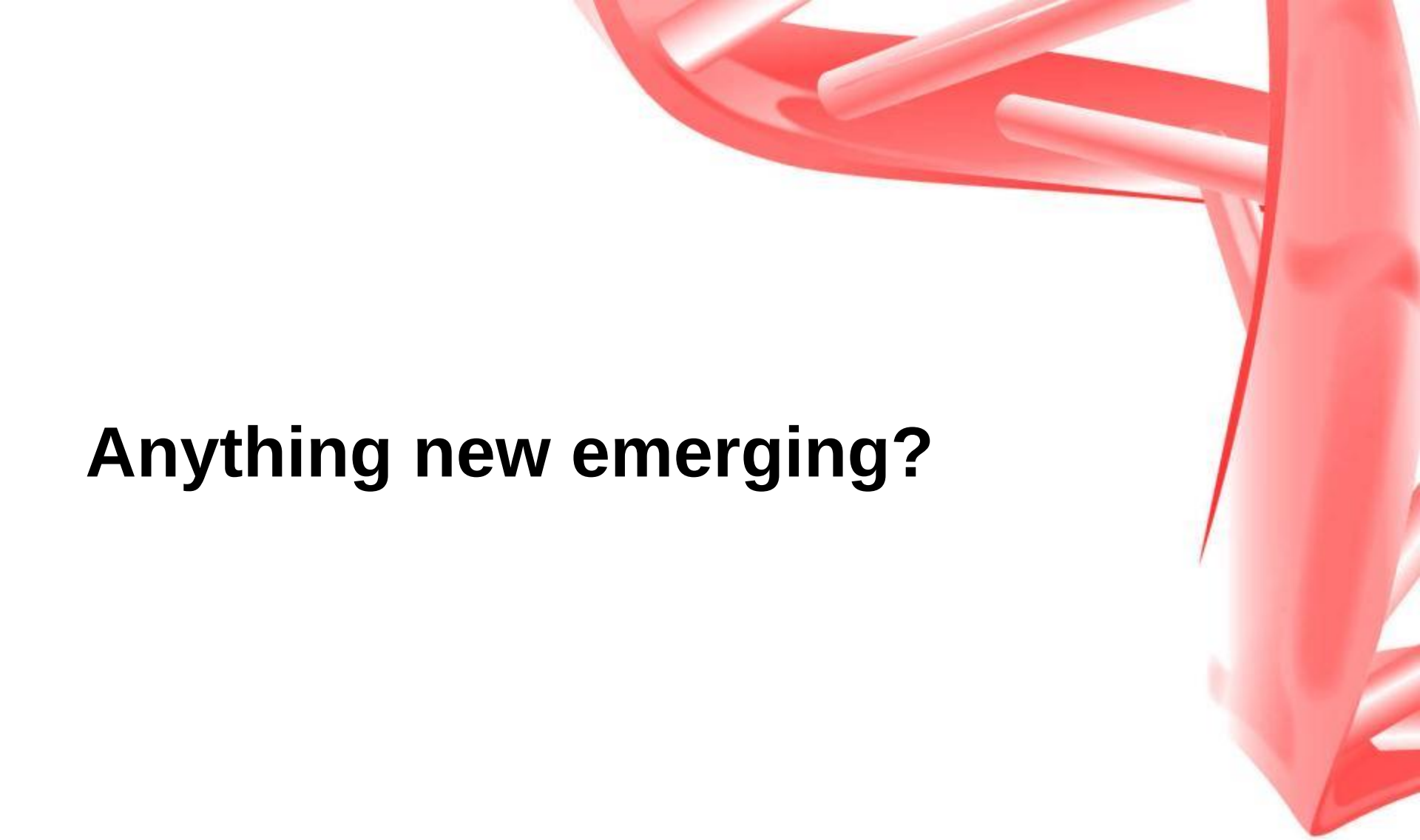
Factor	Direction	P*	R^2*	P†	R^2†
24-hour infusion (vs 4 hour)	24-hour higher	$< 2 \times 10^{-16}$	38%	$< 2 \times 10^{-16}$	38%
DI (vs no DI)	DI lower	.0010	0.5%	.0022	0.4%
Age	Older lower	9×10^{-7}	1.1%	7×10^{-7}	1.2%
Sex	Boys greater	.00028	0.6%	.00027	0.5%
rs4149056 T > C	C lower			2.1×10^{-11}	2%

DI indicates delayed intensification; direction, direction of association with clearance, ie, those receiving the 24-hour infusion had greater clearance than those receiving the 4-hour infusion; *P*, association of the factor with average methotrexate clearance based on a multivariate analysis; and R^2, the amount of interindividual variation explained by each factor.

*P and R^2 values for the multivariate model, including infusion length, use of DI, age, and sex.

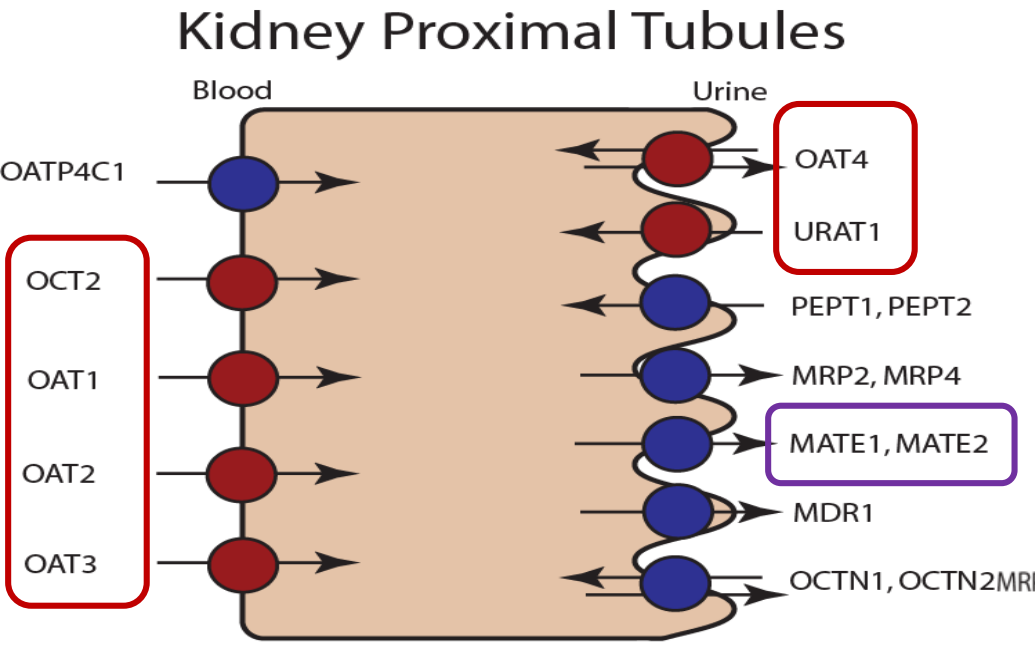
†P and R^2 value for the multivariate model and also including the rs4149056 genotype.

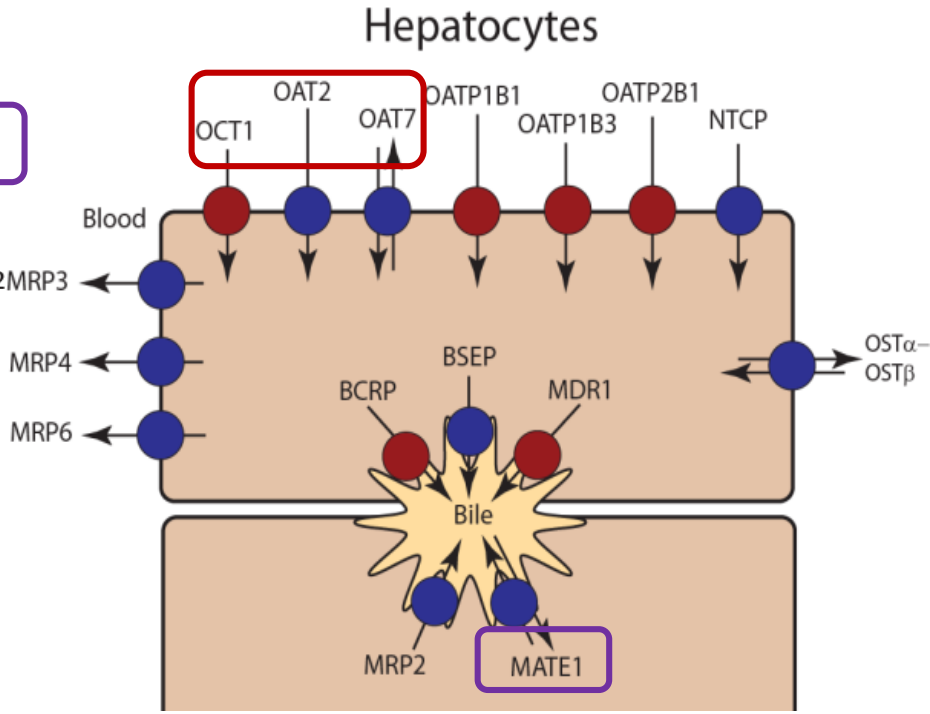
Ramsey et al, Blood 121:6 2013.



Anything new emerging?

SLC22 and SLC47 Family Transporters





= SLC22 Family

= SLC47 Family

Giacomini et al. (2010) Nature Reviews Drug Discovery.

Genetics of the Human OCTs and MATEs

Name	Gene	Location	Mutation	Notes
OCT1	SLC22A1	Liver (sinusoidal) Intestinal Epithelial (basolateral)	Variety of reduced function, reduced expression and deletion variants	Metformin PK and PD and other emerging drugs (Level 3)
OCT2	SLC22A2	Kidney (proximal tubules)	Reduced function variants	Metformin PK (Level 3)
OCT3	SLC22A3	Ubiquitous	Reduced expression variants	No clinical correlates to date. (Level 3)
MATE1	SLC47A1	Kidney, Liver	Multiple decreased function variants	Metformin efficacy. (Level 3)
MATE2K	SLC47A2	Kidney	Reduced function variants	Metformin PK and efficacy (Level 2B)

Drugs Transported by OCT1

Metformin
Cimetidine
Ciprofloxacin
Quinidine
Mitoxantrone
Irinotecan
Oxaliplatin
Paclitaxel
Imatinib
Sorafenib
Erlotinib
Gefitinib
Amantadine
Furamidine
Levodopa
Acyclovir
Lamivudine
Sulpiride
Ondansetron
Tropisetron
O-Desmethyltramadol

Lozano et al. BioMed Res Inter 2013.

DDI's Attributed to OCT1

Overall Effect	Object	Precipitant	% Change AUC	Source
In Vivo Induction > 20% Effect	metformin	rifampin	13.4	Cho et al. Clin Pharmal Ther 2011
In Vivo Inhibition > 20% Effect	metformin	trimethoprim	29.7	Muller et al. Eur J Clin Pharmcol 2015
In Vivo Inhibition > 20% Effect	metformin	verapamil	7.5 (PD effect	Cho et al Br J Clin Pharm 2014

Condensed information from University of Washington DDI database.

Criteria for Clinically Important Transporter Polymorphisms

- (i) genome-wide association studies have identified them to be significantly associated with the pharmacokinetics or pharmacodynamics of one or more drugs at genome-wide level significance
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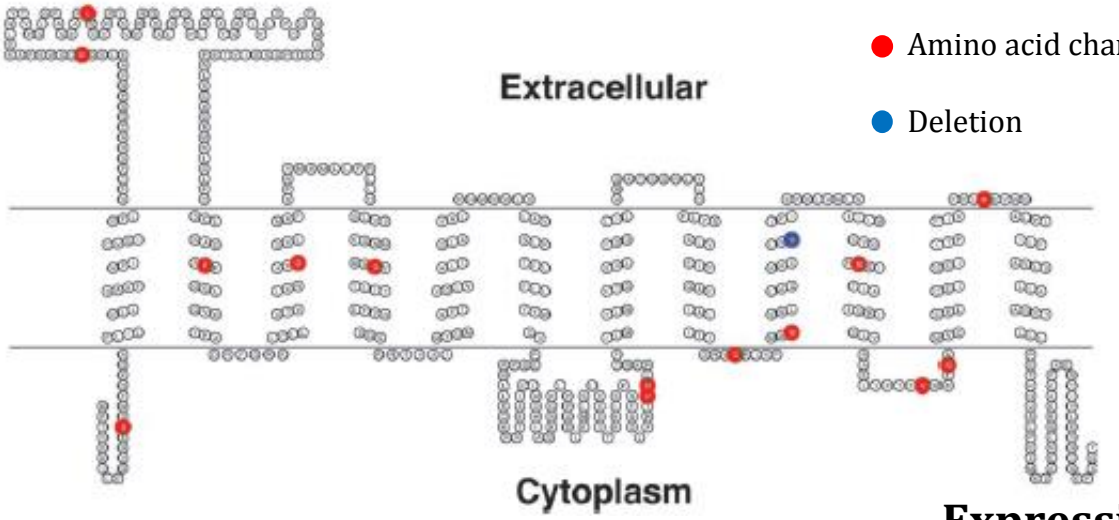
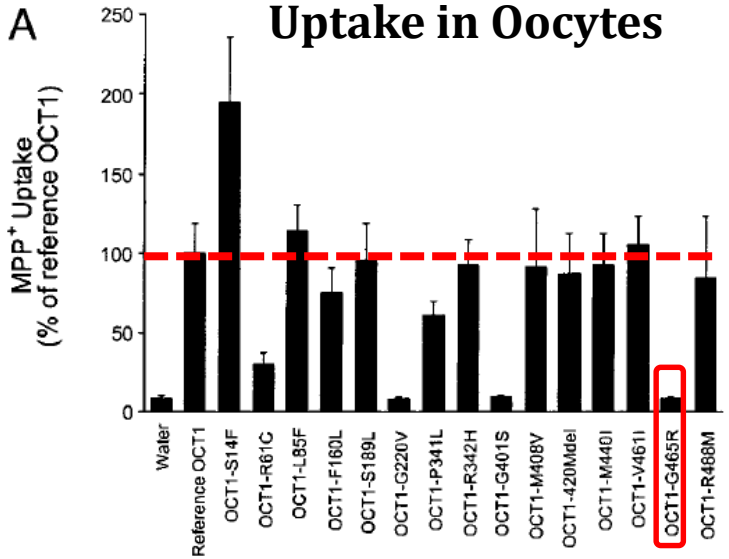
- (iii) the polymorphisms have exhibited functional changes in in vitro studies

Giacomini et al, Clin Pharm & Ther, 94:23-26, 2013.

In Vitro Charaterization of OCT1 Variants

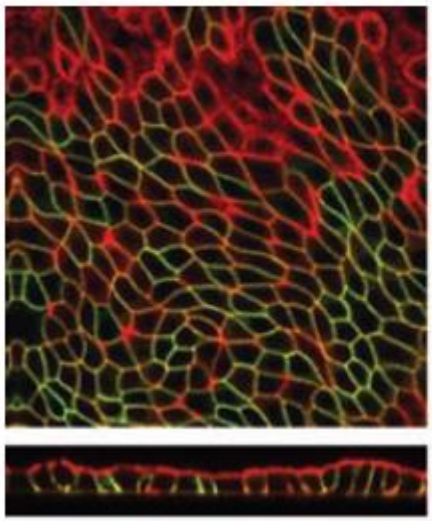


- Coding region variants with both increased and decrease function.
- Reduced function and deletion variants are rare.

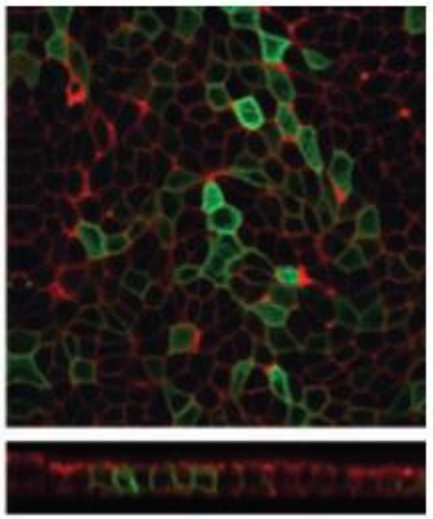


Expression of GFP-OCT in MDCK Cells

GFP-OCT1



GFP-OCT1-G465R



Shu et al. PNAS 2003.

Differential Effects of Variants on IC50's for OCT1 with Metformin as Substrate

Table 4 IC_{50} values and the IC_{50} ratios for the OCT1-reference, M420del and V408M

	Frequency (%)[a]	*Reported C_{max} (μM)*[b]	*Predicted $C_{max,\ portal}$ (μM)*[c]	*Reference IC_{50} (μM)*	*M420del IC_{50} (μM)*	*V408M IC_{50} (μM)*	*Ratio Ref/M420del*[d]	*Ratio Ref/V408M*
Verapamil	4.9	0.60	15.05	0.62 (±1.07)	0.09 (±1.87)	0.63 (±1.25)	6.84	0.99
Amitriptyline	3.2	0.72	33.0	6.99 (±1.39)	4.70 (±1.56)	4.55 (±1.19)	1.49	1.54
Glibenclamide	37.0	0.73	1.41	199 (±1.47)	85.8 (±1.97)	—	2.32	—
Pioglitazone	21.3	4.49	12.3	185 (±1.46)	178 (±2.62)	—	1.04	—
Simvastatin	20.7	0.13	9.03	89.0 (±1.25)	26.5 (±1.87)	—	3.36	—

[a]The treatment frequency of the drugs was derived from prescription data for 11 319 US patients treated with metformin, the type 2 diabetes drug.
[b]The reported total C_{max} obtained from Goodman and Gillman's and Clarke's isolation and identification of drugs.
[c]Predicted portal vein concentration as described by Ito *et al.* [23]
[d]IC_{50} ratios between OCT1-reference and M420del/V408M.
IC_{50} values were derived from concentration-dependent inhibition curves of metformin uptake.

Ahlin et al (2010). The Pharmacogenomics Journal. 1–12.

Role of OCT1 Reduced Function Variants on Metformin Plasma Concentrations

Plasma pharmacokinetics of metformin after oral administration (after second dose of 1,000 mg)

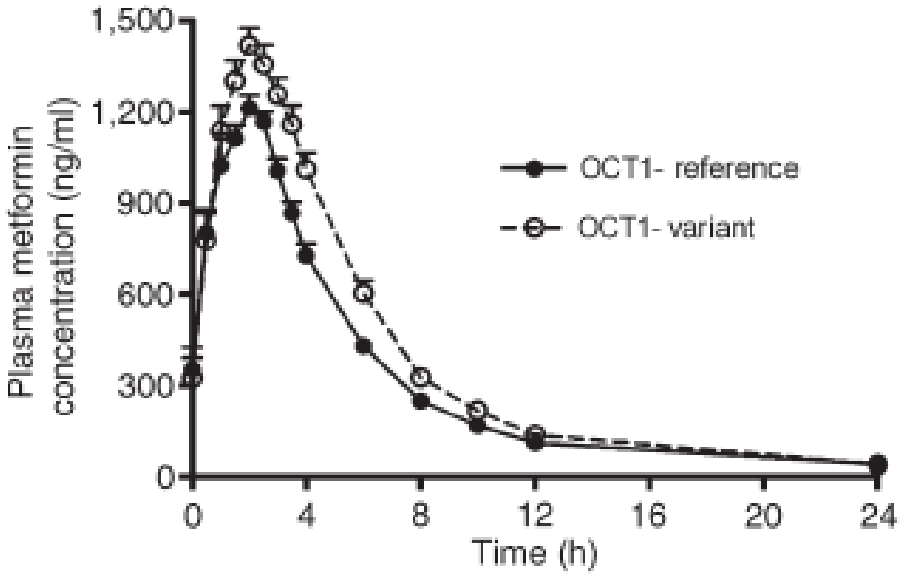


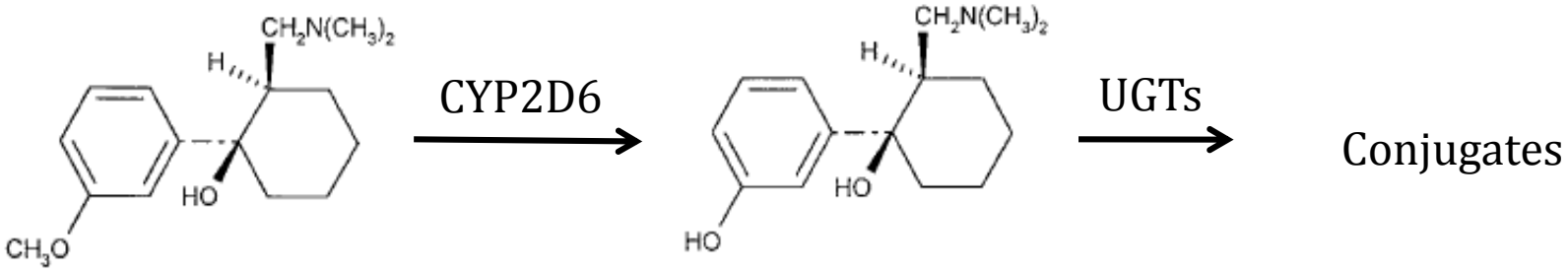
Table 3 Metformin pharmacokinetic parameters from healthy individuals who only carry OCT1-reference alleles (OCT1-reference) and those who carry an OCT1 variant allele

	OCT1-reference (n=8)[a]		OCT1-variant (n=12)[a]	
	Mean	SD	Mean	SD
$T_{1/2}$ (h)	7.3	2.3	5.8	1.2
T_{max} (h)	1.9	0.52	2.2	0.72
C_{max} (μg/ml)	1.3	0.10	1.5*	0.19
AUC_A (h μg/l)	7,700	970	9,200**	1,200
AUC_B (h μg/l)	4,500	1,200	6,900*	1,600
V/F (l)	2,600	1,800	1,200**	400
CL/F (l/h)	240	73	150*	37
CL_R (l/h)	40	16	38	21
$f_{e,u}$ (%)	19	8.8	28	16

Variants are a combination of R61C (n=4), G401S (n=3), 420del (n=1), 420del and G465R (n=3), G174S and 420del (n=1)

Shu et al. Clin Pharm Ther. 83: 2, 2008.

Tramadol: Interplay of CYP2D6 and OCT1 Genetics



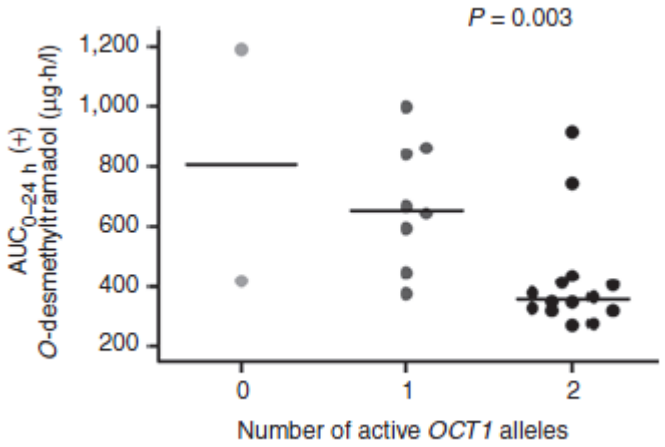
Tramadol

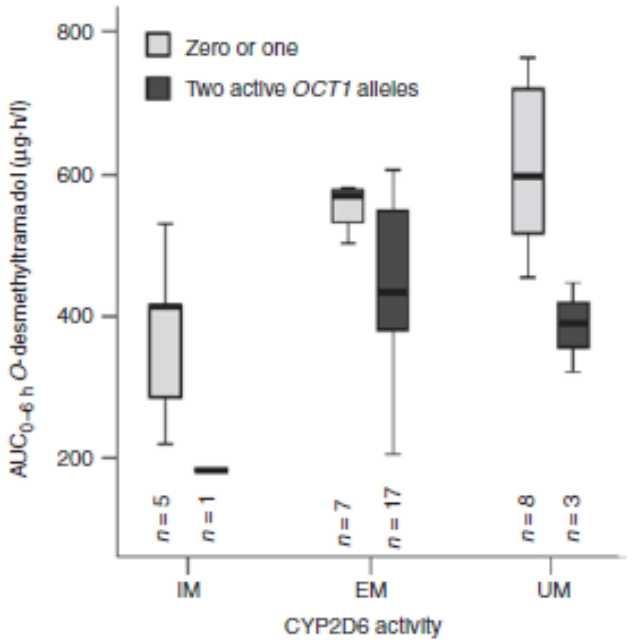
O-desmethyltramadol
(Active Metabolite)

- Tramadol is a mu-opiod receptor agonist
- Tramadol is not a substrate of OCT1
- The active desmethyl metabolite is a substrate for OCT1

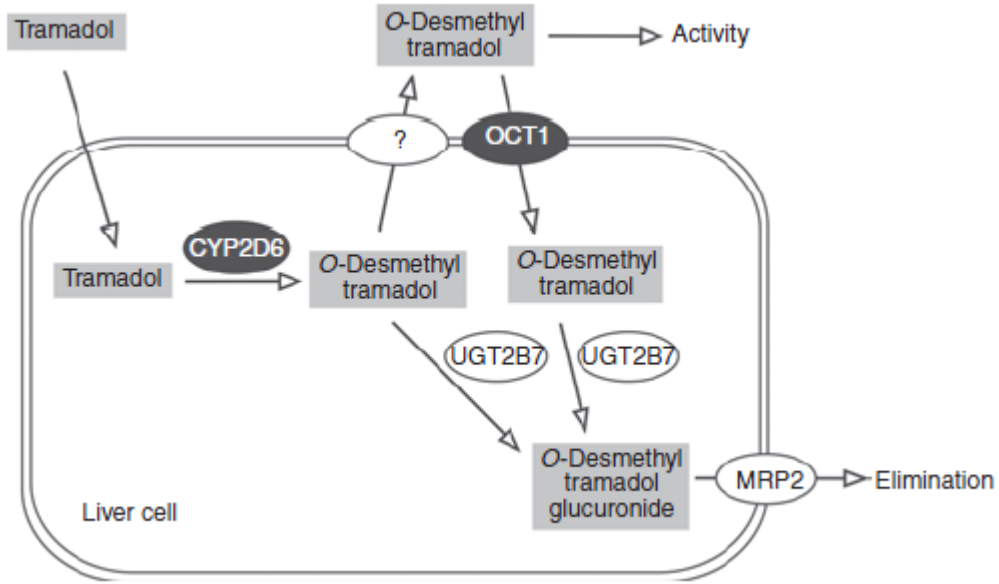
Tzvetkov et al Clin Pharm and Ther (2011) 90:1, pp 143-150.

Tramadol: Interplay of CYP2D6 and OCT1 Genetics





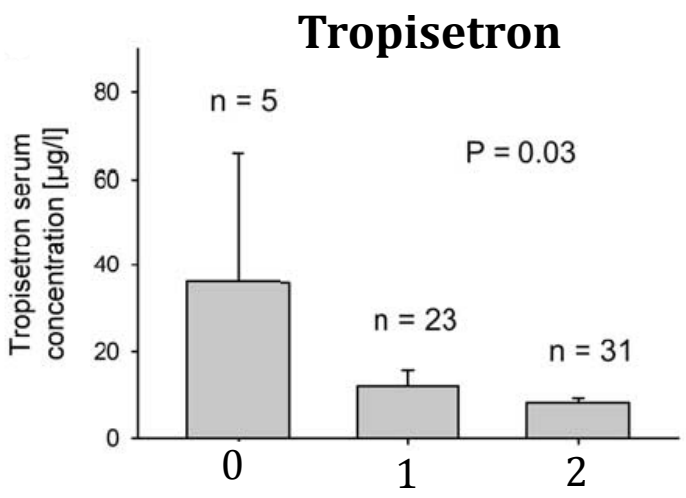
- OCT expression had no effect on parent exposure
- Number of active OCT1 alleles correlated with both exposure and pupil diameter (measure of efficacy)

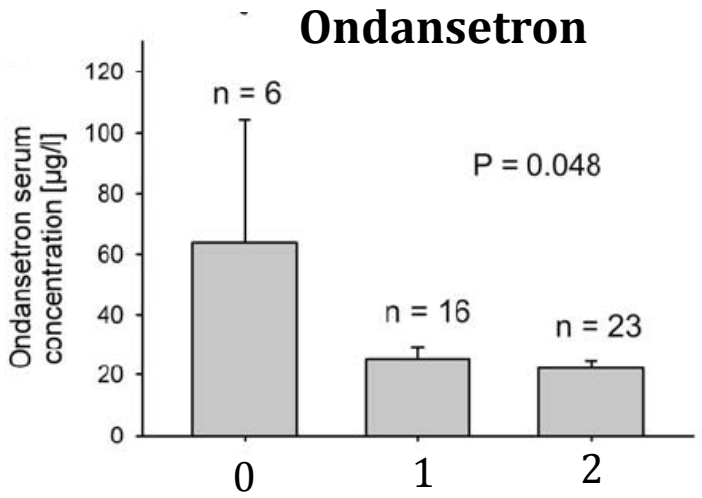


Tzvetkov et al Clin Pharm and Ther (2011) 90:1, pp 143-150.

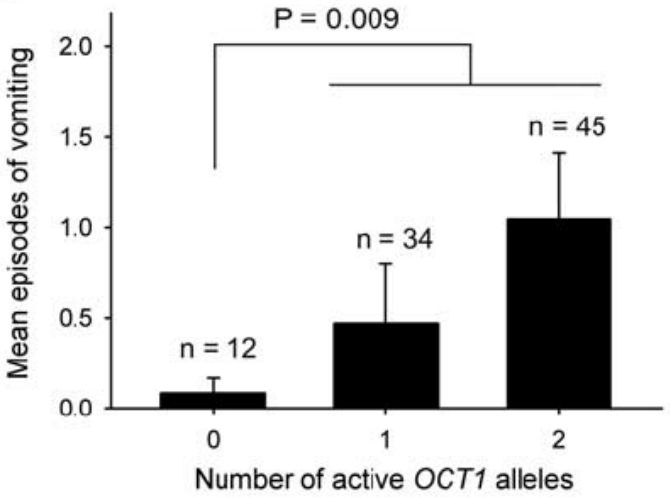
Effect of Number of OCT1 Active Alleles on 5HT3 Antagonists

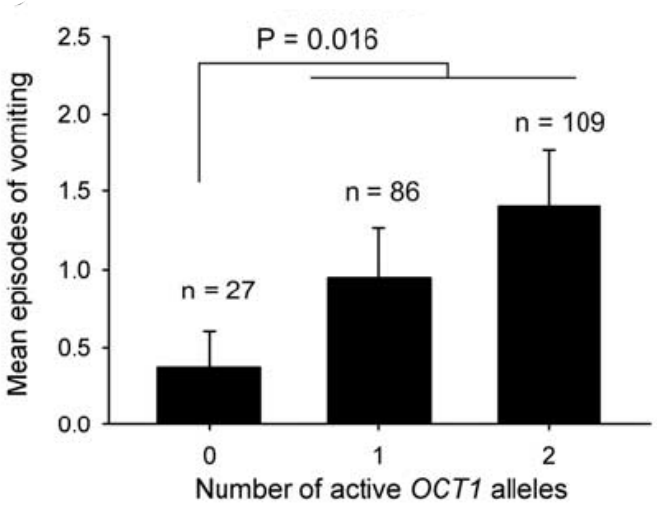
3 hr Serum Concentration





PD



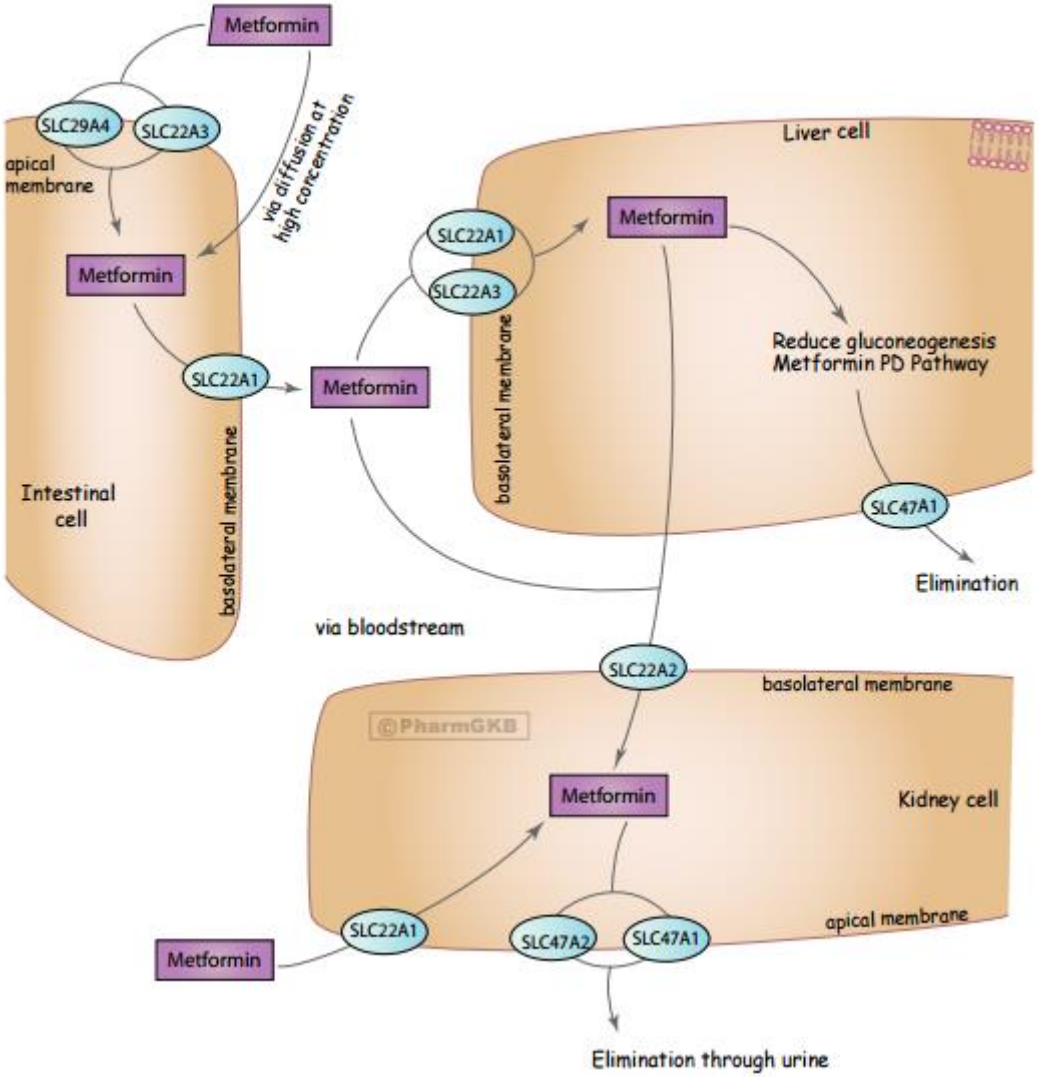


Tzvetkov et al (2010), The Pharmacogenomics Journal.1–8.

GWAS Studies for SLC22A1

- No GWAS studies linking SLC22A1 to metformin PK or PD
- Positive GWAS studies with SLC22A1
  - Metabolite transport (isobuyrylcarnitine)
  - Prostate Cancer
- Why?
  - Not important in Drug Disposition
  - SLCO22A1 variants are rare
    - Not on the platform or linked to a SNP that is?
    - GWAS population not large enough?
    - Can the rare variants be combined for the GWAS?

Metformin Pharmacokinetic Pathway



Multiple genes involved in the pharmacokinetics of metformin.

Li et al.. "Metformin pathways: pharmacokinetics and pharmacodynamics" *Pharmacogenetics and genomics* (2012).

GWAS Studies for SLC22A1

- Will this change?
  - More comprehensive arrays
  - Whole genome sequencing
  - Larger multicenter studies
  - Algorithms to combine SNPs

- Stay Tuned!

Acknowledgements

- Sook Wah Yee
- Kathy Giacomini

Clinical Annotation Levels of Evidence

Level 1A
Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.

Level 1B
Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.

Level 2A
Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

Level 2B
Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Level 3
Annotation for a variant-drug combination based on a single significant (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.

Level 4
Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.