NR1I2 VIP Summary

Written in 2010; Posted on PharmGKB 2017
Authors: Connie Oshiro

Overview

The *NR1I2* gene codes for the pregnane X receptor (PXR) - also referred to as pregnane activating receptor (PAR) and steroid xenobiotic receptor (SXR)) - a member of the nuclear receptor (NR) superfamily of transcription factors that regulates the induction of many genes. (In this summary, we will use the term *NR1I2* to refer to the gene and PXR to refer to the protein encoded by gene.) PXR is a well established regulator of CYP3A4 expression (references listed in Table 1), an enzyme involved in the metabolism of 40-50% of all drugs [Articles:16954191, 9187528] as well as many other genes. The *NR1I2* gene maps to chromosome 3q12-13 and has ten exons although only nine form the reference transcript (see [Article:16101575] Figure 3 for a representation of exons and transcripts and section below, Splice Variants for *NR1I2*). The reference transcript encodes a protein of 434 amino acids and has the domain structure characteristic of the nuclear receptor superfamily: there is an N-terminus region; a DNA binding domain (DBD), consisting of two zinc fingers (amino acids 41-107); a hinge region (amino acids 107-141) and ligand binding domain (LBD) containing the ligand binding pocket and a ligand-dependent activation function 2 (AF-2) domain (amino acids 141-434) [Articles:16101574, 14657421]. Unique to PXR is an approximately 60 amino acid sequence in the LBD that appears to allow accommodation of a wide variety of ligands; see [Articles:11408620, 15705662] and other references in Structure section below.

A simplified view of the steps in PXR gene regulation is as follows: PXR is activated by a ligand, forms a heterodimer with 9-cis retinoic acid receptor RXRalpha [Articles:9784494, 9727070, 9489701, 11706036], that binds to specific DNA response elements in the target gene [Articles:9784494, 9489701, 11706036, 12372848, 9727070], and induces gene expression. The full story of transcriptional regulation is much more complicated: PXR is constitutively inactive and is generally thought to reside in the nucleus regardless of the presence or absence of its inducers [Articles:11264453, 14709632] (although work by Squires, et al [Article:15347657] in mouse livers, show that PXR is localized in the cytoplasm and translocates to the nucleus upon ligand binding.) Ligand-free PXR is bound to corepressors NCOR1 [Article:11329060] and NCOR2 (also known as the silencing mediator of retinoid and thyroid hormone receptor; SMRT) [Articles:11329060, 16219912]; ligand binding causes dissociation of this complex [Article:16219912]. Ligand binding and PXR activation of gene transcription also involves recruitment of other proteins, in particular, the Steroid receptor coactivator 1 (SRC-1, NCOA1) [Articles:16455805, 9727070, 15650019, 17998298], but other proteins are also involved, including PGC-1 (PPRC1) [Article:16455805] and Hepatic Nuclear Factor 4 alpha

(HNF4A), another NR [Articles:16455805, 12514743, 20086032] and protein arginine methyltransferase 1 (PRMT1) another co-activator [Article:19144646].

Expression of *NR1I2* itself is regulated by other NRs, including the glucocorticoid receptor (GR, NR3C1) [Articles:10908304, 12511605, 16718615], HNF4A [Article:17827783], farnesoid X receptor (FXR), NR1H4) [Article:16682417] and FOXA2 [Article:19934400]. Expression of *NR1I2* is repressed by interleukin-6 [Article:10924340], small heterodimer partner, (SHP, NR0B2), another NR [Articles:12805410, 16455805], NF-kb p65 (RELA) [Article:16608838] and protein kinase c alpha (PRKCA) [Article:15710363]; consequently repression of PXR-mediated *CYP3A4* induction occurs.

Gene Targets

PXR, like other NRs, regulates transcription of many genes, in particular those genes that metabolize and transport drugs. The most-studied PXR gene target is *CYP3A4* (see Table 1 for list of references). Other gene targets listed in Table 1 and identified via functional assays include *ABCB1* [Articles:11329060, 20041327, 11297522], *ABCC2* [Articles:11466304, 11706036], *ABCC3* [Article:11323161], *ALAS1* [Article:12181440], *AHR* [Article:12181440], *ALDH1A1* [Article:12181440], *CYP1A1* [Articles:12181440, 19326768], *CYP1A2* [Articles:12181440, 10820139], *CYP2A6* [Articles:12181440, 19326768], *CYP2B6* [Articles:16718615, 12181440, 11560876, 18096673, 19326768, 15761118, 19520773, 9157990, 10820139], *CYP2C8* [Articles:12181440, 11329060, 9157990], *CYP2C9* [Articles:16718615, 12181440, 11560876, 18096673, 19369937, 17513950, 11466304, 9157990, 11714868, 14600250], *CYP3A5* [Articles:18725505, 15252010], *GSTA2* [Article:12181440], *POR* [Article:12181440], *SULT1A1* [Article:12181440]. Additionally, PXR DNA binding elements have been found in other genes, via in silico analysis, then verified experimentally; these genes are *UGT1A6* [Article:15316010], *UGT1A3* [Articles:15316010, 15077869], *UGT1A4* [Article:15077869], *CASP10* [Article:15316010]. Microarray experiments [Article:11714868] with rifampin identified other genes presumed to be PXR targets: *CYP2A6* , *CYP3A7* , *CYP4F3* , *CYP1B1* , *GSTA1* , *GSTA3* , *SLC22A5* , *TTR* , *MAOB* , *FMO4* , *FMO5* , *GSTA2* , *GSTM1* , *GSTP1*. There are conflicting data about *UGT1A1* [Articles:15077869, 16718615, 12181440, 15316010], *CYP1A2* [Articles:11714868, 12181440], *CYP2E1* [Articles:11714868, 12181440].

In addition to transactivation of genes, PXR is also involved with inhibition/repression: Rifampin-liganded PXR suppresses *SULT2A1* expression by interfering with HNF4A activity [Article:17687072]; PXR inhibits *CYP7A1* gene transcription [Article:15331348]; activation of PXR by rifampin and other agonists inhibits NF-kB signaling [Article:16841097]. PXR is also involved in regulation of *CYP4F12* that does not involve rifampin [Article:19129222].

Drugs/Substrates

Originally an orphan receptor, PXR was found first to respond to endogenous pregnanes, which gave rise to its name, but was subsequently shown to be activated by other endogenous ligands, as well as a wide variety of xenobiotics, including clinical drugs [Articles:9770465, 9784494, 9489701, 9727070].

The list of reported PXR agonists - and inducers of gene transcription - is enormous; it has been the subject of many in vitro studies because of the need to identify potential drug-drug interactions resulting from induction of metabolizing enzymes. However, an accurate compilation of hPXR ligands is difficult for several reasons: (1) In testing for PXR ligands, the increase in *CYP3A4* (or other target gene) mRNA is often measured. But, as is the case for *CYP3A4* , gene expression is regulated by several different NRs, besides PXR, such as the Constitutive Androstane Receptor (CAR, NR1I3), GR, HNF4A, FXR and the Vitamin D Receptor (VDR)[Article:17442683]. Therefore, the actual NR responsible for the induction may not always be certain; i.e., the ligand may be binding to a NR other than PXR that is responsible for the induction and increase in mRNA [Article:17442683]. (2) A molecule may have an effect via an indirect interaction with PXR. Some ligands bind not only to PXR, but also to other NRs that are involved with PXR regulation. For example, dexamethasone has been reported as a ligand for PXR [Articles:9727070, 12065438], but it is also a ligand for GR [Article:12151000] and GR is associated with regulation of NR1I2 [Articles:10908304, 12511605, 16718615]. (3) Human, rabbit, and rodent PXRs display marked differences in response to different xenobiotics [Articles:10935643, 10628745, 11336976, 9727070], so care must be taken to identify only hPXR ligands. For example, hPXR responds to rifampin, but rat PXR does not; in contrast, rodent PXR responds to pregnenolone-16a-carbonitrile (PCN), but hPXR does not [Articles:10935643, 10628745, 11336976]. This difference is related to the difference in the amino acid composition of the LBD: While the DBD is very similar across species, the LBDs of the PXRs are very different [Article:12372848]; the human and rat PXR share only 76% amino acid identity in their LBD [Article:12372848].

For the reason described above, we therefore list in Table 1 below, those ligands where the researcher his/herself declared them to be "hPXR ligands/activators". We also report conflicting data, where available, that might dispute this. Note that the classic PXR agonist is rifampin.

All agonists listed in Table 1 were identified via functional cell-based assays. Where there is also in vivo clinical data for a ligand, such data is included; this may be consistent or inconsistent with the induction of the target gene. The vast majority of the drugs listed do not have such clinical data. (The exceptions are rifampin, ifosfamide, st. john's wort (hyperforin), efavirenz, carbamazepine and phenytoin, where there are several in vivo human studies consistent with the increased CYP3A4 metabolism; although, for the latter 3 drugs, there is data to suggest that these are hCAR ligands, rather than hPXR ligands [Articles:17041008, 15123723, 17041008]). While it might be tempting to assume that an in

vitro PXR agonist is actually an in vivo inducer of a gene such CYP3A4, such extrapolation can be dangerous. There are other, competing ligand-protein interactions in the body so the net systemic effect of a PXR ligand may not be clear cut. The competing interactions: (1) The intracellular concentration of the agonist is mediated by a transporter that controls its efflux or influx, when it is also a substrate for the transporter; Schuetz et al. [Article:8633005] demonstrated that ABCB1 modulates the extent of CYP3A induction through regulating intracellular concentration of rifampin. (2) As described by Tang, et al, [Article:15673596] a PXR ligand can be metabolized at different rates, depending upon an individual's metabolic phenotype; the induction in such individuals would thus be different. For example, omeprazole [Articles:16413245, 16093273] and mephenytoin [Articles:19661214, 8110777] are metabolized by CYP2C19; genetic polymorphisms in this gene results in individuals being "extensive metabolizers" (EM), or "poor metabolizers" (PM) of these drugs - the individual's metabolic phenotype [Article:12222994]. While omeprazole has been shown, in vitro, to be an inducer of CYP1A [Articles:8169844, 11336975], in in vivo studies, therapeutic doses of omeprazole induces CYP1A2 metabolism of S-mephenytoin in PM, but have only minor effects in EM [Article:1505152]. On the other hand, Zhou et al. [Article:2223426] found that induction by rifampin of the metabolism of mephenytoin was only observed with EMs, but not with PMs. (3) The PXR ligands themselves interact with other proteins, other than PXR, with the result that these other interaction dominates. A good example of this is ketoconazole: it has been reported as an activator of PXR [Article:17998298], but is also a strong inhibitor of CYP3A4 [Articles:19702536, 16954191, 10709776]; as a result, this drug is applied for therapeutic purposes to effectively increase the dosage of another drug, such as cyclosporine [Article:10709776]. (Ketoconazole is not listed in the table because of its clinically large inhibitory effect on *CYP3A4*).

PXR antagonists are few; they include A-792611 [Article:18096673], sulforaphane (molecule present in broccoli) [Articles:18725505, 17028159], ecteinascidin-743 [Article:11329060].

Phenotypes/Diseases

Besides regulating many xenobiotic metabolizing enzymes and transporters, PXR also plays a role in cholesterol homeostasis [Article:11607932] and bile acid metabolism [Articles:11248085, 11509573]. Its involvement has been implicated in resistance to some cancers [Articles:17636047, 17279585, 17974979, 18765524] as well as, Inflammatory Bowel Diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) [Articles:16472590, 17828778].

Structural Data

The crystal structure of the LBD of hPXR was first solved in 2001 [Article:11408620]; as of May 1010, there are 9 crystal structures of the LBD of hPXR in the Protein Data Bank [Article:10592235]. We briefly list the structures here: 1ILG (apo structure, resolution=2.52

A) [Article:11408620]; 1ILH (bound to SR12813, resolution=2.76 A) [Article:11408620]; 1M13 (bound to hyperforin, resolution=2.15 A) [Article:12578355]; 1NRL (bound to SR12813 and peptide from SRC-1 co-activator, resolution=2.0 A) [Article:12909012]; 1SKX (bound to rifampin, resolution=2.8 A) [Article:15705662]; 2O9I (bound to T0901317 and peptide from SRC-1, resolution=2.8 A) [Article:17215127]; 2QNV (bound to colupulone , resolution=2.8 A) not in PubMed; 3CTB (apo structure, tethered to peptide from SRC-1, resolution=2.0 A) [Article:18456871]; 3HVL (bound to SR12813; tethered to peptide from SRC-1 co-activator, resolution=2.1 A) [Article:18456871].

Overall, the crystal structures show how a diverse group of ligands can be bound to the same protein. The binding cavity is substantially larger than that of other NRs [Article:11408620]; in 1ILH, SR12813 is found in 3 distinct, different binding modes [Article:11408620]. In the structure of rifampin and hyperforin, several regions near the protein binding pocket are disordered, suggesting that there is a large degree of protein flexibility that is used to effectively enlarge to ligand binding pocket [Articles:15705662, 12578355].

Splice Variants

There are many isoforms of PXR due to alternative splicing [Articles:10473093, 15364541, 12413960, 15364541, 12413960] or defective splicing [Article:12413960]. The reference transcript (PXR.1) encoded by 9 exons contains 434 amino acids [Article:11668216]; alternatively spliced forms (PXR.2, PXR.3) arise from a deletion of 37 or 41 amino acids from exon 5 [Articles:10473093, 15364541]; the deletion of 238 bp from 5' end of exon 5 leads to a truncated amino acid sequence [Article:15364541]. There are several other splice forms, some of which encoded all 10 exons [Article:12413960]. (For a list of alternative splice forms, see UniProt AccessionID=O75469)

Pharmacogenomics

As of May 2010, there are 256 human SNPs deposited in dbSNP build 131 [Article:11125122]. Approximately half of these variants were studied using cell-based or tissue-based functional assays [Articles:11602521, 11668216, 12663745, 14586772, 14709632, 15618712, 15864135, 16568343, 16580901, 17050801, 17876342, 17924830, 17925385, 18056193, 18220558, 18294295, 18800312, 18981011, 19173680, 19855097, 19940802, 20082578, 20107201]. Very few variants have been characterized functionally (and clinically) by more than one study. The interpretation and clinical impact of these cell-based and tissue-based studies is difficult for several reasons: (1) Many of the variants were associated with altered CYP3A4 basal metabolism, but because PXR is not constitutively active and the endogenous ligand was not identified, the actual mechanism of altered basal CYP3A4 metabolism is not clear. (2) *CYP3A4* expression in liver samples is significantly higher in females than in males [Article:19934400] independent of *NR1I2* genotype; there can be a need to segregate fold-

induction based upon sex [Article:17925385]; which is not always done. (3) Variants with a lower CYP3A4 basal metabolism often show a greater drug-induced-fold induction [Article:17925385], so the net clinical overall effect with respect to potential drug-drug interactions can be difficult to predict. For these reasons, for this summary, we briefly describe a handful of the functional-based studies, organized by the studies themselves, and concentrate on those studies where larger numbers of variants were studied. We separately describe clinical studies, organized in the same manner. The one variant that has been examined by several different groups is described last and separately. Overall, the contribution of genetic variants of *NR1I2* to the large variability in human drug response is unclear.

Zhang, et al, [Article:11668216], in vitro studies (and in vivo studies, described below), identified 38 SNPs in *NR1I2* several (but not all) were correlated with increased fold-induction of *CYP3A4*, and others with lower levels of *ABCB1* induction and one variant rs12721608 (R122Q) had significantly decreased affinity for the DNA binding sequence. Hustert, et al [Article:11602521] studied 6 genotypic variants and splice variants and found that variant D163G rs72551374 and splice variant PXR-2 (lacking 37 amino acids in the LBD) did not show any basal activity; however, the allelic frequencies of these variants are a minuscule fraction of the populations studied. Lambda, et al [Article:17925385] identified 89 SNPs in the promoter region and intron 1, many in linkage disequilibrium; 5 variants were consistently associated with altered basal or inducible metabolism. Finally, Koyano et al [Article:14709632] found 4 variants, 3 of which had reduced transactivation of CYP3A4; one of these, rs72551371 (R98C), had a dramatic reduction in DNA binding.

Fewer *NR1I2* variants have been studied clinically; many of these studies are of small size and a few do not show a correlation between genotype and pharmacokinetics. Zhang, et al, [Article:11668216] in the study of 14 patients, found that those carrying -25385C>T (rs3814055) and -24113T>A (GenBank Accession AF364606) had a 2 fold higher metabolism of erythromycin, using the erythromycin breath test (ERMBT), following rifampin treatment; biopsies of intestinal samples of 10 patients found higher induction of *CYP3A4* following rifampin treatment, for several other patients. He, et al [Article:17050801] in a study of 26 healthy volunteers, identified 3 linked *NR1I2* variants (g.252A>G (rs1464603), g.275A>G (rs1464602), and g.4760G>A ; AF364606) significantly ($P < .05$) associated with oral midazolam clearance in the African American subpopulation ($n = 14$) but not in European Americans ($n = 9$). Fanta, et al [Article:20107201], in a study of 91 kidney transplant patients, found that the patients of the (g.-25385C (rs3814055), g.-24381A (rs1523127), g.-205_-200GAGAAG (rs72554003), g.7635G (rs6785049), g.8055C) haplotype had about one-tenth lower bioavailability, per allele, than did noncarriers of this haplotype ($P = .04$). Wang,et al, [Article:19173680] in a study of 10 healthy Han volunteers, found that ingestion of St. John's wort greatly increased nifedipine metabolism of 2 haplotypes. Sandanaraj et al [Article:18981011] studied doxorubicin clearance in 100 Malay, 100 Chinese and 100 Indian breast cancer patients and found that those patients harboring the (rs3814058 and rs2276707) haplotype had significantly lower clearance of doxorubicin compared to patients not carrying this haplotype ($P = 0.022$). While these

clinical studies found an association between phenotype and genotype, others did not. Zhang, et al, [Article:11668216] found that the one person heterozygous for rs12721608 (R122Q) - the variant with significantly decreased DNA binding - had normal cyp3a4 metabolism. And, studies of 95 and 101 breast cancer patients did not find any association between docetaxel clearance and NR1I2 genotype [Articles:17876342, 18056193].

All results remain to be validated.

One variant (rs3814055) (-25385 C>T, AF364606) has been studied by several researchers, for both disease risk and pharmacogenomics impact, with conflicting results. See Variant Summary for more details.

Table 1. Agonists/ligands of hPXR and target genes. Column 1 lists drugs and molecules identified by functional assays (FA) to be ligands of PXR, organized by class; column 2 lists the target genes that were up-regulated by the drug-bound PXR in the FA (in the case no specific target gene was mentioned, the term PXR activation is used); Column 3 lists references for the FA; Column 4 lists references related to clinical data in support of, or in conflict with, the FA data. In the event there is conflicting data, drug or reference is in italics

DRUGS	**TARGET GENES**	**REFERENCES FA / *in vivo***	**REFERENCES (clinical)**
ANTIBACTERIALS,BETA-LACTAM ANTIBACTERIALS, PENICILLINS			
amoxicillin	*CYP3A4*	[Article:18505790]	
ampicillin	*CYP3A4*	[Article:18505790]	
dicloxacillin	*CYP3A4*	[Article:18505790]	
nafcillin	*CYP3A4*	[Article:18505790]	
penicillin V	*CYP3A4*	[Article:18505790]	
ANTIBACTERIAL CEPHALOSPORINS			
cefaclor	*CYP3A4*	[Article:18505790]	
cefadroxil	*CYP3A4*	[Article:18505790]	
cefuroxime	*CYP3A4*	[Article:18505790]	
cephalexin	*CYP3A4*	[Article:18505790]	
cefradine	*CYP3A4*	[Article:18505790]	
ANTIBACTERIAL LINCOSAMIDE			
clindamycin	CYP3A4	[Article:18505790]	

ANTIBACTERIAL SULFONAMIDES			
sulfamethazine	*CYP3A4*	[Articles:12065438, 18505790]	[Articles:3082414, 6130373]
sulfisoxazole	*CYP3A4*	[Article:18505790]	
ANTIBACTERIAL, MACROLIDES			
erythromycin	*CYP3A4*	[Article:18505790]	
troleandomycin	*CYP3A4*	[Article:18505790]	
troleandomycin	*CYP3A4*	[Article:18505790]	
ANTIBIOTIC (FOR TREATMENT OF TUBERCULOSIS)			
rifabutin	*PXR* activation	[Articles:16724927, 18647599]	
rifampin	*CYP3A4, ABCB1, ABCC2, ABCC3, ALAS1, AHR, ALDH1A1, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2E1, GSTA2, POR, SULT1A1, UGT1A1*	[Articles:10628745, 9770465, 9727070, 17998298, 16724927, 12065438, 18505790, 10748001, 11329060, 11297522, 19520773, 11706036, 11323161]	[Articles:11503007, 9157990, 7751591, 12426514, 17381666, 16176119, 6487483, 19417618, 9871429, 9024169, 16580903, 11180018, 11240975, 9542475, 10223773, 19369937, 2223426]
rifapentine	*PXR* activation	[Article:16724927]	
ANTIBIOTIC/ANTIBACTERIAL TETRACYCLINE			
demeclocycline	*CYP3A4*	[Article:18505790]	
doxycycline	*CYP3A4*	[Article:18505790]	
minocycline	*CYP3A4*	[Article:18505790]	
tetracycline	*CYP3A4*	[Article:18505790]	
ANTICONVULSANT			
topiramate	*CYP3A4*	[Article:18505790]	[Article:9070594]
ANTIEPILEPTICS			
carbamazepine	*CYP3A4*	[Articles:17112801, 12065438]	[Articles:2126946, 14691614, 8598183, 10613614]

carbamazepine possible hCAR ligand		[Article:17041008]	
phenobarbital	*ALDH1A1, CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP3A4 & GSTA2, ABCB1, SULT1A1, ALAS1, AHR, POR*	[Articles:12181440, 9727070, 10628745, 12065438, 12642468, 14600250, 15252010, 16724927, 18647599]	[Articles:7408397, 33926674, 12242602]
phenytoin	*CYP3A4*	[Articles:12065438, 16724927, 18647599]	[Articles:7408397, 21269466, 8598183, 19855097, 4049465, 9485556, 10613614]
phenytoin hCAR ligand		[Article:15123723]	
valproic acid	*CYP3A4*	[Article:17392393]	[Article:9070594] [Article:9156377]
ANTIFUNGAL			
griseofulvin	*CYP3A4*	[Article:18505790]	
terbinafine	*CYP3A4*	[Article:18647599]	[Article:8869684]
ANTIFUNGAL/ANTIMYCOTIC			
clotrimazole	*CYP3A4, CYP3A5*	[Articles:10748001, 10628745, 9770465, 9727070, 15252010, 17998298]	
econazole	*CYP3A4*	[Article:17998298]	
miconazole	*CYP3A4*	[Article:17998298]	
oxiconazole	*CYP3A4*	[Article:17998298]	
ANTIGOUT PREPARATIONS			
sulfinpyrazone	*CYP3A4*	[Articles:12065438, 16724927, 18647599]	[Article:11124491]
ANTIHYPERTENSIVES			
bosentan	PXR activation	[Articles:12206849, 18669588]	[Articles:12047483, 12603176]
reserpine	*CYP3A4*	[Article:17041008]	
ANTIINFLAMMATORY/ANTIRHEUMATIC			

phenylbutazone	PXR activation	[Article:16724927]	
ANTIMALARIALS			
artemisinin	*CYP2B6, CYP3A4, ABCB1*		[Article:15761118]
artemisinin hCAR ligand			[Articles:16919048, 18332078]
ANTINEOPLASTIC ALKYLATING AGENTS			
cyclophosphamide	*CYP2B6, CYP2C8, CYP2C9, CYP3A4, ABCB1*	[Articles:9157990, 17041008, 20041327]	[Article:3058371]
ifosfamide	*CYP2B6, CYP2C8, CYP2C9, CYP3A4, ABCB1*	[Articles:9157990, 20041327]	[Articles:7720176, 17106751, 11503007, 8161344] [Article:17464949]
ANTINEOPLASTIC PLATINUM COMPOUND			
cisplatin	*CYP3A4, ABCB1*	[Article:15650019]	
ANTINEOPLASTIC TAXANE			
docetaxel	*ABCB1*	[Article:20041327]	
docetaxel no PXR activation		[Articles:11329060, 15650019]	
paclitaxel	*ABCB1,CYP2C8, CYP3A4*	[Articles:11329060, 15650019, 20041327]	
ANTINEOPLASTIC, OTHER			
bexarotene	*CYP3A*	[Article:10628745]	
ANTINEOPLASTIC, VINCA ALKALOIDS			
vinblastine	*ABCB1*	[Article:20041327]	
ANTIPARASITIC			
permethrin	*CYP3A4, CYP1A1, CYP3A5, CYP2B6, CYP2A6*	[Article:19326768]	
ANTIPSYCHOTIC			
chlorpromazine	*CYP3A4*	[Article:17041008]	

BILE ACID			
lithocholic acid	PXR activation	[Article:11248085] (rat)	
BLOOD GLUCOSE LOWERING SULFONAMIDE UREA			
glibenclamide	PXR activation	[Article:12206849]	
BLOOD GLUCOSE LOWERING THIAZOLIDINEDIONE			
troglitazone	*CYP3A4*	[Articles:10628745, 16724927, 17041008]	[Articles:10197300, 9753209]
troglitazone	CYP3A4	[Articles:10628745, 16724927, 17041008]	[Articles:10197300, 9753209]
rosiglitazone	*CYP3A4*	[Article:12642470]	
pioglitazone	*CYP3A4*	[Article:12642470]	[Article:12463723]
CALCIUM CHANNEL BLOCKERS			
isradipine	*CYP3A4, CYP2B6 and CYP2C9*	[Article:11560876]	
nicardipine	*CYP3A4, CYP2B6, and CYP2C9*	[Articles:11560876, 17041008]	
nifedipine	*CYP3A4, CYP2B6 and CYP2C9*	[Articles:11560876, 9784494, 9770465]	
HMG COA REDUCTASE INHIBITORS			
atorvastatin	*CYP2C9*	[Article:17513950]	
fluvastatin	*CYP2C9*	[Article:17513950]	
lovastatin	*CYP3A4*	[Articles:9727070, 17513950, 17041008]	
mevastatin	*CYP3A4*	[Articles:12235278, 17041008]	
simvastatin	*CYP3A4*	[Article:17041008]	
HYDRAZIDES (FOR TREATMENT OF TUBERCULOSIS)			

isoniazid	*CYP2E1*	[Article:12642468]	
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
efavirenz	*CYP3A4*	[Article:18096673]	[Articles:1251999, 12189360, 17998298, 19620877, 17041008]
efavirenz possible hCAR ligand		[Article:17041008]	
nevirapine	*CYP3A4*	[Article:17041008]	[Article:10421616]
nevirapine possible hCAR ligand		[Article:17041008]	
NUTRACEUTICAL			
Ginkgo biloba	*ABCB1, CYP3A4, CYP3A5*	[Article:18725505]	
guggulipid	PXR activation	[Article:18768384]	
st john's wort (hyperforin)	*CYP3A4, CYP2C8, ABCB1, ABCC2*	[Articles:10852961, 11329060, 16724927, 11329060, 10852961, 11706036]	[Articles:11673747, 14663455, 19924124, 15537555, 10683008]
OPIOD			
methadone	*CYP2B6, CYP3A4, UGT1A1*	[Article:19520773]	
OTHER PLANT COMPONENT OR EXTRACT			
coumestrol	PXR activation	[Article:9784494]	
coumestrol antagonist?		[Article:18096694]	
forskolin	*CYP3A*	[PMIDs:16724927, 15459237)	
colupulone (active ingredient of hops)	PXR activation xtl structure	[Article:18768384]	
PROTEASE INHIBITORS			
ritonavir	*CYP3A4, CYP2B6, CYP2C9, ABCC2*	[Articles:18096673, 16724927, 12065438, 11466304, 18647599]	[Article:9723818] [Article:10801241]
saquinavir	PXR activation	[Article:11466304]	

PROTON PUMP INHIBITORS			
lansoprazole	*CYP3A, CYP1A*	[Article:8169844]	
omeprazole	*CYP3A, CYP3A4, CYP3A5, CYP1A*	[Articles:11336975, 8169844, 12235278, 15252010, 17041008, 18647599]	[Article:1505152]
PSYCHOSTIMULANTS			
modafinil	*CYP1A2, CYP2B6, CYP3A4/5*	[Article:10820139]	[Article:11823757]
STEROID			
pregnenolone	*CYP3A4*	[Articles:9784494, 9727070]	
STEROID (CORTICOSTEROID)			
budesonide	*CYP3A4*	[Article:19138736]	
corticosterone	*CYP3A*	[Articles:10628745, 9784494]	
hydrocortisone (cortisol)	*CYP3A4*	[Article:9770465]	
dexamethasone	*CYP3A4*	[Articles:9727070, 12065438]	[Articles:3058371, 11061575]
STEROID (HORMONE)			
17a-Hydroxyprogesterone	*CYP3A*	[Article:10628745]	
dehydroepiandrosterone (DHEA)	*PXR* activation	[Article:9784494]	
estradiol	*CYP3A, CYP3A4*	[Articles:9770465, 9784494, 10628745]	
progesterone	*CYP3A4*	[Articles:9770465, 9727070]	
diethylstilbestrol (DES)	*PXR* activation	[Article:9784494]	
STEROID (HORMONE METABOLITE)			
dihydrotestosterone	*CYP3A*	[Article:10628745]	
STEROID (PREGNANE-RELATED)			
5 beta-Pregnane-3,20-dione	*CYP3A4*	[Articles:10748001, 10628745, 9770465, 9727070]	

STEROID (ANTIANDROGEN)			
cyproterone	*CYP3A4*	[Article:9727070]	
flutamide	*ABCB1*	[Article:20041327]	
spironolactone	*CYP3A4*	[Article:9727070]	
STEROID (ANTIESTROGEN)			
tamoxifen	*CYP3A4, ABCB1*	[Articles:18299335, 20041327]	[Articles:11487258, 10499602]
STEROID (ANTIESTROGEN METABOLITE)			
4-hydroxytamoxifen	*CYP3A4*	[Article:18299335]	
STEROID (ANTIPROGESTOGEN)			
mifepristone (RU486)	*CYP3A4 , CYP3A5*	[Articles:12235278, 15252010, 16724927, 10748001, 10628745, 9770465, 9727070]	
TEST FOR PITUITARY FUNCTION			
metyrapone	*CYP3A4*	[Articles:10611146, 17041008, 10917608]	
OTHER			
SR12813	*CYP3A4, ABCC2*	[Articles:11466304, 10628745, 10748001, 11329060, 16724927]	

Alphabetical list of abbreviations (that are not gene symbols)

CD=Crohn's disease, DBD=DNA binding domain, EM=extensive metabolizers, ERMBT=erythromycin breath test, FA=functional assay, FXR=farnesoid X receptor, GR=glucocorticoid receptor, IBD=Inflammatory Bowel Diseases, LBD=ligand binding domain, NR=nuclear receptor, PAR=pregnane activating receptor, PM=poor metabolizers, PXR=pregnane X receptor, RXRa=9-cis retinoic acid receptor, SMRT=silencing mediator of retinoid and thyroid hormone receptor, SNP=single nucleotide polymorphism, SRC-1=Steroid receptor coactivator 1, SXR=steroid xenobiotic receptor, UC=ulcerative colitis.

rs3814055

One variant, rs3814055 (-25385 C>T, AF364606) has been studied by several researchers, for both disease risk and pharmacogenomics impact, with conflicting results. The C allele has been associated with Inflammatory Bowel Diseases (IBD) [Article:16472590] in a European population; the T allele, as part of the haplotype rs3814055 T; rs6784598 C; rs2276707 C was associated with a risk for ulcerative colitis (UC) (but not rs3814055 T in alone) in a Spanish population [Article:17828778]. Other studies did not find any association between this NR1I2 polymorphism (in linkage disequilibrium with rs1523127) and IBD, Crohn's disease (CD), UC [Articles:17047126, 18381611]. Lambda et al [Article:17925385] found the T allele had lower NR1I2 expression in male livers (that would be associated with lower CYP3A4 induction and metabolism). Consistent with this finding, in a study of 91 kidney transplants, the -25385 C allele was part of a haplotype where the bioavailability of cyclosporine was significantly less than other haplotypes (indicating that there was increased metabolism of cyclosporine) [Article:20107201]. On the other hand, Zhang [Article:11668216] found for the -25385 T allele (and -24113 A allele) a 2-fold higher ERMBT after rifampin treatment (indicating greater metabolism).

All results remain to be validated.

Appendix Genomic Variant & GenBank ID: 45005C>T on AF364606 . mRNA Variant & GenBank ID: 705C>T on NM_003889.3 . GoldenPath Position: chr3:120982725 .

rs12721608

Zhang, et al, [Article:11668216], in vitro studies identified 38 SNPs in NR1I2 several (but not all) were correlated with increased fold-induction of CYP3A4, and others with lower levels of ABCB1 induction. One variant rs12721608 (R122Q) had significantly decreased affinity for the DNA binding sequence. Zhang, et al, [Article:11668216] found that the one person heterozygous for rs12721608 (R122Q) had normal *cyp3a4* metabolism.

See NAT2 VIP summary for more information.