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The Pharmacogene Variation (PharmVar) Consortium: update

PharmVar
Pharmacogene Variation Consortium

The Pharmacogene Variation (PharmVar) Consortium is a central repository for pharmacogene (PGx) variation that focuses on haplotype structure and allelic variation.

The information in this resource facilitates the interpretation of pharmacogenetic test results to guide precision medicine.

PharmVar

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PharmVar API Services are now available for third party use. For more information, visit the API Servic

What's New 1

Follow us on Twitter

PharmVar Publications

Articles published by PharmVar are available on the resources page.

Original content from the cypalleles.ki.se site is available through the archiv

What's new on PharmVar

NEW December 21, 2021

Database Updated to Version 5.1.5

Changes to Gene CYP2C9 Include:

1. Added new alleles *72,*73,*74, and *75.

IMPROVEMENT November 17, 2021

Database Updated to Version 5.1.4

Changes include:

1. CYP3A5: Updated core variant definitions for multiple alleles to show SNP's that are variant on build GRCh37 only. For more information see the Read Me Document for CYP3A5

2. CYP3A5: Updated *9 variant to indicate functional change.

3. CYP2D6: Updated core variant definitions for multiple alleles to show SNP's that are variant on build GRCh37 only. For more information see the Read Me Document for CYP2D6

4. CYP2D6: Corrected GRCh37 translation for variant rs28735595.

Publications

2017

The Pharmacogene Variation (PharmVar) Consortium: Incorporation of the Human Cytochrome P450 (*CYP*) Allele Nomenclature Database

Andrea Gaedigk[1], Magnus Ingelman-Sundberg[2], Neil A. Miller[3], J. Steven Leeder[1], Michelle Whirl-Carrillo[4], Teri E. Klein[4] and the PharmVar Steering Committee

2018

The Evolution of PharmVar

Andrea Gaedigk[1,2], Katrin Sangkuhl[3], Michelle Whirl-Carrillo[3], Greyson P. Twist[2,4], Teri E. Klein[3] and Neil A. Miller[2,4] on behalf of the PharmVar Steering Committee

PharmVar and the Landscape of Pharmacogenetic Resources

Andrea Gaedigk[1,*], Michelle Whirl-Carrillo[2], Victoria M. Pratt[3], Neil A. Miller[4] and Teri E. Klein[2]

2019

Pharmacogene Variation Consortium: A Global Resource and Repository for Pharmacogene Variation

Andrea Gaedigk[1,2,*], Scott T. Casey[3], Michelle Whirl-Carrillo[4], Neil A. Miller[3] and Teri E. Klein[4,5]

2021

GeneFocus Reviews

PharmVar GeneFocus: *CYP2D6*

2019

Charity Nofziger[1,†], Amy J. Turner[2,3,†], Katrin Sangkuhl[4], Michelle Whirl-Carrillo[4], José A.G. Agúndez[5,6], John L. Black[7], Henry M. Dunnenberger[8], Gualberto Ruano[9], Martin A. Kennedy[10], Michael S. Phillips[11], Houda Hachad[12], Teri E. Klein[4] and Andrea Gaedigk[13,14,*]

PharmVar GeneFocus: *CYP2C19*

2020

Mariana R. Botton[1], Michelle Whirl-Carrillo[2], Andria L. Del Tredici[3], Katrin Sangkuhl[2], Larisa H. Cavallari[4], José A. G. Agúndez[5], Jorge Duconge[6], Ming Ta Michael Lee[7], Erica L. Woodahl[8], Karla Claudio-Campos[4], Ann K. Daly[9], Teri E. Klein[2], Victoria M. Pratt[10], Stuart A. Scott[11,12,†] and Andrea Gaedigk[13,*,†]

PharmVar GeneFocus: *CYP2C9*

2021

Katrin Sangkuhl[1], Karla Claudio-Campos[2], Larisa H. Cavallari[3], Jose A.G. Agundez[4], Michelle Whirl-Carrillo[1], Jorge Duconge[5], Andria L. Del Tredici[6], Mia Wadelius[7], Mariana Rodrigues Botton[8], Erica L. Woodahl[9], Stuart A. Scott[10,11], Teri E. Klein[1], Victoria M. Pratt[12], Ann K. Daly[13] and Andrea Gaedigk[14,15,*]

PharmVar GeneFocus: *CYP2B6*

2021

Zeruesenay Desta[1], Ahmed El-Boraie[2], Li Gong[3], Andrew A Somogyi[4], Volker M. Lauschke[5], Collet Dandara[6], Kathrin Klein[7,8], Neil A. Miller[9,10], Teri E. Klein[3], Rachel F. Tyndale[2], Michelle Whirl-Carrillo[3,†] and Andrea Gaedigk[11,12,*,†]

In revision (2022)
GeneFocus *CYP3A5*

In preparation
GeneFocus *SLCO1B1*

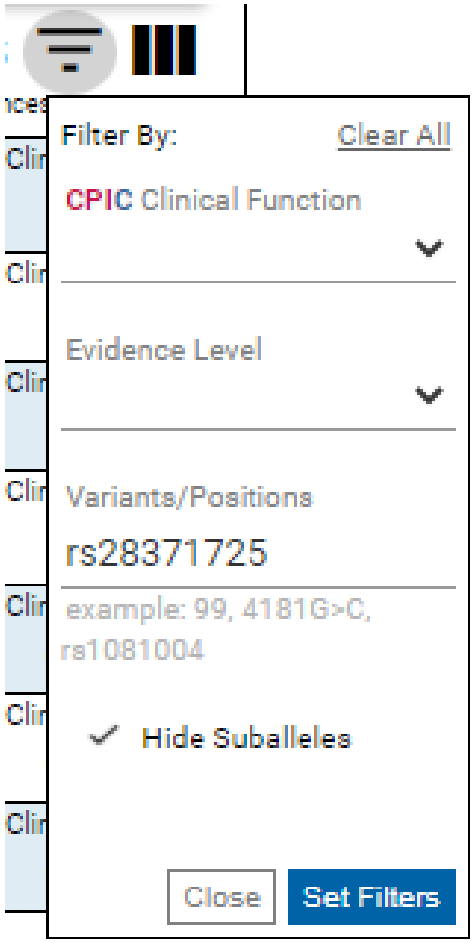
Standardization

- PharmVar uses most recent genomic RefSeqs
  - Derived from the gene's MANE[1] Select transcript
  - This transcript matches GRCh38 and is 100% identical with its RefSeq for 5'UTR, CDS, splicing and 3'UTR
  - LRGs (if existing) are cross-referenced in the Read Me (Table 1)

- Lifting star allele definitions to a newer RefSeq may cause
  - "SNP switching"
  - Changes in variant positions on the genomic RefSeq

[1] MANE – Matched Annotation from NCBI and EMBL-EBI

Filter Options



"rs28371725" **AND** "Hide Suballeles"

Allele Name	PharmVar ID	Variants (Impact) variant = variants with dbSNP rsID	References
CYP2D6*32	PV00456	2851C>T (R296C), 2989G>A (splice defect), 3854G>A (E410K), 4181G>C (S486T)	CPIC Clinical Function
CYP2D6*41	PV00465	2851C>T (R296C), 2989G>A (splice defect), 4181G>C (S486T)	CPIC Clinical Function
CYP2D6*69	PV00491	100C>T (P34S), 2851C>T (R296C), 2989G>A (splice defect), 4181G>C (S486T)	CPIC Clinical Function
CYP2D6*91	PV00508	1736G>C (C161S), 2851C>T (R296C), 2989G>A (splice defect)	CPIC Clinical Function
CYP2D6*119	PV00536	2989G>A (splice defect)	CPIC Clinical Function
CYP2D6*123	PV00633	2851C>T (R296C), 2870T>C (L302P), 2989G>A (splice defect), 4181G>C (S486T)	CPIC Clinical Function
CYP2D6*138	PV00722	2851C>T (R296C), 2989G>A (splice defect), 4145G>A (R474Q), 4181G>C (S486T)	CPIC Clinical Function

The SNV causing a splice defect is present not only in *CYP2D6*41*, but also **32, *69, *91, *119, *123* and **138*

SLCO1B1

The Clinical Pharmacogenetics Implementation Consortium

(CPIC) guideline for *SLCO1B1, ABCG2*, and *CYP2C9* and statin-associated

musculoskeletal symptoms

Authors:

*Rhonda Cooper-DeHoff[1,2], *Mikko Niemi[3,4,5], Laura B. Ramsey[6,7], Jasmine A. Luzum[8], E. Katriina Tarkiainen[3,4,5], Robert J. Straka[9], Li Gong[10], Sony Tuteja[11], Russell A. Wilke[12], Mia Wadelius[13], Eric A. Larson[12], Dan M. Roden[14,15], Teri E. Klein[10], Sook Wah Yee[16], Ronald M. Krauss[17], Richard M. Turner[18], Latha Palaniappan[19], Andrea Gaedigk[20], Kathleen M. Giacomini[16], Kelly E. Caudle[22], Deepak Voora[23]

This guideline uses the new PharmVar *SLCO1B1* nomenclature

New PharmVar Gene: *SLCO1B1*

- PharmVar introduced its first drug transporter in Oct 2021
  - Star nomenclature was utilized before, but no oversight
    - Loosely followed rules first established for CYPs
    - Authors self-assigned star numbers
    - Many haplotypes were only partially characterized or selected information not included when allele definitions were published (e.g., synonymous SNPs)
    - Some alleles had more than one star number
  - Expert panel reviewed all published information
    - Designated several alleles which were published w/o star number
    - Several haplotypes were merged, revised and/or corrected
  - PharmVar Team utilized WGS data to substantiate existing allele definitions and discover novel haplotypes

New gene: *SLCO1B1*

SLCO1B1

Official Symbol	SLCO1B1
Official Full Name	solute carrier organic anion transporter family member 1B1
Synonyms	OATP-C, OATP2, OATPC, SLCO1B1, ENSG00000134538, OATP1B1, LST-1, HBLRR, SLC21A6, LST1
External Resources	EntrezGene:10599 HGNC:10959 PharmGKB:PA134865839

Download Gene Data

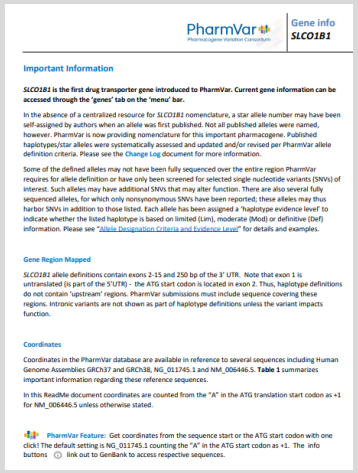
Additional Data Download Information

Read Me for SLCO1B1 | Change Log for SLCO1B1 | Structural Variation for SLCO1B1

NG_011745.1 (LRG_1022) | NM_006446.5 | GRCh37 (NC_000012.11) | GRCh38 (NC_000012.12)

Compare View

Count From: Sequence ATG Start


PharmVar Gene info SLCO1B1

Important Information

SLCO1B1 is the first drug transporter gene introduced to PharmVar. Current gene information can be accessed through the 'genes' tab on the 'menu' bar.

In the absence of a centralized resource for *SLCO1B1* nomenclature, a star allele number may have been self-assigned by authors when an allele was first published. Not all published alleles were named, however. PharmVar is now providing nomenclature for this important pharmacogene. Published haplotypes/star alleles were systematically assessed and updated and/or revised per PharmVar allele definition criteria. Please see the Change Log document for more information.

Some of the defined alleles may not have been fully sequenced over the entire region PharmVar requires for allele definition or have only been screened for selected single nucleotide variants (SNVs) of interest. Such alleles may have additional SNVs that may alter function. There are also several fully sequenced alleles, for which only nonsynonymous SNVs have been reported; these alleles may thus harbor SNVs in addition to those listed. Each allele has been assigned a 'haplotype evidence level' to indicate whether the listed haplotype is based on limited (Lim), moderate (Mod) or definitive (Def) information. Please see "Allele Designation Criteria and Evidence Level" for details and examples.

Gene Region Mapped

SLCO1B1 allele definitions contain exons 2-15 and 250 bp of the 3' UTR. Note that exon 1 is untranslated (is part of the 5'UTR) - the ATG start codon is located in exon 2. Thus, haplotype definitions do not contain 'upstream' regions. PharmVar submissions must include sequence covering these regions. Intronic variants are not shown as part of haplotype definitions unless the variant impacts function.

Coordinates

Coordinates in the PharmVar database are available in reference to several sequences including Human Genome Assemblies GRCh37 and GRCh38, NG_011745.1 and NM_006446.5. **Table 1** summarizes important information regarding these reference sequences.

In this ReadMe document coordinates are counted from the "A" in the ATG translation start codon as +1 for NM_006446.5 unless otherwise stated.

PharmVar Feature: Get coordinates from the sequence start or the ATG start codon with one click! The default setting is NG_011745.1 counting the "A" in the ATG start codon as +1. The info buttons ⓘ link out to GenBank to access respective sequences.

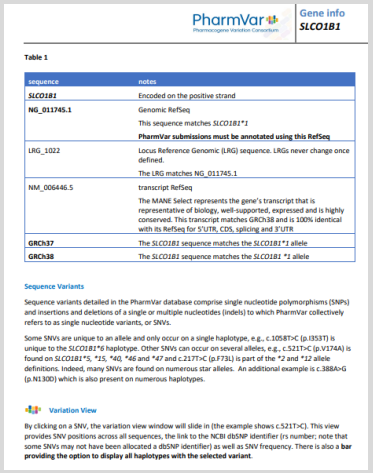

PharmVar Gene info SLCO1B1

Table 1

sequence	notes
SLCO1B1	Encoded on the positive strand
NG_011745.1	Genomic RefSeq This sequence matches *SLCO1B1*1* **PharmVar submissions must be annotated using this RefSeq**
LRG_1022	Locus Reference Genomic (LRG) sequence. LRGs never change once defined. The LRG matches NG_011745.1
NM_006446.5	transcript RefSeq The MANE Select represents the gene's transcript that is representative of biology, well-supported, expressed and is highly conserved. This transcript matches GRCh38 and is 100% identical with its RefSeq for 5'UTR, CDS, splicing and 3'UTR.
GRCh37	The *SLCO1B1* sequence matches the *SLCO1B1*1* allele
GRCh38	The *SLCO1B1* sequence matches the *SLCO1B1 *1* allele

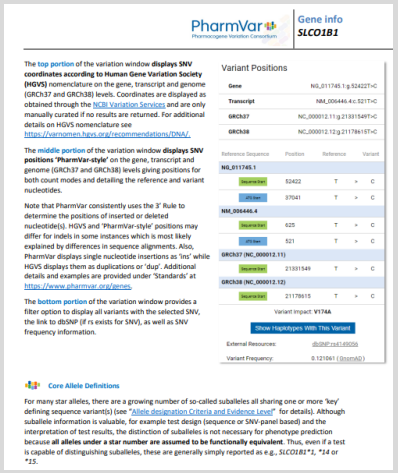
Sequence Variants

Sequence variants detailed in the PharmVar database comprise single nucleotide polymorphisms (SNPs) and insertions and deletions of a single or multiple nucleotides (indels) to which PharmVar collectively refers to as single nucleotide variants, or SNVs.

Some SNVs are unique to an allele and only occur on a single haplotype, e.g., c.1058T>C (p.I353T) is unique to the *SLCO1B1*6* haplotype. Other SNVs can occur on several alleles, e.g., c.521T>C (p.V174A) is found on *SLCO1B1*5*, **15*, **40*, **46* and **47* and c.217T>C (p.F73L) is part of the **2* and **12* allele definitions. Indeed, many SNVs are found on numerous star alleles. An additional example is c.388A>G (p.N130D) which is also present on numerous haplotypes.

Variation View

By clicking on a SNV, the variation view window will slide in (the example shows c.521T>C). This view provides SNV positions across all sequences, the link to the NCBI dbSNP identifier (rs number; note that some SNVs may not have been allocated a dbSNP identifier) as well as SNV frequency. There is also a **bar providing the option to display all haplotypes with the selected variant**.


PharmVar Gene info SLCO1B1

The top portion of the variation window **displays SNV coordinates according to Human Gene Variation Society (HGVS)** nomenclature on the gene, transcript and genome (GRCh37 and GRCh38) levels. Coordinates are displayed as obtained through the NCBI Variation Services and are only manually curated if no results are returned. For additional details on HGVS nomenclature see https://varnomen.hgvs.org/recommendations/DNA/.

The middle portion of the variation window **displays SNV positions 'PharmVar-style'** on the gene, transcript and genome (GRCh37 and GRCh38) levels giving positions for both count modes and detailing the reference and variant nucleotides.

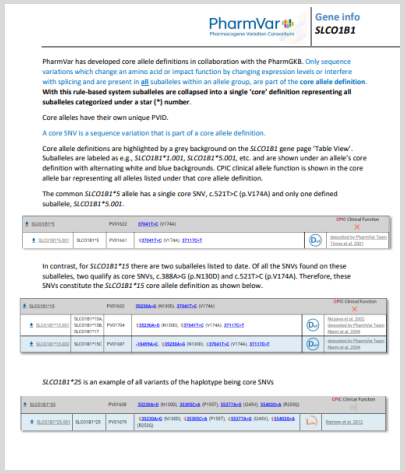
Note that PharmVar consistently uses the 3' Rule to determine the positions of inserted or deleted nucleotide(s). HGVS and 'PharmVar-style' positions may differ for indels in some instances which is most likely explained by differences in sequence alignments. Also, PharmVar displays single nucleotide insertions as 'ins' while HGVS displays them as duplications or 'dup'. Additional details and examples are provided under 'Standards' at https://www.pharmvar.org/genes.

The bottom portion of the variation window provides a filter option to display all variants with the selected SNV, the link to dbSNP (if rs exists for SNV), as well as SNV frequency information.

Variant Positions

Core Allele Definitions

For many star alleles, there are a growing number of so-called suballeles all sharing one or more 'key' defining sequence variant(s) (see "Allele designation Criteria and Evidence Level" for details). Although suballele information is valuable, for example test design (sequence or SNV-panel based) and the interpretation of test results, the distinction of suballeles is not necessary for phenotype prediction because **all alleles under a star number are assumed to be functionally equivalent**. Thus, even if a test is capable of distinguishing suballeles, these are generally simply reported as e.g., *SLCO1B1*1*, **14* or **15*.


PharmVar Gene info SLCO1B1

PharmVar has developed core allele definitions in collaboration with the PharmGKB. Only sequence variations which change an amino acid or impact function by changing expression levels or interfere with splicing and are present in all suballeles within an allele group, are part of the **core allele definition**. **With this rule-based system suballeles are collapsed into a single 'core' definition representing all suballeles categorized under a star (*) number.**

Core alleles have their own unique PVID.

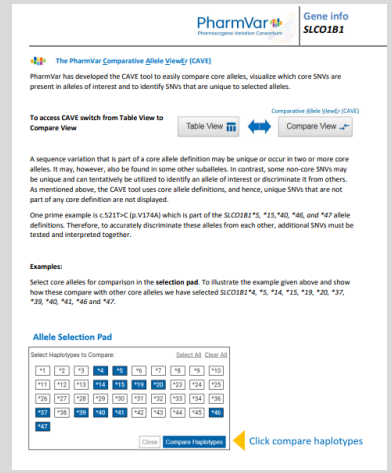
A core SNV is a sequence variation that is part of a core allele definition.

Core allele definitions are highlighted by a grey background on the *SLCO1B1* gene page 'Table View'. Suballeles are labeled as e.g., *SLCO1B1*1.001*, *SLCO1B1*5.001*, etc. and are shown under an allele's core definition with alternating white and blue backgrounds. CPIC clinical allele function is shown in the core allele bar representing all alleles listed under that core allele definition.

The common *SLCO1B1*5* allele has a single core SNV, c.521T>C (p.V174A) and only one defined suballele, *SLCO1B1*5.001*.

In contrast, for *SLCO1B1*15* there are two suballeles listed to date. Of all the SNVs found on these suballeles, two qualify as core SNVs, c.388A>G (p.N130D) and c.521T>C (p.V174A). Therefore, these SNVs constitute the *SLCO1B1*15* core allele definition as shown below.

*SLCO1B1*25* is an example of all variants of the haplotype being core SNVs


PharmVar Gene info SLCO1B1

The PharmVar Comparative Allele ViewEr (CAVE)

PharmVar has developed the CAVE tool to easily compare core alleles, visualize which core SNVs are present in alleles of interest and to identify SNVs that are unique to selected alleles.

To access CAVE switch from Table View to Compare View

Table View | Compare View

A sequence variation that is part of a core allele definition may be unique or occur in two or more core alleles. It may, however, also be found in some other suballeles. In contrast, some non-core SNVs may be unique and can tentatively be utilized to identify an allele of interest or discriminate it from others. As mentioned above, the CAVE tool uses core allele definitions, and hence, unique SNVs that are not part of any core definition are not displayed.

One prime example is c.521T>C (p.V174A) which is part of the *SLCO1B1*5*, **15*,**40*, **46*, *and *47* allele definitions. Therefore, to accurately discriminate these alleles from each other, additional SNVs must be tested and interpreted together.

Examples:

Select core alleles for comparison in the **selection pad**. To illustrate the example given above and show how these compare with other core alleles we have selected *SLCO1B1*4*, **5*, **14*, **15*, **19*, **20*, **37*, **39*, **40*, **41*, **46* and **47*.

Allele Selection Pad

Select Haplotypes to Compare: Select All Clear All

*1 *2 *3 *4 *5 *6 *7 *8 *9 *10 *11 *12 *13 *14 *15 *19 *20 *23 *24 *25 *26 *27 *28 *29 *30 *31 *32 *33 *34 *36 *37 *38 *39 *40 *41 *42 *43 *44 *45 *46 *47

Close | Compare Haplotypes

Click compare haplotypes

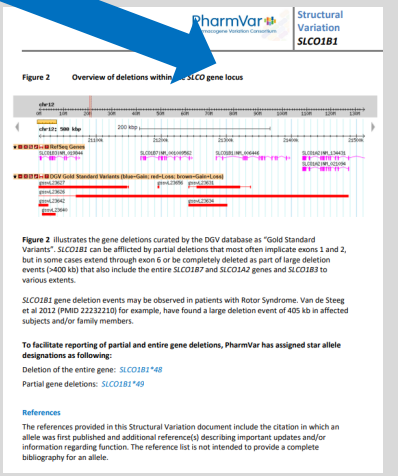

PharmVar Structural Variation SLCO1B1

Figure 2 Overview of deletions within the *SLCO* gene locus

Figure 2 illustrates the gene deletions curated by the DGV database as "Gold Standard Variants". *SLCO1B1* can be afflicted by partial deletions that most often implicate exons 1 and 2, but in some cases extend through exon 6 or be completely deleted as part of large deletion events (>400 kb) that also include the entire *SLCO1B7* and *SLCO1A2* genes and *SLCO1B3* to various extents.

SLCO1B1 gene deletion events may be observed in patients with Rotor Syndrome. Van de Steeg et al 2012 (PMID 22232210) for example, have found a large deletion event of 405 kb in affected subjects and/or family members.

To facilitate reporting of partial and entire gene deletions, PharmVar has assigned star allele designations as following:

Deletion of the entire gene: *SLCO1B1*48*

Partial gene deletions: *SLCO1B1*49*

References

The references provided in this Structural Variation document include the citation in which an allele was first published and additional reference(s) describing important updates and/or information regarding function. The reference list is not intended to provide a complete bibliography for an allele.

Merged Haplotypes (examples)

SLCO1B1*14		PV01631	35230A>G (N130D), 35305C>A (P155T)		CPIC Clinical Function ↗
SLCO1B1*14.001	SLCO1B1*14	PV01691	35230A>G (N130D), 35305C>A (P155T)	Lim	Tirona et al. 2001
SLCO1B1*14.002	SLCO1B1*18	PV01677	35230A>G (N130D), 35253G>A, 35305C>A (P155T), 37091T>C, 37117C>T	Def	Tirona et al. 2001 deposited by PharmVar Team
SLCO1B1*14.003		PV01705	35230A>G (N130D), 35305C>A (P155T), 37117C>T	Def	deposited by PharmVar Team
SLCO1B1*15		PV01632	35230A>G (N130D), 37041T>C (V174A)		CPIC Clinical Function ✕
SLCO1B1*15.001	SLCO1B1*15A, SLCO1B1*15B, SLCO1B1*17	PV01704	35230A>G (N130D), 37041T>C (V174A), 37117C>T	Def	deposited by PharmVar Team Nozawa et al. 2002 Niemi et al. 2004
SLCO1B1*15.002	SLCO1B1*15C	PV01687	-10499A>C, 35230A>G (N130D), 37041T>C (V174A), 37117C>T	Def	Niemi et al. 2004 deposited by PharmVar Team
SLCO1B1*20		PV01635	35230A>G (N130D), 97468A>C (L643F)		CPIC Clinical Function ↗
SLCO1B1*20.001	SLCO1B1*20, SLCO1B1*21, SLCO1B1*35	PV01714	35230A>G (N130D), 37117C>T, 97468A>C (L643F)	Def	Ramsey et al. 2012 deposited by PharmVar Team Niemi et al. 2004
SLCO1B1*20.002		PV01693	-10690T>C, 35230A>G (N130D), 37117C>T, 97468A>C (L643F)	Def	deposited by PharmVar Team

Re-assigned Some **1* Haplotypes

SLCO1B1*37		PV01649	35230A>G (N130D)		CPIC Clinical Function →
SLCO1B1*37.001	SLCO1B1*1B, SLCO1B1*1F	PV01716	35230A>G (N130D)	Def	deposited by PharmVar Team Pasanen et al.
SLCO1B1*37.002	SLCO1B1*1G, SLCO1B1*1H	PV01694	35230A>G (N130D), 37117C>T	Def	deposited by PharmVar Team Pasanen et al.

SLCO1B1*38		PV01650	35297G>A (R152L)		CPIC Clinical Function
SLCO1B1*38.001	SLCO1B1*1C	PV01688	35297G>A (R152L), 37440G>A	Lim	Niemi et al. 2004

Added Novel Haplotypes and CNVs

SLCO1B1*39	PV01651	35230A>G (N130D), 55401C>T (R253X)	CPIC Clinical Function
SLCO1B1*40	PV01652	37041T>C (V174A), 97468A>C (L643F)	CPIC Clinical Function
SLCO1B1*41	PV01653	35324G>T (splice defect)	CPIC Clinical Function
SLCO1B1*42	PV01654	35230A>G (N130D), 37038A>G (Y173C)	CPIC Clinical Function
SLCO1B1*43	PV01655	35230A>G (N130D), 35305C>A (P155T), 55377A>G (I245V), 64457A>G (I499V)	CPIC Clinical Function
SLCO1B1*44	PV01656	35230A>G (N130D), 55377A>G (I245V), 64457A>G (I499V)	CPIC Clinical Function
SLCO1B1*45	PV01657	80781C>T (R580X)	CPIC Clinical Function
SLCO1B1*46	PV01658	35230A>G (N130D), 37041T>C (V174A), 80781C>T (R580X)	CPIC Clinical Function
SLCO1B1*47	PV01659	35230A>G (N130D), 37041T>C (V174A), 58970C>G (P336R)	CPIC Clinical Function
SLCO1B1*48	PV01732	SLCO1B1 full gene deletions; see Structural Variation for SLCO1B1	CPIC Clinical Function
SLCO1B1*49	PV01734	SLCO1B1 partial gene deletions; see Structural Variation for SLCO1B1	CPIC Clinical Function

39 - *47
novel haplotypes

48* and *49
full and partial gene deletions

Impact on Genotype Test Interpretation and Phenotype Prediction

Genotype Before	Phenotype Before	Genotype updated	Phenotype Updated
**15/*17*	Poor function	**15/*15*	Poor function
**14/*17*	**Indeterminate Function**	**14/*15*	**Decreased function**
**17/*21*	**Indeterminate Function**	**15/*20*	**Decreased function**
**1B/*35*	**Possibly decreased function**	**37/*20*	**Normal function**

Many genotypes which were ‘indeterminate’ or had a ‘possible’ are now having a definitive function assignment

PHARMGKB https://www.pharmgkb.org/page/slco1b1RefMaterials

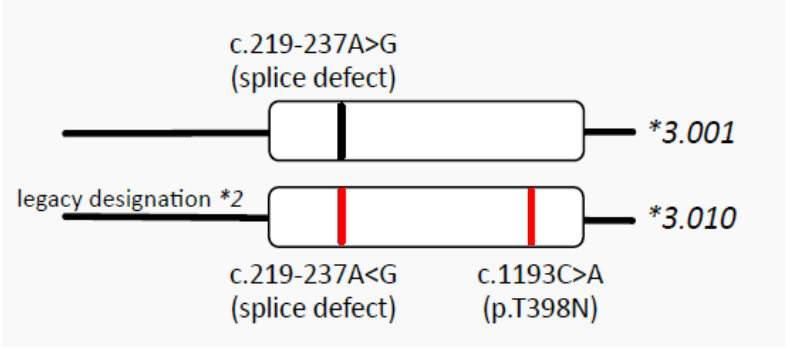
CYP3A4

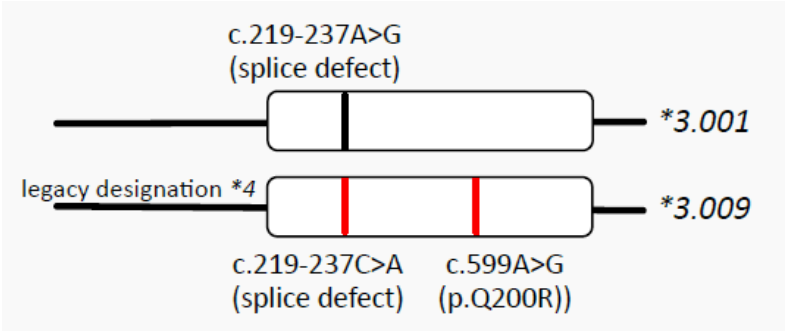
- *CYP3A4* was transitioned into the PharmVar database
  - Allele definitions lifted to NG_008421.1
    - Changes are summarized in the Change Log document
    - Genomic positions changed
      - The position of the *22 SNV changed by 9 bp from 15389 to 15398 (ATG=+1)
    - -392A>G switched to -392G>A
      - Legacy RefSeq has A at -392 while NG_00841.1 has G at this position
      - Consequently, all alleles that previously had this variant 'lost' it while all others 'gained' it
    - Merged suballeles (e.g., **15A* and **15B*)
    - Removed suballeles which only differed by having intronic SNVs or SNVs outside the region now used for allele definition (e.g., **1F, J, K, L, N, P, Q, R* and *S*)
    - PharmVar Team utilized WGS data to substantiate existing allele definitions and discover novel haplotypes
    - *1G designation is pending

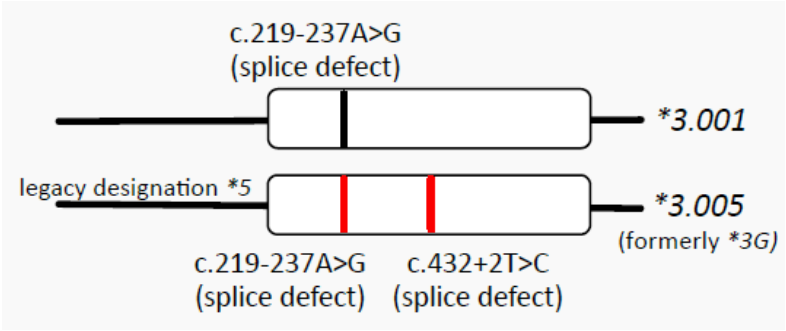
CYP3A5

- *CYP3A5* was transitioned into the PharmVar database
  - Allele definitions lifted to NG_007938.2
    - Genomic positions changed
      - Positions after 14660 (ATG=+1) are shifted by -5 bp
    - Removed several suballeles due to uncertainty
      - SNVs being present/absence or insufficient support of haplotypes (e.g., **1B, *1C, *1E, *3C*)
  - PharmVar Team utilized WGS data to substantiate existing allele definitions and discover novel haplotypes
    - Data showed that *CYP3A5*2, *4* and **5* SNPs are on the **3* haplotypes

*CYP3A5*2, *4* and **5* (to be retired)







- Samples were homozygous for the *CYP3A5*3* SNV and heterozygous for the **2* SNV (top), **4* SNV (middle) or **5* SNP (bottom)
- All samples with **2, *4* or **5* were heterozygous or homozygous for the **3* splice variant
- No evidence was found that suggested that the **2, *4* and **5* SNVs occur by themselves
- *CYP3A5*6, *7* and **8* confirmed
- Genotype data for 1 subject suggests that *CYP3A5*9* holds up

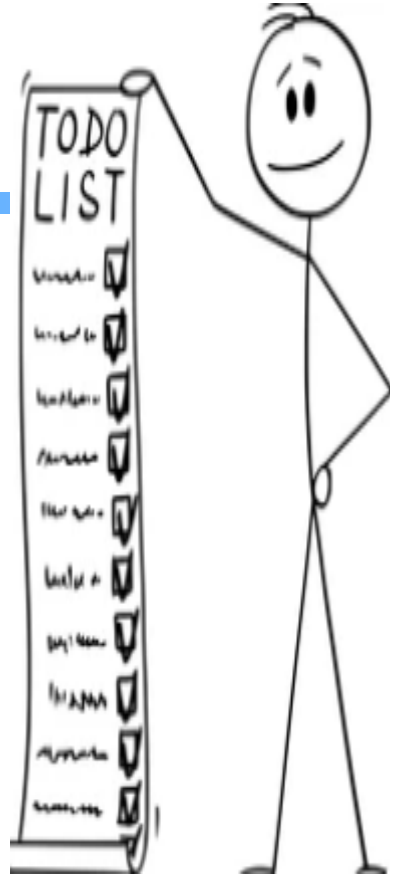
CYP2A6 Coming Soon

CYP2A6 allele nomenclature

Allele	Protein	Nucleotide changes		Trivial name	Effect	Enzyme activity		References
		cDNA * *To be considered *CYP2A6*1A*, the cDNA reference sequence must be changed to 51G.	Gene * *To be considered *CYP2A6*1A*, the genomic reference sequence must be changed to 51G.			In vivo	In vitro	
*CYP2A6*1A*	CYP2A6.1	None	None			Normal	Normal	Yamano *et al.*, 1990
*CYP2A6*1B1* (formerly *CYP2A6*1B*; has also been called *CYP2A6*1C*)	CYP2A6.1	gene conversion in 3′ flanking region				Incr.?		Yamano *et al.*, 1990 Nakajima *et al.*, 2001 Pitarque *et al.*, 2004
*CYP2A6*1B2* (has also been called *CYP2A6*1B*)	CYP2A6.1	gene conversion in the 3′ flanking region	-1013A>G; gene conversion in the 3′ flanking region					Oscarson *et al.*, 1999b Ariyoshi *et al.*, 2000 Pitarque *et al.*, 2004
*CYP2A6*1B3* (formerly *CYP2A6*1C*)	CYP2A6.1	gene conversion in 3′ flanking region	-395G>A; gene conversion in 3′ flanking region					Kiyotani *et al.*, 2002
*CYP2A6*1B4*	CYP2A6.1	gene conversion in 3′ flanking region	gene conversion in 3′ flanking region; gene conversion at 7073-7082					Mwenifumbo *et al.*, 2010
*CYP2A6*1B5* Tentative allele	CYP2A6.1	gene conversion in 3′ flanking region	-1680A>G; -1579T>C; -1301A>C; -1289G>A; -1013A>G; 1620T>C; gene conversion in 3′ flanking region					Haberl *et al.*, 2005
*CYP2A6*1B6* Predicted haplotype/ Tentative allele	CYP2A6.1	gene conversion in 3′ flanking region	-1680A>G; -1579T>C; -1301A>C; -1289G>A; -1013A>G; 1620T>C; 6285A>G; 6293T>C; gene conversion in 3′ flanking region					Haberl *et al.*, 2005
*CYP2A6*1B7* Predicted haplotype/ Tentative allele	CYP2A6.1	gene conversion in 3′ flanking region	-1680A>G; -1579T>C; -1464A>T; -1301A>C; -1289G>A; 1620T>C; gene conversion in 3′ flanking region					Haberl *et al.*, 2005
*CYP2A6*1B8* Tentative allele	CYP2A6.1	gene conversion in 3′ flanking region	-1680A>G; -1579T>C; -1464A>T; -1301A>C; -1289G>A; -1013A>G; 1620T>C; gene conversion in 3′ flanking region					Haberl *et al.*, 2005
*CYP2A6*1B9* Predicted haplotype/ Tentative allele	CYP2A6.1	gene conversion in 3′ flanking region	-1680A>G; -1579T>C; -1464A>T; -1301A>C; -1289G>A; -1013A>G; 1620T>C; 6390C>G; gene conversion in 3′ flanking region					Haberl *et al.*, 2005
*CYP2A6*1B10* Predicted	CYP2A6.1	gene conversion in 3′ flanking	-1680A>G; -1579T>C; -1464A>T; -1301A>C;					Haberl *et al.*, 2005

- CYP2A6 major enzyme for nicotine metabolism
- Complex gene locus
  - High similarity with *CYP2A7*
  - Copy number variation; rearrangements with *CYP2A7*
- Massive curation efforts over the last two years
- Aim to roll this out in spring/early summer 2022

No changes since the CYP nomenclature site transitioned to PharmVar in 2017



Long To-Do List

- Introduction into the PharmVar database
  - *CYP2A6* (spring/early summer 2022)
  - *CYPs 1A1, 1A2, 1B1* and *2E1* (need major curation)
- Need of data
  - *CYP4F2* in PharmVar database but only 3 star alleles
    - WGS data indicates there are more
  - Data mining will likely reveal many new haplotypes for other *CYPs* that have not been extensively investigated yet
- Next ‘new’ gene?
  - Suggestions?
- Database functionality improvements
  - Online submission portal

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