

**Andrea Gaedigk, PhD**  
Children's Mercy Kansas City, MO, USA  
Director, PharmVar

## The Pharmacogene Variation (PharmVar) Consortium: update



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.

# Objectives



- Resources and tools
- New Gene
- Standardization
- In progress

# Resources

- Reorganized content under Menu tab
- PharmVar publications now easier to find
- **New!** API services



## PharmVar API Services <sup>0.1</sup>

[ Base URL: [www.pharmvar.org/](http://www.pharmvar.org/) ]  
[/v2/api-docs](#)

PharmVar now provides a beta version of a RESTful API service to facilitate convenient utilization of genes, alleles, and variants defined in the PharmVar Database served in JSON format. For information about available services, please see the documentation below. Limitations: Please limit usage to 2 service calls per second to ensure service stability for all users.

[Send Us Your Feedback](#)

# Gene Pages

**CYP2D6**

Official Symbol: CYP2D6  
 Official Full Name: cytochrome P450 family 2 subfamily D member 6  
 Synonyms: CYP11D6, P450-DB1, P450C2D, CYP2D7BP, CYP2D6, CYP2D, CPD6, CYP2D7AP, ENSG00000100197, CYP2D7P2, CYP2DL1, CYP2D8P2, P450DB1  
 External Resources: EntrezGene:1565 HGNC:2625 PharmGKB:PA128

[Download Gene Data](#)  [Additional Data Download Information](#)

Gene name(s), links to external resources, download gene information

[Read Me for CYP2D6](#) [Change Log for CYP2D6](#) [Structural Variation for CYP2D6](#) Important gene documents: [Read Me](#), [Change log](#) and structural information

NG\_008376.3 | NM\_000106.5 | GRCh37 (NC\_000022.10) | GRCh38 (NC\_000022.11) | M33388

CAVE tool  Count From: Sequence Start  ATG Start

select mode

Haplotype	Legacy Label	PharmVar ID	Variants (Impact) variant - variants with dbSNP rsID	Evidence Level	References
<b>CYP2D6*1</b> PV00454 normal function					
<a href="#">CYP2D6*1.001</a>	CYP2D6*1A	PV00126			Kimura et al. 1989
<a href="#">CYP2D6*1.002</a>	CYP2D6*1B	PV00125	<a href="#">3829G&gt;A</a>		deposited by Nofziger Marez et al. 1997 Twist et al 2016
<a href="#">CYP2D6*1.003</a>	CYP2D6*1C	PV00128	<a href="#">1979C&gt;T</a>		Marez et al. 1997
<a href="#">CYP2D6*1.004</a>	CYP2D6*1D	PV00127	<a href="#">2576C&gt;A</a>		Marez et al. 1997
<b>CYP2D6*2</b> PV00456 <a href="#">2851C&gt;T</a> (R296C), <a href="#">4181G&gt;C</a> (S486T) Core allele definition function normal function					
<a href="#">CYP2D6*2.001</a>	CYP2D6*2A	PV00129	<a href="#">-1584C&gt;G</a> , <a href="#">-1235A&gt;G</a> , <a href="#">-740C&gt;T</a> , <a href="#">-678G&gt;A</a> , <a href="#">214G&gt;C</a> , <a href="#">221C&gt;A</a> , <a href="#">223C&gt;G</a> , <a href="#">227T&gt;C</a> , <a href="#">232G&gt;C</a> , <a href="#">233A&gt;C</a> , <a href="#">245A&gt;G</a> , <a href="#">310G&gt;T</a> , <a href="#">745C&gt;G</a> , <a href="#">842T&gt;G</a> , <a href="#">1662G&gt;C</a> , <a href="#">2851C&gt;T</a> (R296C), <a href="#">3385A&gt;C</a> , <a href="#">3585G&gt;A</a> , <a href="#">3791C&gt;T</a> , <a href="#">4181G&gt;C</a> (S486T), <a href="#">4482G&gt;A</a>		deposited by Gaedigk et al and by Nofziger Johansson et al. 1993 Panserat et al. 1994 Raimundo et al. 2000 Sakuyama et al. 2008
<a href="#">CYP2D6*2.002</a>	CYP2D6*2B	PV00150	<a href="#">1038C&gt;T</a> , <a href="#">1662G&gt;C</a> , <a href="#">2851C&gt;T</a> (R296C), <a href="#">4181G&gt;C</a> (S486T)		Marez et al. 1997
<a href="#">CYP2D6*2.003</a>	CYP2D6*2C	PV00149	<a href="#">1662G&gt;C</a> , <a href="#">2471T&gt;C</a> , <a href="#">2851C&gt;T</a> (R296C), <a href="#">4181G&gt;C</a> (S486T)		Marez et al. 1997

Variants mapped to g. and c. RefSeqs, GRCh37 and 38 and M33388 – click to change view

Create custom views with the Haplotype Filter and Column Selector tools

Haplotype evidence levels

# Comparative Allele ViewEr (CAVE)

Select all core alleles for comparison in the selection pad. For illustration purposes, we have selected 5 core alleles all having 100C>T as a core SNV. *CYP2D6*\*4 was selected because 100C>T is present on suballeles, but is not a core SNV.

Click COMPARE HAPLOTYPES  
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	*17	*18	*19	*20	*21
*22	*23	*24	*25	*26	*27	*28	*29	*30	*31
*32	*33	*34	*55	*36	*37	*38	*39	*40	*41
*42	*43	*44	*45	*46	*47	*48	*49	*50	*51
*52	*53	*54	*55	*56	*57	*58	*59	*60	*61
*62	*63	*64	*65	*68	*69	*70	*71	*72	*73
*74	*75	*81	*82	*83	*84	*85	*86	*87	*88
*89	*90	*91	*92	*93	*94	*95	*96	*97	*98
*99	*100	*101	*102	*103	*104	*105	*106	*107	*108
*109	*110	*111	*112	*113	*114	*115	*116	*117	*118
*119									

Close Compare Haplotypes

Click compare haplotypes

## Comparative Allele ViewEr (CAVE)

	*4	*10	*36	*49	*100	*114
100C>T		100	100	100	100	100
1612T>A				100		
1759G>A						100
1847G>A	100					
2829delC					100	
2851C>T						100
Ex9Conv						
4181G>C						

- Variant is present
- Variant is present on some suballeles
- Variant is unique for selected haplotypes
- Variant alters function

CAVE graphically displays all SNVs present on each selected core allele.

100C>T (boxed), is shown in blue for \*10, \*36, \*49, \*100 and \*114 indicating that it is part of their respective core allele definitions, and in gray for \*4 indicating that 100C>T is not present in all suballeles. In contrast, 1847G>A is the \*4 core SNV and exclusively found on \*4 haplotypes.

CAVE also indicates whether a SNV alters function and/or is unique to a haplotype.

# PharmVar GeneFocus

REVIEW

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 107 NUMBER 1 | JANUARY 2020

## PharmVar GeneFocus: *CYP2D6*

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

The Pharmacogene Variation Consortium (PharmVar) provides nomenclature for the highly polymorphic human *CYP2D6* gene locus. *CYP2D6* genetic variation impacts the metabolism of numerous drugs and, thus, can impact drug efficacy and safety. This GeneFocus provides a comprehensive overview and summary of *CYP2D6* genetic variation and describes how the information provided by PharmVar is utilized by the Pharmacogenomics Knowledgebase (PharmGKB) and the Clinical Pharmacogenetics Implementation Consortium (CPIC).

### Templates for authors to

- Describe genotyping methods | report alleles tested | describe allele/diplotype frequencies

# New look: PharmVar GENES page

## Genes

- Data downloads are now available for genes that have been transitioned into the PharmVar database (🚩). See the [Downloads Page](#) for additional information on data downloads.
- Important information for each gene is available in the Read Me and Change Log documents found on each Gene Page.

### PharmVar Genes

### Legacy Genes

### PharmVar Standards

#### CYP1 family

[CYP1A1](#)

[CYP1A2](#)

[CYP1B1](#)

#### CYP2 family

[CYP2A6](#)

[CYP2A13](#)

[CYP2B6](#)

[CYP2C8](#)

[CYP2C9](#)

[CYP2C19](#)

[CYP2D6](#)

[CYP2E1](#)

[CYP2F1](#)

[CYP2J2](#)

[CYP2R1](#)

[CYP2S1](#)

[CYP2W1](#)

#### CYP3 family

[CYP3A4](#)

[CYP3A5](#)

[CYP3A7](#)

[CYP3A43](#)

#### CYP4 family

[CYP4F2](#)

#### Non-Cytochrome P450

[DPYD](#)

[NUDT15](#)

# New look: PharmVar GENES page

## Genes

- Data downloads are now available for genes that have been transitioned into the PharmVar database (🚩). See the [Downloads Page](#) for additional information on data downloads.
- Important information for each gene is available in the Read Me and Change Log documents found on each Gene Page.

### PharmVar Genes

#### CYP1 family

[CYP1A1](#)  
[CYP1A2](#)  
[CYP1B1](#)

#### CYP2 family

[CYP2A6](#)  
[CYP2A13](#)  
[CYP2B6](#)  
[CYP2C8](#)  
[CYP2C9](#)  
[CYP2C19](#)  
[CYP2D6](#)  
[CYP2E1](#)  
[CYP2F1](#)  
[CYP2J2](#)  
[CYP2R1](#)  
[CYP2S1](#)  
[CYP2W1](#)

### Legacy Genes

[TBXAS1](#)  
[PTGIS](#)  
[POR](#)  
[CYP4A11](#)  
[CYP4A22](#)  
[CYP4B1](#)  
[CYP17A1](#)  
[CYP19A1](#)  
[CYP21A2](#)  
[CYP26A1](#)

### PharmVar Standards

#### CYP4 family

[CYP4F2](#)

#### Non-Cytochrome P450

[DPYD](#)  
[NUDT15](#)

# New gene: *DPYD*

- PharmVar introduced second non-CYP gene



- **New!** Page format

- Large gene (843kb), difficult to determine haplotypes
- Many variants are rare, and if detected, clinicians will likely act upon it regardless of the presence of other SNVs in the haplotype
- Expert panel recommended using rs numbers instead of star alleles
- Page launched with SNPs (n=458) vetted by Mayo group

# New gene: *DPYD*

**DPYD**

Official Symbol: DPYD  
 Official Full Name: dihydropyrimidine dehydrogenase  
 Synonyms: ENSG00000188641, DPYD, DPD, DHPDHASE, DHP  
 External Resources: [EntrezGene:1806](#) [HGNC:3012](#) [PharmGKB:PA145](#)

[Download Gene Data](#)   
[Additional Data Download Information](#)

[Read Me for DPYD](#) [Change Log for DPYD](#)

LRG\_722 [i](#) NM\_000110.3 [i](#) GRCh37 (NC\_000001.10) [i](#) GRCh38 (NC\_000001.11) [i](#)

Count From: Sequence Start   ATG Start

[Download Allele Data](#)

Allele Name	Legacy Label	PharmVar ID	Variants (Impact) <small>variant = variants with dbSNP rsID</small>	Frequency	CPIC Clinical Function	References
<a href="#">rs1801265</a>	DPYD*9A	PV00910	<a href="#">85T&gt;C</a> (C29R)	28.05%		<a href="#">He et al. 2008</a>
<a href="#">rs1801159</a>	DPYD*5	PV00908	<a href="#">1627A&gt;G</a> (I543V)	17.54%		<a href="#">Offer et al. 2013</a>
<a href="#">rs2297595</a>		PV00943	<a href="#">496A&gt;G</a> (M166V)	9.01%		<a href="#">Offer et al. 2014</a>
<a href="#">rs17376848</a>		PV00906	<a href="#">1896T&gt;C</a> (F632F)	4.59%		<a href="#">Offer et al. 2013</a>
<a href="#">rs75017182</a> <a href="#">rs56038477</a>	HapB3	PV01077	<a href="#">1129-5923C&gt;G</a> , <a href="#">1236G&gt;A</a>	1.34%		<a href="#">Nie et al. 2017</a>

- rsID = allele name
- Sort by frequency
- Other sorting options via filtering
- ‘function’ now specified as CPIC clinical function
- List contains only two intronic SNPs, both causing aberrant splicing

 Retained one ‘legacy’ haplotype

# Standardization

## ■ PharmVar

- Uses RefSeqs or LRGs to annotate SNPs
- Developed allele designation criteria
- Goal: to consistently apply criteria across all genes
  - Encourage stakeholders to adopt standardized pharmacogene variation annotations
- Revisions are made as needed as a gene is transitioned into the PharmVar database

## ■ *CYP2C19*

- One of 3 genes with which PharmVar was launched in 2017
- Inconsistent designations remained for *CYP2C19*\*1 suballeles

# Standardization: CYP2C19

CYP2C19*1			PV00598	normal function
↓ CYP2C19*1.001	CYP2C19*1A	PV00081		Def Romkes et al. 1991
↓ CYP2C19*1.002	CYP2C19*1B	PV00076	99C>T, 80161A>G (I331V)	Def deposited by Gaedigk et al. Richardson et al. 1997
↓ CYP2C19*1.003	CYP2C19*1C	PV00077	80161A>G (I331V)	Lim Blaisdell et al. 2002
↓ CYP2C19*1.004		PV00421	-1418C>T, -889T>G, 80161A>G (I331V), 80229C>T, 87313A>C	Def deposited by Gaedigk et al.
↓ CYP2C19*1.005		PV00425	-1418C>T, -889T>G, 80161A>G (I331V)	Def deposited by Gaedigk et al. Novkovic et al. 2018
↓ CYP2C19*1.006	CYP2C19*27	PV00073	-1041G>A, 99C>T, 80161A>G (I331V)	Def deposited by Gaedigk et al. Drogemöller et al. 2010

- Inconsistent \*1 suballele designation in regard of I331V
- All but one suballele have this amino acid change
  - \*1 suballeles with I331V are considerably more common compared to those without
- Unclear why \*1 suballeles with I331V did not receive their own star number (on the old 'Karolinska' site)
- Expert panel recommended, and the Steering Committee approved, to revise \*1.001 to \*38.001
  - \*1 core allele definition with gain a core SNP, i.e. 80161A>G (I331V)
  - \*38 will not have any core SNPs because it matches the RefSeq (as well as the recently published LRG)

# Standardization: *CYP2C19*

- The \*1.001 to \*38 revision is detailed in our latest PharmVar GeneFocus paper
- Database change is being coordinated with Epub and announcements
- PharmGKB will update all table accordingly

## PharmVar GeneFocus: *CYP2C19*

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

CLINICAL PHARMACOLOGY & THERAPEUTICS about to be E-published



Member communication



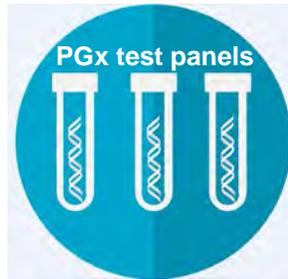
- Transition into the PharmVar database
  - *CYP3A5*
  - *CYP2A6*
- Transition to core allele view
  - *CYP2C8*
  - *CYP2A13*
- Next 'new' gene (first drug transporter)
  - *SLCO1B1*
- Waiting list
  - *CYP3A4, CYP2E1 CYPs 1A1, 1A2 and 1B1*



## Pharmacogene Variation Database



**Clinical PGx test reports**  
Many pharmacogenes are reported using star nomenclature



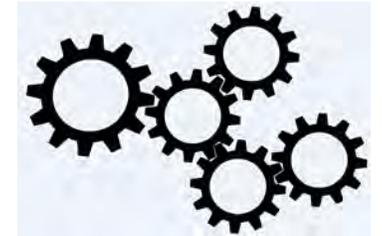
**Clinical genotyping allele selection**  
Recommendations by the AMP and CAP



**PGx reference materials**  
Provision of genotype information for widely-available DNA samples



**PharmGKB**  
PGx data curation for researchers and clinicians  
**PharmCat**  
Generation of report with PGx-based prescribing recommendations



**Bioinformatic tools**  
Facilitate diplotype calling from genotype data; essential for NGS-based testing



**Individualized Drug Therapy**  
**ADME Research**





## PharmVar

Neil Miller  
Scott Casey  
**expert panelists**

## PharmGKB

Teri Klein  
Michelle Whirl-Carrillo  
Katrin Sangkuhl



PharmVar is funded by NIGMS R24GM123930