

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.

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PharmVar Publications

Articles published by PharmVar are available on the [resources](#) page.

Original content from the [cypalleles.ki.se](#) site is available through the [archive](#)

Children's Mercy Kansas City

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Feedback or suggestions? Please contact us at support@pharmvar.org

CYP Nomenclature - 1996



In order to provide the science field with a unified nomenclature, the star (*) allele nomenclature has been devised to “encourage scientists worldwide to speak the same language” and to avoid home-made allele designations that can confuse the scientific literature.



A group of experts came together in the mid 1990s to devise the first pharmacogene nomenclature to “encourage scientists worldwide to speak the same language”. The new Star (*) nomenclature was first applied to CYP2D6, a major drug metabolizing enzyme, for which there was a growing number of allelic variants. The star (*) nomenclature was expanded in 2000 to include all other polymorphic CYP genes.

Human P450 Gene Nomenclature - 2000



Pharmacogenetics 2000, **10**:91-93

Letter to the editor

Human cytochrome P450 (CYP) genes: recommendations for the nomenclature of alleles

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Pharmacogenetics 1051-93 © 2000 Lippincott Williams & Wilkins

In the nomenclature system for CYP alleles, we propose using the same general rules as have already been described for the human *CYP2D6* gene (Daly *et al.*, 1996), as discussed by Nebert (2000), to take into consideration the anticipated SNP explosion during the next several years. These rules are also consistent with those of the Human Allele Nomenclature Working Group (Shows *et al.*, 1987; Antonarakis *et al.*, 1998).

The star (*) nomenclature was expanded in 2000 to include other polymorphic CYP genes

The Human Cytochrome P450 (CYP) Allele Nomenclature Database

Allele nomenclature for Cytochrome P450 enzymes

Inclusion criteria - New criteria regarding variants identified by NGS

Cytochrome P450 Oxidoreductase:

[POR](#)

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:

[CYP4A11](#); [CYP4A22](#); [CYP4B1](#); [CYP4F2](#)

CYP>4 families:

[CYP5A1](#); [CYP8A1](#); [CYP19A1](#); [CYP21A2](#); [CYP26A1](#)

SNP information on [CYP17A1](#) can be found [here](#)

Drug Metab. Pharmacokin. 17 (6): 491-495 (2002).

Review

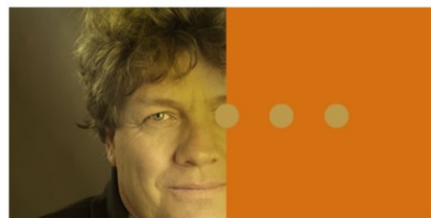
*CYPalleles: A Web Page for Nomenclature of Human
Cytochrome P450 Alleles*

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The number of allelic variants was growing fast – too many to keep updates in paper format. The Human CYP P450 Allele Nomenclature Database was launched in 2002 under the direction of Magnus Ingelman-Sundberg at the Karolinska Institutet in Stockholm, Sweden.

Allele	Activity Score
*1	2
*2	2
*3	0
*4	1
*5	1
*6	0
*7	1
*8	1
*9	1
*10	1
*11	1
*12	1
*13	1
*14	1
*15	1
*16	1
*17	1
*18	1
*19	1
*20	1
*21	1
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*79	1
*80	1
*81	1
*82	1
*83	1
*84	1
*85	1
*86	1
*87	1
*88	1
*89	1
*90	1
*91	1
*92	1
*93	1
*94	1
*95	1
*96	1
*97	1
*98	1
*99	1
*100	1

Tables rely on allele definitions

Table 1 Assignment of likely CYP2D6 phenotypes based on genotypes

Phenotype ^a	Activity score	Genotype	Examples of CYP2D6 diplotypes ^b
Metabolizer			
CYP2D6 ultrarapid metabolizer	> 2.0	An individual carrying duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN ^c
CYP2D6 normal metabolizer	1.5 and 2.0	An individual carrying two normal function alleles or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2,
CYP2D6 normal metabolizer or intermediate metabolizer (controversy remains) ^d	1.0	An individual carrying two decreased function alleles or one normal function and one no function allele. An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared to those with an AS of 1.5 or 2.	*1/*4, *1/*5, *41/*41
CYP2D6 intermediate metabolizer	0.5	An individual carrying one decreased function and one no function allele	*4/*10, *4/*41, *5/*9
CYP2D6 poor metabolizer	0	An individual carrying only no functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

CPIC guideline for tamoxifen

CPIC guidelines provide recommendations based on diplotypes for a number of genes including CYP2C9, CYP2C19 and CYP2D6 as shown for the CYP2D6/tamoxifen guideline. Allele definitions are based on those provided by PharmVar.

PharmGKB and CPIC use * alleles

[Stargazer: a software tool for calling star alleles from next-generation sequencing data using CYP2D6 as a model](#)

Lee SB, Wheeler MM, Patterson K, McGee S, Dalton R, Woodahl EL, Gaedigk A, Thummel KE, Nickerson DA.
Genet Med. 2018 Jun 6. doi: 10.1038/s41436-018-0054-0. [Epub ahead of print]
PMID: 29875422 Free PMC Article



Gene-specific Information Tables for CYP2D6

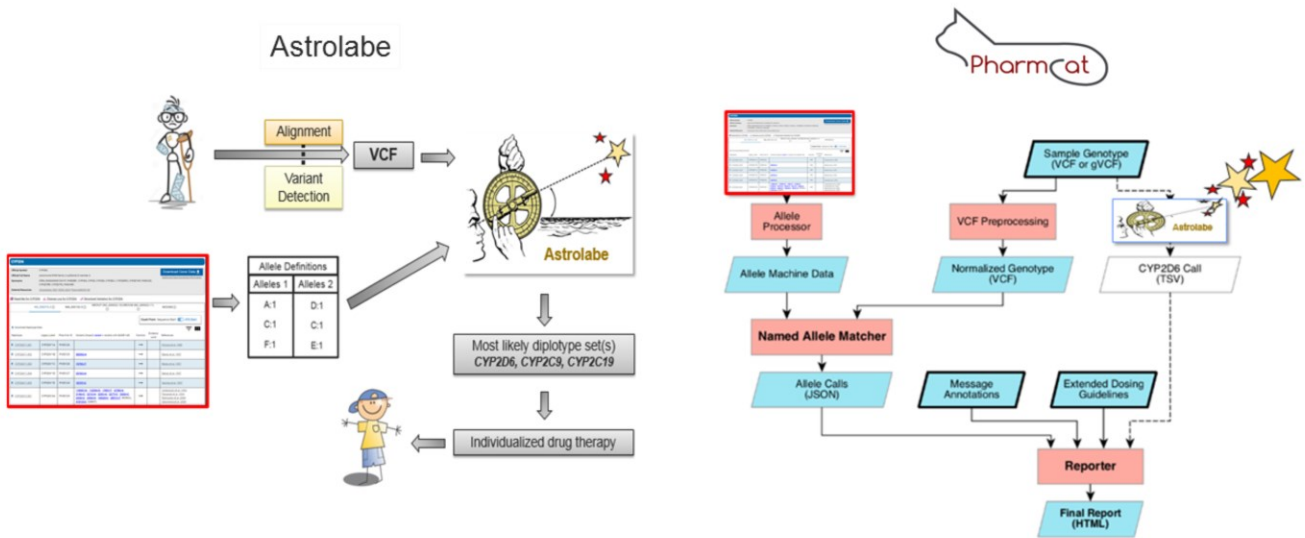
This page contains reference materials created by PharmGKB and CPIC. The files support CPIC guidelines, but are also general resources for CYP2D6.

- **CYP2D6 Allele Definition Table**
 - Information about what variants define star (*) alleles
 - Mapping of variants to the human genome GRCh38, the RefSeq Gene sequence and protein sequence, and provides mIDs, if available
 - Allele functionality using CPIC standardized terms
- **CYP2D6 Allele Functionality Table**
 - References for the allele functionality provided in the Allele Definition Table
- **CYP2D6 Frequency Table**
 - Population-based allele frequency reported by references
 - Calculated allele frequency by major ethnic groups based on frequencies reported by references
 - Worldwide race/ethnic designations correspond to the Human Genome Diversity Project - Centre d'Etude du Polymorphisme Humain (HGDP-CEPH) (Articles 1635252, 12493913), with the addition of the African American category
 - Calculated diplotype frequency
 - Calculated phenotype frequency
- **CYP2D6 DiploTYPE-Phenotype Table**
 - Mapping of each diplotype to possible phenotype
 - Mapping of possible phenotype to EHR priority result notation and consultation text
- **CYP2D6 Gene Resource Mappings**
 - Mapping of gene to ID or code for HGNC, NCBI, Ensembl and PharmGKB

- Published literature typically refers to * alleles rather than individual variants for *CYPs* and some other PGx genes
- Most supporting tables for CPIC are based on * alleles for *CYP* genes: allele frequency and function, diplotype-phenotype mapping
- PharmGKB/CPIC allele definition tables are used for
 - CPIC guideline evidence review and prescribing recommendations
 - PharmGKB literature annotations
 - CPIC and PharmGKB submissions to ClinVar require allele definitions
 - PharmCAT tool determines * alleles from VCF files

Star allele designations are widely used.

Tools call star alleles from NGS data



http://www.childrensmc.org/Health_Care_Professionals/Research/Pediatric_Genomic_Medicine/Software_Tools/

www.pharmgkb.org/page/pharmacat

Bioinformatic tools such as Astrolabe (developed at CMH) and Stargazer rely on allele/haplotype definitions. PharmCAT, another bioinformatic tool for calling PGx diplotypes using star allele definitions is a Pharmacogenomics Research Network (PGRN) initiative in collaboration with the PharmGKB.

Clinical Test Reports also Use Star Nomenclature

05/27/2014 10:33 AM

Doe, Jane

Antiplatelet Metabolism

Test Summary: Abnormal Drug Metabolism Predicted

Result electronically approved and reported on by

Gene	Tested Alleles	Common Genotype	Patient Genotype	Predicted Patient Phenotype
CYP2C19	*1, *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17	*1/*1	*1/*2	IM
CYP3A4	*1, *1B, *2, *3, *12, *16, *17, *22	*1/*1	*1/*1	EM
CYP3A5	*1, *1D, *2, *3A, *3B, *3C, *6, *7, *8, *9	*1/*1	*3A/*3A	IM



Unified nomenclature facilitates standardized test reporting

Genotype results

Gene	Genotype	
CYP1A2	*1F/*1K	
CYP2B6	*1/*1	
CYP2C9	*1/*3	
CYP2C19	*17/*17	
CYP2D6	*2A/*35B	

As highlighted in yellow, the star (*) nomenclature is almost exclusively used to display patients' genotypes on PGx test reports.

www.cypalleles.ki.se/



After more than 15 years the Human Cytochrome P450 (CYP) Allele Nomenclature Database has transitioned...



...to the Pharmacogene Variation (PharmVar) Consortium at www.PharmVar.org

PharmVar will serve as a central repository for pharmacogene variation to facilitate allele (haplotype) designation and the interpretation of pharmacogenetic test results to guide precision medicine
PharmVar is a PGRN resource funded by NIGMS.

After September 26, 2017, please visit www.PharmVar.org to access content of the original P450 Nomenclature Database

After dedicating many years of his distinguished career to developing and maintaining the CYP Allele Nomenclature resource together with Sarah Sim who served as the Webmaster for twelve years, both Magnus Ingelman-Sundberg and Sarah Sim have retired from the nomenclature site to focus on other projects.

The Nomenclature site has transitioned to PharmVar on September 26 of 2017.

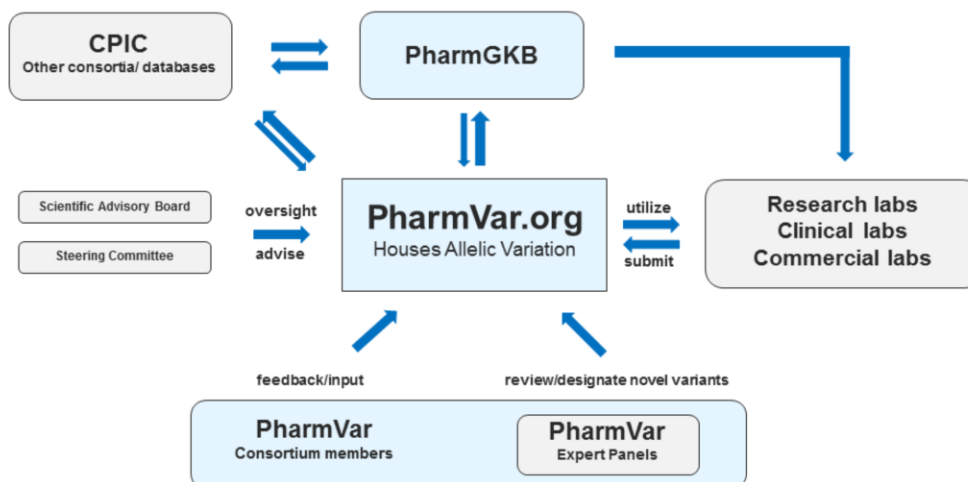


The screenshot shows the PharmVar website homepage. At the top, the PharmVar logo is followed by the text "is a PGRN Resource". Below this is a dark navigation bar with links: Home, What is PGRN?, Members, Data & Tools, PGRN Resources (highlighted), News, and Meetings. A sidebar on the right lists various resources: Clinical Implementation, Functional Pharmacogenes, PGRN Hub, PGRN-PiLS Resource, PGRN-RIKEN, PharmGKB, PharmVar (highlighted with a yellow arrow), and RPGEH. The main content area features two large white boxes. The left box is titled "CYP database is now PharmVar.org" and contains an image of a DNA helix with a PharmVar logo and the text "The Human CYP Allele Nomenclature Database". Below the image, it states: "After more than 15 years the Human Cytochrome P450 (CYP) Allele Nomenclature Database has transitioned... ...to the Pharmacogene Variation (PharmVar) Consortium at PharmVar.org". A button at the bottom of this box says "Learn more & become a member". The right box is titled "RFA: Pharmacogenomics iPSC Pilot Gene Editing Service" and contains an image of a test tube with a label. Below the image, it states: "PGRN Pharmacogenomics iPSC Library and Service (PiLS), is seeking applications for pilot projects, to utilize gene edited iPSC clones for SNP validation studies for pharmacogenomics research. Three projects will be selected for service at minimal cost to the investigators." A button at the bottom of this box says "Learn more & Apply". In the bottom right corner of the website, the text "1R24GM123930-01" is visible.

Once again, a group of experts came together and mutually agreed that the Nomenclature database is an invaluable resource to the entire field of PGx (research, clinical, commercial) and must not disappear. Andrea Gaedigk (Children's Mercy Kansas City) and Teri Klein (PharmGKB) devised a plan to continue: The PharmVar Consortium is the new kid on the block (aka PGRN resource, see <http://www.pgrn.org/pharmvar.html>).

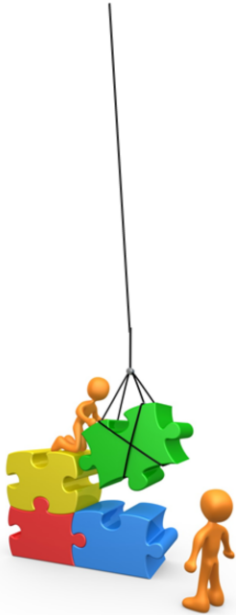
PharmVar

Pharmacogene Variation Consortium



Overview of the PharmVar Consortium. Community input and active participation is key. PGx experts are encouraged to become a member and volunteer to participate (e.g. serving as a gene expert). PharmVar currently has 116 members. Efforts are coordinated between PharmVar, PharmGKB and CPIC with the goal to utilize standardized PGx nomenclature.

Gene Expert Panels



- Each panel consist of a chair and co-chair, 3-7 experts and PharmGKB representatives
 - Experts have research, clinical and/or industry backgrounds – ideally all are represented in a panel
 - International representation
 - Curate allele definitions as they are transferred into the PharmVar database
 - Review submissions and recommend allele designation(s)
 - Instrumental role in reviewing and building nomenclature for new PharmVar genes, develop documents and contribute to progress reports or gene summary papers
 -

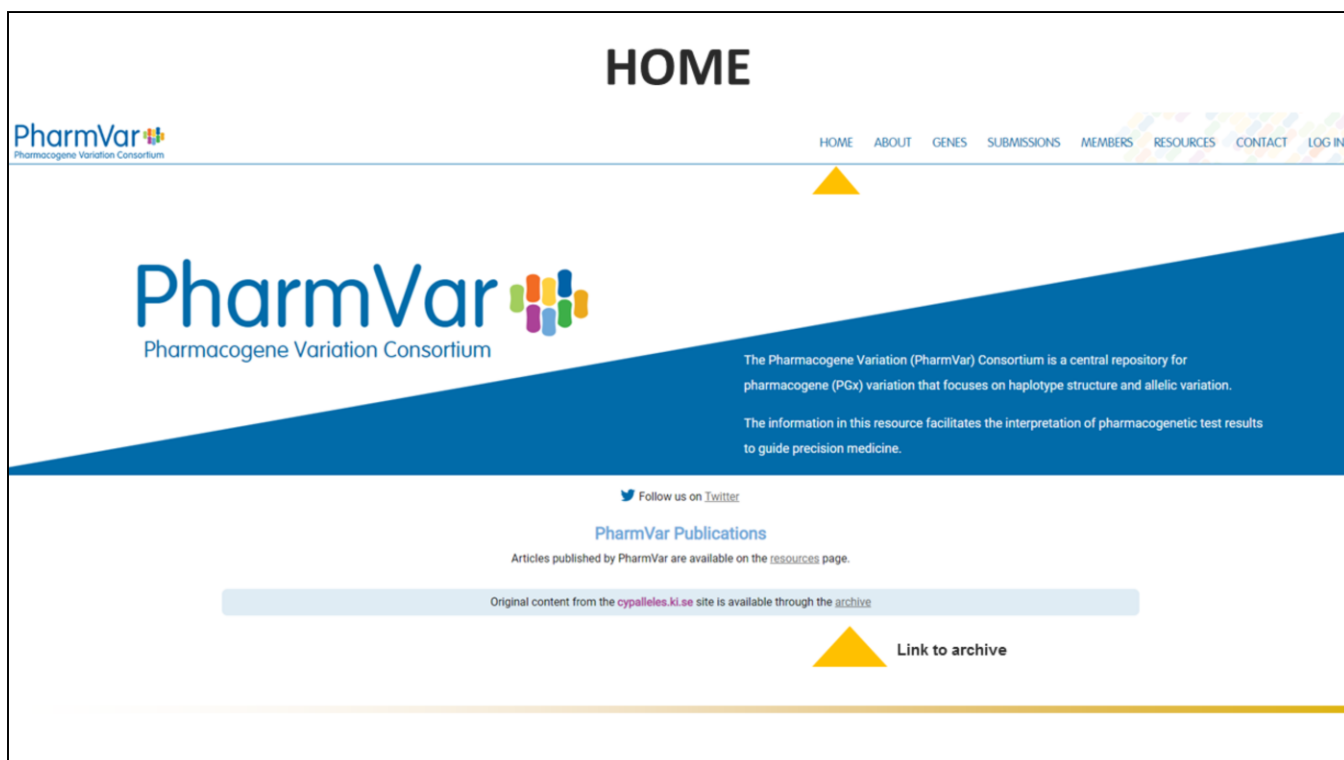
Overview of what gene experts do

Many *CYP* genes including *CYPs 2C9, 2C19* and *2D6* have been transitioned into the PharmVar database.

Notable database features include:

- All variants are consistently mapped to current reference sequences (RefSeqs), GRCh37 and GRCh38
- No more counting – simply click ‘count from sequence start’ or ‘ATG start’
- Redesigned gene pages with customizable display features make it easier to find the information you need
- The new revised haplotype naming system allows cataloging of suballeles
- Each haplotype now has a unique PharmVar ID number
- Evidence levels indicating how strong the information is for a haplotype definition
- Core allele definitions and Comparative Allele ViewEr (CAVE) tool 
- Download options in different formats

The new PharmVar database has many more features compared to the original Nomenclature website. As *CYP* genes are transitioned into the PharmVar database allele definition display will be updated to current RefSeqs and edited to facilitate standardized and uniform reporting of variants across fields. Gene pages have been redesigned to provide information in user-friendly and intuitive ways. PharmVar also continues to improve cataloguing by introducing a revised haplotype naming system and unique PharmVar ID numbers to track each haplotype (see Gaedigk et al. CPT Jan;105(1):29-32).



PharmVar celebrated its first birthday in September 2018 and graduated to a new **HOME** page (no longer showing the transition of the Nomenclature page to PharmVar).

From here, [gene pages](#) can be accessed through the **GENES** tab in the menu bar. The content of the Nomenclature site (cypalleles.ki.se) as of Sept 26, 2017, is available through the **ARCHIVE** link.

ABOUT

The PharmVar Consortium

The Pharmacogene Variation (PharmVar) Consortium is the new home for P450 gene nomenclature serving as a centralized "Next-Generation" Pharmacogene Variation data repository. The major focus of PharmVar is to catalogue allelic variation of genes impacting drug metabolism, disposition and response and provide a unifying designation system (nomenclature) for the global pharmacogenetic/genomic community.

The Human Cytochrome P450 (CYP) Allele Nomenclature Database formerly hosted at <http://www.cypalleles.ki.se/> has transitioned to Children's Mercy in Kansas City, USA. Many CYP genes have already been integrated into the new PharmVar database that launched on March 21st, 2018. PharmVar.org is developed and maintained by Scott Casey.

Please cite PharmVar as following: Pharmacogene Variation Consortium (PharmVar) at www.PharmVar.org

An overview of PharmVar is provided in this [presentation](#)

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- Michael Phillips, PhD, Sequence Bio
- Vicky Pratt, PhD, Indiana University
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- Amber Beitelshues, PhD, University of Maryland
- Sara Van Oost, MD, PhD, Vanderbilt University

Find important information about the PharmVar Consortium under the **ABOUT** tab in the menu bar including of how to cite PharmVar.

SUBMISSIONS

Allele Submission

PharmVar is accepting submissions for CYP allele designations. While we are working on the online submission portal, please use the [submission form](#) and email to submission@pharmvar.org with the gene name in the subject line.

Important information for submissions

A standardized submission form has been developed to collect complete sets of high-quality data across all genes. To that end, all submissions MUST be provided in reference to the gene's RefSeqGene sequence (RefSeq IDs are provided on the RefSeq tab of the submission form).

Only complete submissions will be accepted and reviewed by the gene expert panels.

The requested information is detailed in each tab and an example is provided; please check out all tabs for a range of examples.

For each gene a minimum of 500 bp of the 5' untranslated and 250 bp of the 3' untranslated regions must be sequenced. Submitters are strongly encouraged to extend the sequenced untranslated regions if they harbor key SNVs defining star (*) alleles. For example, for CYP2C19 there are two SNPs at positions -806 and -1041 that are key to define *17 and *27, respectively.

To facilitate allele/haplotype definitions, genes under 10 kb in length (defined as exon 1 through exon 9) MUST be entirely sequenced. See RefSeq tab on submission form whether gene of interest falls into this category.

For genes over 10 kb in length (defined as exon 1 through exon 9), all exons and 50 bp of flanking introns must be sequenced. See RefSeq tab on submission form whether gene of interest falls into this category. Submitters are strongly encouraged to also cover intronic regions that harbor key SNVs defining star (*) alleles. Examples are CYP2C19 12662A>G in intron 2 defining the *35 allele and CYP3A5 6986A>G in intron 3 defining the *3 allele.

To adequately capture structural and copy number variation, there are separate tabs for CYP2A6 and CYP2D6. For CYP2A6 submissions covering the entire gene are encouraged although submissions fulfilling the requirements for exon and flanking regions are also accepted. For CYP2D6 the entire gene must be sequenced including 1600 bp of the untranslated region to include the SNP at position -1584 which is part of many haplotype definitions and tested on many genotyping platforms.

There is a separate tab for NUDT15 submissions to accommodate specific requirements for this gene.

Novel sequence variations detected by Next Gen Sequencing must be confirmed by orthogonal methods.

[Download Submission Form](#)

The form for new haplotype submissions can be found under the **SUBMISSIONS** tab of the menu bar. The **allele definition and evidence level criteria document** can also be found under this tab.

STANDARDS

PharmVar uses a number of conventions for storing and displaying allelic data consistently. As summarized in the [STANDARDS document](#), PharmVar relies on public standards and data sources wherever possible. Note that this may cause some variant positions to shift especially variants in repeat or homopolymer sequences.

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.
- Conventions used for storing and display allelic data are described in the [Standards Document](#).

Under the GENES tab, check out the [STANDARDS document](#) describing how data are displayed

The same standards are being applied to all genes in the PharmVar database as detailed in the **STANDARDS** document. Please familiarize yourself with these standards before you start using the database.

(each haplotype's unique ID number) and **evidence levels**. Users can now also customize page views using the **Haplotype Filters** and **Column Selection** tools.

In collaboration with the PharmGKB, PharmVar is introducing **core allele definitions** (see **STANDARDS** and **READ ME** documents for details). Core alleles are highlighted by gray background and core SNVs are flagged with the PharmVar logo. Since function is believed to be the same for all alleles with the same star number, function is now displayed in the core allele line.

The Comparative Allele ViewEr (**CAVE**) tool allows graphical **comparisons of core alleles**. The user can access the CAVE tool via the Graphical View button. **Please consult the READ ME document for more information and examples before using CAVE.**

Database Overview

Slide-in window
upon clicking on a
SNV

Variant Positions		×
Reference	HGVS	
NG_008376.3		
Sequence Start	NG_008376.3:g.2617C>G	
JTS Start	NG_008376.3:g.-1584C>G	
GRCh37		
Sequence Start	NC_000022.10:g.42528382C>C	
GRCh38		
Sequence Start	NC_000022.11:g.42132375G>C	
M33388		
Sequence Start	M33388:g.36C>G	
JTS Start	M33388:g.-1584C>G	
Show Haplotypes With This Variant		
External Resources:		dbSNP:rs1080985

Variant positions for both count
modes across all RefSeqs, GRCh37
and 38

New feature
Click to view all variants with this SNV

The **Variant Positions Window** shows positions of a SNV on all reference sequences and both genome builds. A link to dbSNP is provided here. Furthermore, the user has the option to view all haplotypes containing that SNV.

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

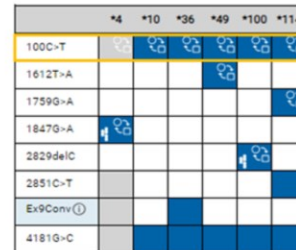
Select Haplotypes to Compare: Select All Clear All

*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	*35	*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	*66	*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	*113	*115	*114	*116	*118	*119	*120	*121

Close Compare Haplotypes

Click compare haplotypes

Comparative Allele ViewEr (CAVE)



- 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.

Select allelic variants for comparison from the **selection pad** and click the 'Compare Haplotypes' button. The **CAVE graph** displays which core SNVs are shared among alleles. Note that a core SNV of a particular haplotype may not be part of the core definition of another, but may be found on one or more suballeles. **More detailed information and examples are provided in the READ ME documents of the genes that have the CAVE feature.** We strongly encourage all users to **consult these documents before using CAVE.**

New kid on the block: *NUDT15*

PharmVar is expanding to include important non-CYP pharmacogenes

- *NUDT15* genetic information is included in the 2018 update of the CPIC guideline on thiopurine dosing recommendations
- No centralized resource for *NUDT15* to keep track of allelic variation

- Expert panel
 - First convened in April 2018
 - Reviewed known/published allelic variants
 - Assessed whether existing *names conform with PharmVar rules for haplotype designation
 - Contacted authors to submit their [published] haplotypes to PharmVar
 - Reviewed and assigned star names
 - Panel reviewed two submissions
- Published *NUDT15* nomenclature published
Yang et al, CPT 105:1091-1094, 2019, PMID [30515762](#)
- *NUDT15* gene page now posted on PharmVar

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In the works.....



- Still transitioning more *CYP* genes into the PharmVar database
- Building nomenclature for other CPIC genes including *DPYD* and *SLCO1B1*
- Implementing HGVS
- **More content and functional features down the road**
 - Convert accompanying information files to HTML
 - Cross-referencing Coriell reference materials with haplotype
 - Graphic display of structural variation
 - Online submission
 - Display of SNV frequencies
 - Sequence alignments
 - Others (suggestions are welcome)

The PharmVAR team and PharmGKB collaborators are keeping busy. The DPYD page is under construction and will go live later this year. We continue to work on additional cool features.



Thank you!

Please feel free to use any slides, but don't forget to credit PharmVar.org