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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 `0.1`

[Base URL: 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

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

Click compare haplotypes

Comparative Allele ViewEr (CAVE)

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

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PharmVar GeneFocus: CYP2D6

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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

ℹ 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	CYP2 family	CYP3 family	CYP4 family	Non-Cytochrome P450
CYP1A1	CYP2A6	CYP3A4	CYP4F2	DPYD
CYP1A2	CYP2A13	CYP3A5		NUDT15
CYP1B1	CYP2B6	CYP3A7		
	CYP2C8	CYP3A43		
	CYP2C9			
	CYP2C19			
	CYP2D6			
	CYP2E1			
	CYP2F1			
	CYP2J2			
	CYP2R1			
	CYP2S1			
	CYP2W1			

New look: PharmVar GENES page

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*

- 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	Bläisdell 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. Drogemoller 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[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[10], Teri E. Klein[2], Victoria M. Pratt[11], Stuart A. Scott[12]* and Andrea Gaedigk[13]*

CLINICAL PHARMACOLOGY & THERAPEUTICS about to be E-published

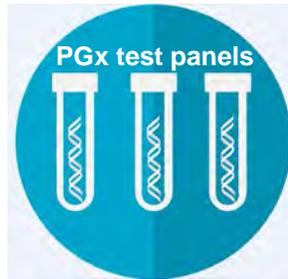**THE PharmGKB BLOG**

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*

PharmVar

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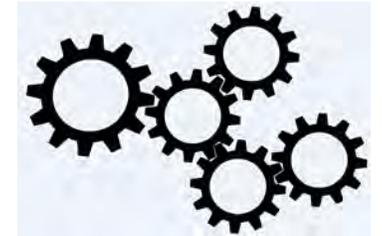
Bioinformatic tools
Facilitate diplotype calling from genotype data; essential for NGS-based testing

CPIC guidelines

Individualized Drug Therapy ADME Research

Introducing the New PGRN

Gaedigk et al (2020) CPT 107:43-46

PharmVar

Neil Miller
Scott Casey
expert panelists

PharmGKB

Teri Klein
Michelle Whirl-Carrillo
Katrin Sangkuhl