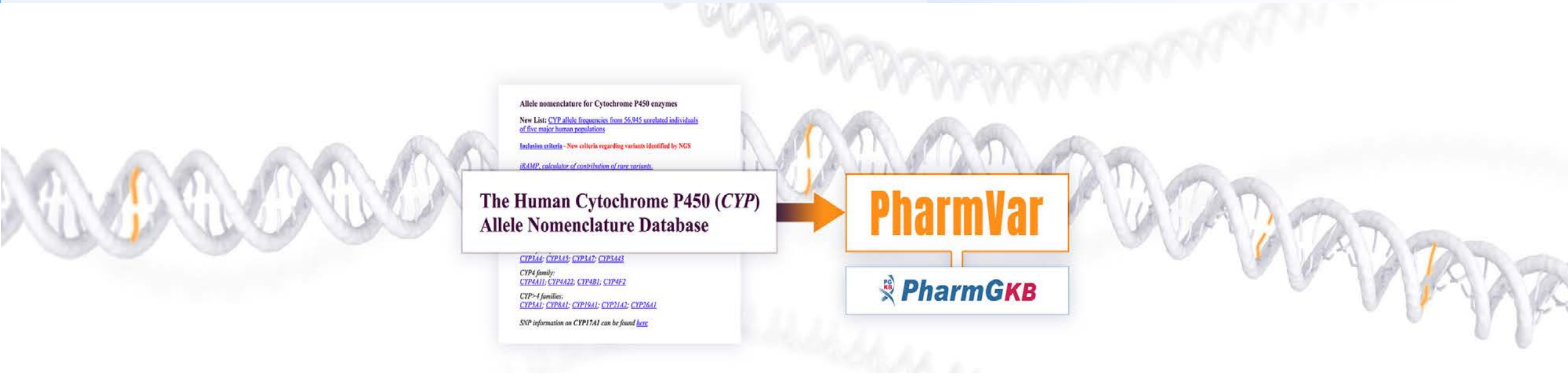
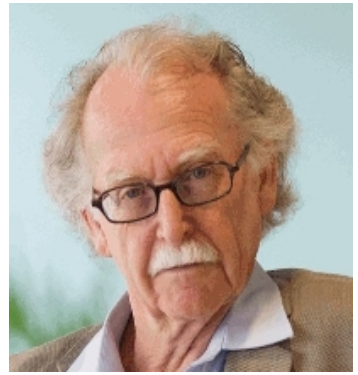
PharmVar

Pharmacogene Variation Consortium

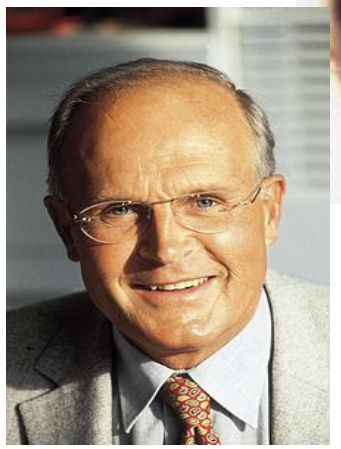


CYP Nomenclature - 1996


In order to provide the science field a 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.



CYP2D6 Nomenclature - 1996

Nomenclature for human *CYP2D6* alleles

A.K. Daly[1*], J. Brockmöller[2], F. Broly[3], M. Eichelbaum[4], W.E. Evans[5], F.J. Gonzalez[6], J.-D. Huang[7], J.R. Idle[1], M. Ingelman-Sundberg[8], T. Ishizaki[9], E. Jacqz-Aigrain[10], U.A. Meyer[11], D.W. Nebert[12], V.M. Steen[13], C.R. Wolf[14] and U.M. Zanger[4]

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

Magnus Ingelman-Sundberg[a], Ann K. Daly[b], Mikael Oscarson[a] and Daniel W. Nebert[c]

[a]Division of Molecular Toxicology, IMM, Karolinska Institutet, Stockholm, Sweden, [b]Department of Pharmacological Sciences, University of Newcastle upon Tyne, Medical School, Newcastle upon Tyne, UK and [c]Center for Environmental Genetics, and Department of Environmental Health, University of Cincinnati Medical Centre, Cincinnati, Ohio, USA

Received 15 November 1999; accepted 15 November 1999

Pharmacogenetics 10:91–93 © 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).

www.cypalleles.ki.se/ - 2002

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

Mikael Oscarson[1] and Magnus Ingelman-Sundberg[2]

[1]*Division of Pharmacology/Neurobiology, Biozentrum, University of Basel, Basel, Switzerland*
[2]*Division of Molecular Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*

Magnus Ingelman-Sundberg
Karolinska Institute, Stockholm, Sweden

CPIC®
Clinical Pharmacogenetics Implementation Consortium

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Guideline for Codeine and CYP2D6

Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers.

Update (April 2014)

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Cytochrome P450 2D6 (CYP2D6) Genotype and Codeine Therapy: 2014 Update
- 2014 supplement
  - Note: supplement was updated online at PharmGKB, August 2015
- CYP2D6 frequency table legend (R2)
- CYP2D6 frequency table (R2)

Original Publication (February 2012)

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype
- 2012 supplement
- CYP2D6 frequency table legend (R2)
- CYP2D6 frequency table

See more on PharmGKB https://www.pharmgkb.org/guideline/PA166104996

Clinical Test Reports also Use Star Nomenclature

05/27/2014 10:33 AM **Doe, Jane**

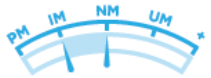
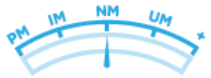
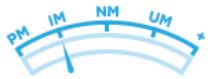
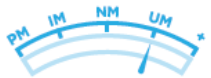
Antiplatelet Metabolism

Test Summary: Abnormal Drug Metabolism Predicted

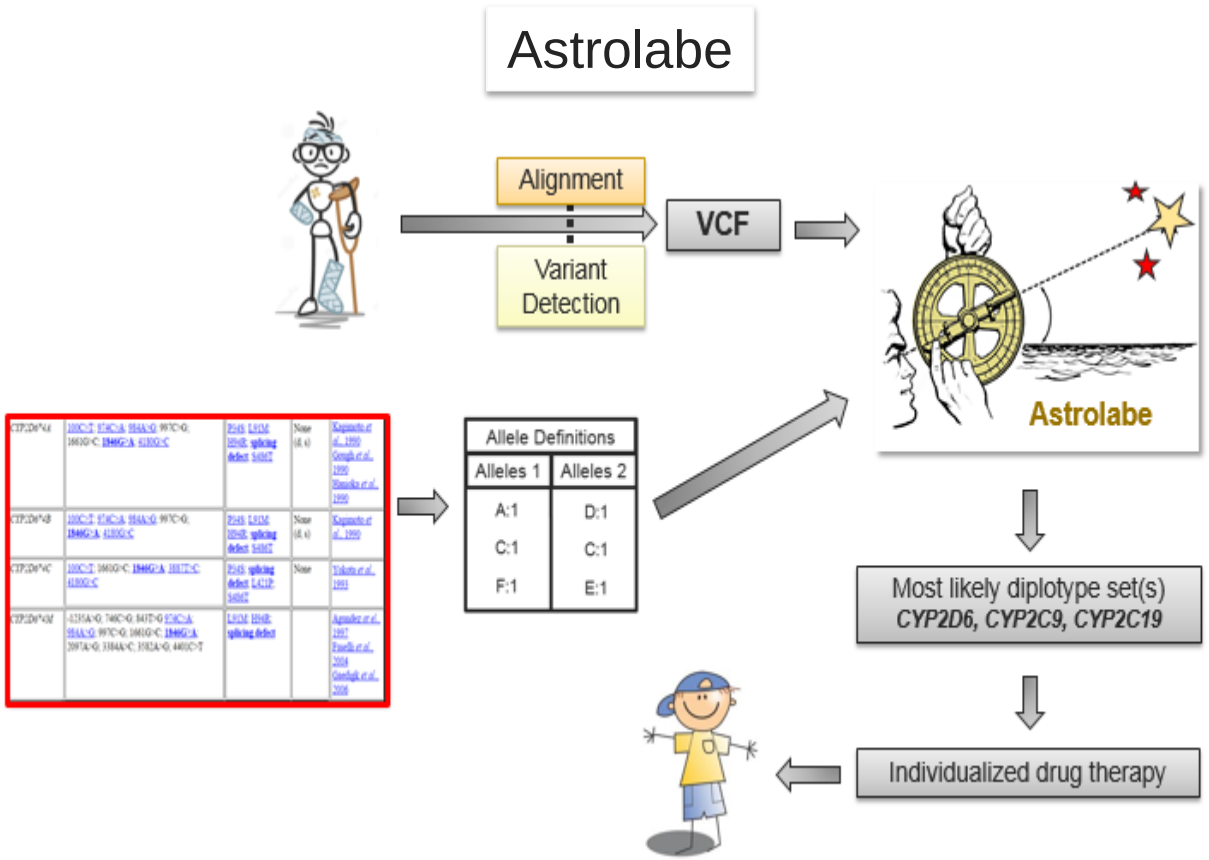
Result electronically approved and reported on by

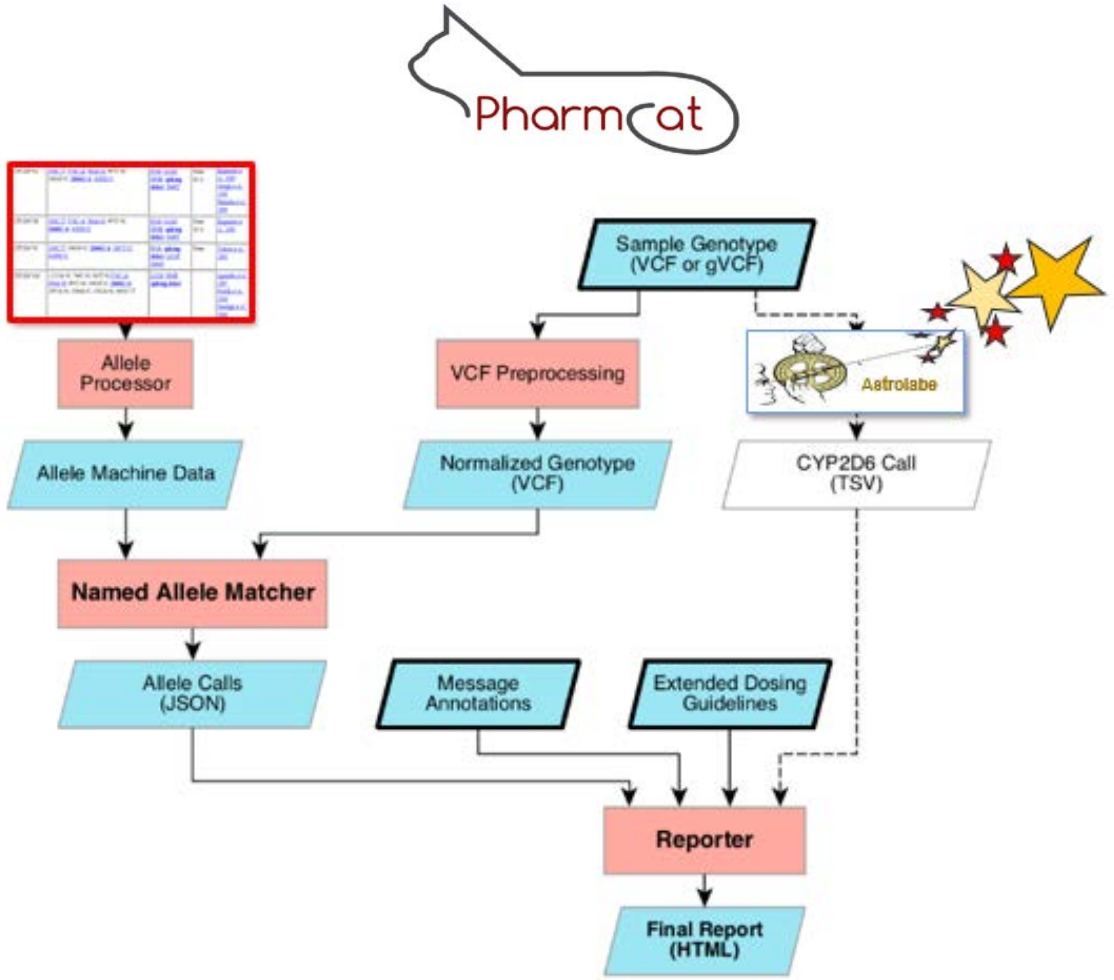
Gene	Tested Alleles	Common Genotype	Patient Genotype	Predicted Patient Phenotype
CYP2C19	*1, *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17	*1/*1	*1/*2	IM
CYP3A4	*1, *1B, *2, *3, *12, *16, *17, *22	*1/*1	*1/*1	EM
CYP3A5	*1, *1D, *2, *3A, *3B, *3C, *6, *7, *8, *9	*1/*1	*3A/*3A	IM

Genotype results

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

Tools to call genotype from NGS data





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

www.pharmgkb.org/page/pharmcat

www.cypalleles.ki.se/

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

…to the **Pharm**acogene **Var**iation (**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

PharmVar is a PGRN Resource

Home | What is PGRN? | Members | Data & Tools | PGRN Resources | News | Meetings

- Clinical Implementation
- Functional Pharmacogenes
- PGRN Hub
- PGRN-PiLS Resource
- PGRN-RIKEN
- PharmGKB
- PharmVar
- RPGEH

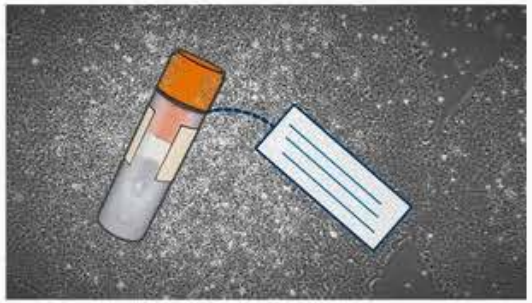
CYP database is now PharmVar.org

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

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

Learn more & become a member

RFA: Pharmacogenomics iPSC Pilot Gene Editing Service



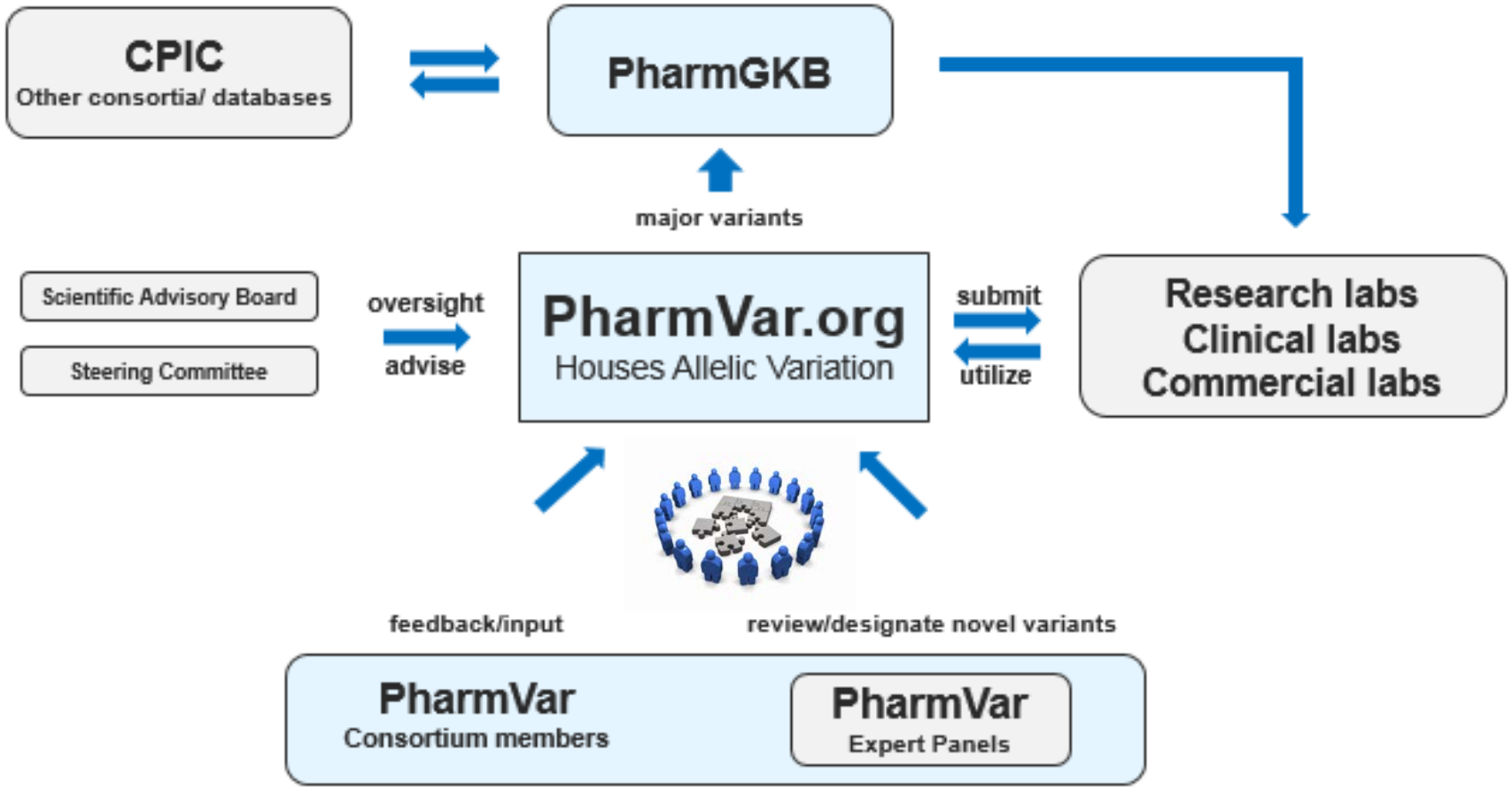
PGRN Pharmacogenomics iPSC Library and Service (PiLS), is seeking applications for pilot projects, to utilize gene edited iPSC clones for SNP validation studies for pharmacogenomics research. Three projects will be selected for service at minimal cost to the investigators.

Learn more & Apply

1R24GM123930-01

PharmVar

Pharmacogene Variation Consortium



Gene Expert Groups

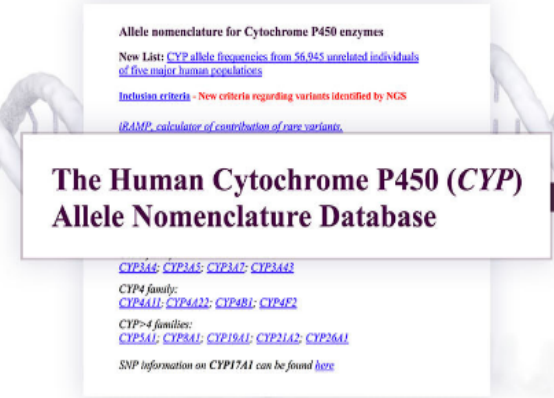
- Consist of chair and co-chair, 3-5 experts and PharmGKB representative
- Experts ideally cover research, clinical and industry
- Review submissions and recommend allele designation(s)
- Participate in PharmVar member calls

- Other tasks include
  - Review submission SOP for “their” gene(s)
  - Provide advice as gene(s) are transitioned to PharmVar db
  - Participate in publications

www.PharmVar.org

PharmVar

home | about | genes | allele designations | member | partners



The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database

PharmVar

PharmGKB

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.

The **Pharm** acogene **Var**iation (PharmVar) Consortium is the new home for PGx gene nomenclature and serves as a centralized "Next-Generation" Pharmacogene Variation data repository. After more than 15 years, the Human Cytochrome P450 (CYP) Allele Nomenclature website has been transitioned from its original location at the Karolinska Institute in Sweden to Children's Mercy in Kansas City, USA. A new interactive database is under development and will be a launched in early 2018. The first version of the PharmVar database will contain the high-priority CYP2C9, CYP2C19 and CYP2D6 genes; other P450 genes will be transferred to PharmVar within the first year of the project (once a gene is transferred into PharmVar, it will receive legacy status on the Nomenclature website). Other PGx genes including clinically actionable CPIC genes will be added in the future.

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

www.PharmVar.org

PharmVar

home | about | genes | allele designations | member | partners

The PharmVAR Consortium

The Pharmacogene Variation (PharmVar) Consortium is the new home for PGx gene nomenclature serving as a centralized 'Next-Generation' Pharmacogene Variation data repository. The major focus of PharmVar is to continue the mission of serving as the official and unified allele designation system for the global PGx 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 and will be integrated into the new PharmVar database that will launch in early 2018. The goal is to transfer all P450 genes into to the PharmVar database within the first year of the project and other high priority PGx genes, including clinically actionable CPIC genes, thereafter.

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

Additional information can be seen in this presentation

Steering Committee

- Andrea Gaedigk, PhD, Children's Mercy, Kansas City
- Steve Leeder, PharmD, PhD, Children's Mercy, Kansas City
- Neil Miller, BA, Children's Mercy, Kansas City
- Greyson Twist, MS, Children's Mercy, Kansas City
- Mark Hoffman, PhD, Children's Mercy, Kansas City
- Mike Lee, PhD, Geisinger Healthcare
- Michael Phillips, PhD, Genomics Medicine Ireland
- Vicki Pratt, PhD, Indiana University
- Magnus Ingelman-Sundberg, PhD, Karolinska Institute
- Stuart Scott, PhD, Mount Sinai
- Markus Paulmichl, MD, Austrian Institute of Technology
- Charity Nofziger, PhD, PharmGenetics GmbH
- Teri Klein, PhD, Stanford University/PharmGKB/CPIC
- Michele Whirl-Carrillo, PhD, Stanford University/PharmGKB/CPIC
- Katrin Sangkuhl, PhD, Stanford University/PharmGKB/CPIC
- Mary Relling, PharmD, St. Jude Children's Research Hospital/CPIC
- Kelly Caudle, PharmD, PhD, BCPS, St. Jude Children's Research Hospital/CPIC
- Rachel Tyndale, PhD, University of Toronto
- Meghan Chenoweth, PhD, University of Toronto

www.PharmVar.org

Submission Form

Allele definition Criteria

Membership Application Form

Membership Directory – coming soon

PharmVar Database – Key Features

- Use standardized numbering/coordinates
  - Consistent use of RefSeqs
  - Obtain Locus Reference Genomic (LRGs)
  - Need to redefine/update some variant definitions
  - Cross-reference to legacy nomenclature/numbering
- Centralized and transparent submission process
- Accept subvariants (starting with *CYP2D6*)
- Variant sequences downloadable
- Easy to use display features
- Long-term goal is to include other clinically relevant non-CYP genes

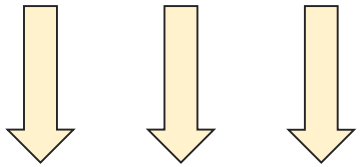
PharmVar db: Variants numbering and coordinates

Select	Reference Sequence
◉	M33388
○	GRCh37 (NC_000022.10)
○	GRCh38 (NC_000022.11)
○	NG_008376.3

Show Position From:

Sequence start ○ ATG start ◉

Haplotype	Variants
CYP2D6*1A	
CYP2D6*1B	3828G>A
CYP2D6*1C	1978C>T
CYP2D6*1D	2575C>A
CYP2D6*1E	1869T>C
CYP2D6*2A	-1584C>G, -1235A>G, -740C>T, -678G>A, 214G>C, 221C>A, 223C>G, 227T>C, 232G>C, 233A>C, 245A>G, 1661G>C, 2850C>T, 4180G>C



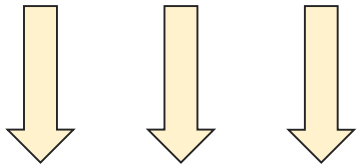
PharmVar db: Variants numbering and coordinates

Select	Reference Sequence
○	M33388
○	GRCh37 (NC_000022.10)
○	GRCh38 (NC_000022.11)
◉	NG_008376.3

Show Position From:

Sequence start ○ ATG start ◉

Haplotype	Variants
CYP2D6*1A	
CYP2D6*1B	3829G>A
CYP2D6*1C	1979C>T
CYP2D6*1D	2576C>A
CYP2D6*1E	1870T>C
CYP2D6*2A	-1584C>G, -1235A>G, -740C>T, -678G>A, 214G>C, 221C>A, 223C>G, 227T>C, 232G>C, 233A>C, 245A>G, 1662G>C, 2851C>T, 4181G>C



PharmVar db: Variants numbering and coordinates

Select	Reference Sequence
○	M33388
◉	GRCh37 (NC_000022.10)
○	GRCh38 (NC_000022.11)
○	NG_008376.3

Show Position From:

Sequence start ◉

The *CYP2D6* sequence in GRCH37 corresponds to a *2 sequence

Haplotype	Variants
CYP2D6*1A	42522312T>C, 42522613G>C, 42523003A>G, 42523209T>C, 42523409G>T, 42523943A>G, 42525132G>C, 42525952C>A, 42526049C>G, 42526484A>C, 42526549C>T, 42526561G>T, 42526562G>C, 42526567G>A, 42526571C>G, 42526573T>G, 42526580G>C, 42527471T>C, 42527533A>G, 42528034T>C, 42528382C>G
CYP2D6*1B	42522312T>C, 42522613G>C, 42522965C>T, 42523003A>G, 42523209T>C, 42523409G>T, 42523943A>G, 42525132G>C, 42525952C>A, 42526049C>G, 42526484A>C, 42526549C>T, 42526561G>T, 42526562G>C, 42526567G>A, 42526571C>G, 42526573T>G, 42526580G>C, 42527471T>C, 42527533A>G, 42528034T>C, 42528382C>G
CYP2D6*1C	42522312T>C, 42522613G>C, 42523003A>G, 42523209T>C, 42523409G>T, 42523943A>G, 42524815G>A, 42525132G>C, 42525952C>A, 42526049C>G, 42526484A>C, 42526549C>T, 42526561G>T, 42526562G>C, 42526567G>A, 42526571C>G, 42526573T>G, 42526580G>C, 42527471T>C, 42527533A>G, 42528034T>C, 42528382C>G
CYP2D6*1D	42522312T>C, 42522613G>C, 42523003A>G, 42523209T>C, 42523409G>T, 42523943A>G, 42524218G>T, 42525132G>C, 42525952C>A, 42526049C>G, 42526484A>C, 42526549C>T, 42526561G>T, 42526562G>C, 42526567G>A, 42526571C>G, 42526573T>G, 42526580G>C, 42527471T>C, 42527533A>G, 42528034T>C, 42528382C>G
CYP2D6*1E	42522312T>C, 42522613G>C, 42523003A>G, 42523209T>C, 42523409G>T, 42523943A>G, 42524924A>G, 42525132G>C, 42525952C>A, 42526049C>G, 42526484A>C, 42526549C>T, 42526561G>T, 42526562G>C, 42526567G>A, 42526571C>G, 42526573T>G, 42526580G>C, 42527471T>C, 42527533A>G, 42528034T>C, 42528382C>G
CYP2D6*2A	42522312T>C, 42523003A>G, 42523209T>C, 42523409G>T, 42525952C>A, 42526049C>G, 42526484A>C, 42528033T>C, 42528034T>C

Read Me documents

PharmVar Pharmacogene Variation Consortium | Read Me *CYP2D6*

Coordinates

Coordinates in the PharmVar database are available in reference to a number of sequences including Human Genome Assemblies GRCh37 and GRCh38, M33388 and NG_008376.3. The following table summarizes important information regarding differences among respective sequences.

sequence	notes
M33388	SNPs were annotated in reference to this sequence on the Nomenclature Website. M33388, however, contains sequencing errors (601insC, 1289-90GC>CG, 1328delG and 1440delC) shifting position numbers when compared to other sequences when the translations start site ATG is used as +1. For example, the G>A SNP defining the *CYP2D6*4* allele is at position 1846 according to M33388, but 1847 on NG_008376.3.
NG_008376.3	The *CYP2D6* Reference Sequence (RefSeq) is identical to AY545216 and matches the *CYP2D6*1* reference allele. PharmVar submissions must be annotated using the RefSeq.
LRG_303 (pending)	Locus Reference Genomic (LRG) sequence. LRGs never change once defined. The pending sequence matches the NG_008376.3 RefSeq.
GRCh37	The *CYP2D6* sequence matches the *CYP2D6*2* allele, which has multiple SNPs compared to the *CYP2D6*1* reference allele. When reporting * (star) alleles from GRCh37 comparisons, these differences need to be accounted for. For example, rs16947 (M33388 2850C>T; NG_008376.3 2851C>T) present on *CYP2D6*2* and numerous other haplotypes, is not identified as a variant when compared to GRCh37.
GRCh38	The CYP2D6 sequence matches the NG_008376.3 RefSeq.

Changes and Edits

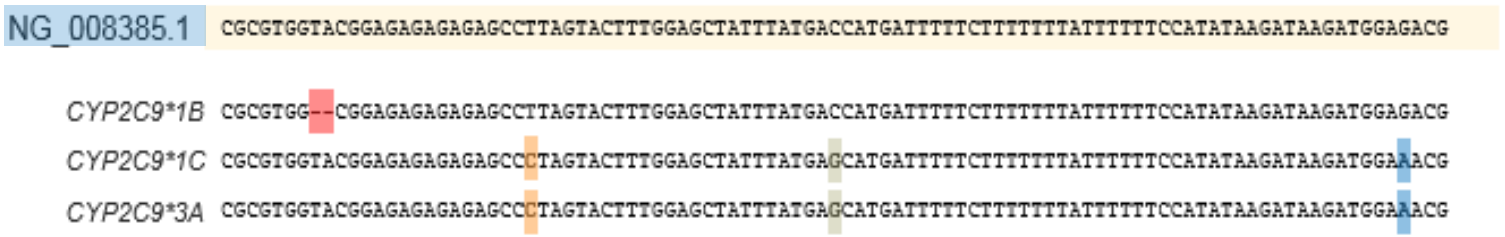
A number of changes and edits have been made to the original allele annotations to standardize annotations across genes and correct errors.

Archived legacy page	change/edit	PharmVar db positions shown in reference to M33388 to facilitate comparison to legacy page
CYP2D7 intron 1 conversion	replaced with actual changes	214G>C;221C>A;223C>G;227T>C;232G>C;233A>C;245A>G
CYP2D7 exon 9 conversion	replaced with actual changes	4124G>C;4128C>G;4131A>G;4133T>C;4155C>T;4156A>C;4158G>C;4164T>G;4166T>C;4167G>A;4168C>G;4169T>C;4172C>T; 4180G>C
CYP2D7 intron 7 onward	replaced with actual changes	3379C>T;3384A>C;3387delT;3392A>G;3478A>G;3544insA;3552C>T;3582A>G;3853G>A;4124G>C;4128C>G;4131A>G;4133T>C;4155C>T;4156A>C;4158G>C;4164T>G;4166T>C;4167G>A;4168C>G;4169T>C;4172C>T;4180G>C;4193T>C
CYP2D7 exon 8 onward	replaced with actual changes	3853G>A;4124G>C;4128C>G;4131A>G;4133T>C;4155C>T;4156A>C;4158G>C;4164T>G;4166T>C;4167G>A;4168C>G;4169T>C;4172C>T;4180G>C;4193T>C
variable number of A's in the region -1258 to -1237	removed	true number of poly-A track difficult to sequence
CYP2D7-like 3'-flanking region	removed	notes to that effect were removed
all variants beyond -1680 (-1770G>A,-1740C>T)	removed	SNVs are not part of M33388 and have not been shown to be functionally relevant

PharmVar db: Graphic displays

NG_008385.1	2361_2362del	3115T>C	3141C>G	3489G>A	3838T>C	4045G>A	47639A>C	47640T>C
*CYP2C9*1B*	●				●			
*CYP2C9*1C*					●			
*CYP2C9*3A*		●	●	●		●	●	
*CYP2C9*3B*		●	●	●	●	●	●	
*CYP2C9*4*								●

Table formats



Sequence alignments

In the works…..

The new home for PGx Variation

- Launch of PharmVar V0.5 in early 2018
- First 3 genes: *CYP2C9, 2C19* and *2D6*
- Building the membership base
- Gene expert groups to be formalized
- First submissions received – review pending


감사합니다
Natick
Grazie
Danke
Ευχαριστίες
Dalu
Obrigado
Thank You
Köszönöm
Tack
Спасибо
Dank
Gracias
谢谢
Merci
Seé
ありがとう