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.

Andrea Gaedigk, MS, PhD

Professor

Children's Mercy Research Institute, Kansas City

University of Missouri-Kansas City

Director, PharmVar

Children's Mercy KANSAS CITY | Research Institute

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PharmVar

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

What's New 3

PharmVar Publications

Articles published by PharmVar are available on the resources page.

What's new on PharmVar

NEW September 03, 2024

Database Updated to Version 6.1.5

CYP2D6

- Added one new star allele, **176*
- Added one new **1* suballele, **1.065*
- Confirmed definition of **144*

NEW August 28, 2024

Database Updated to Version 6.1.4

DPYD

- Added six intragenic deletion events: exon 4 deletion, exon 6 deletion, exon 9+10 deletion, exon 11 deletion, exon 12 deletion, and exon 14-16 deletion (listed at the bottom of the DPYD gene page)
- A new Structural Variation document is available on the *DPYD* gene page providing more information about copy number variation

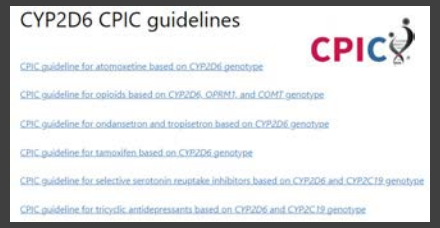
NEW June 29, 2024

Database Updated to Version 6.1.3

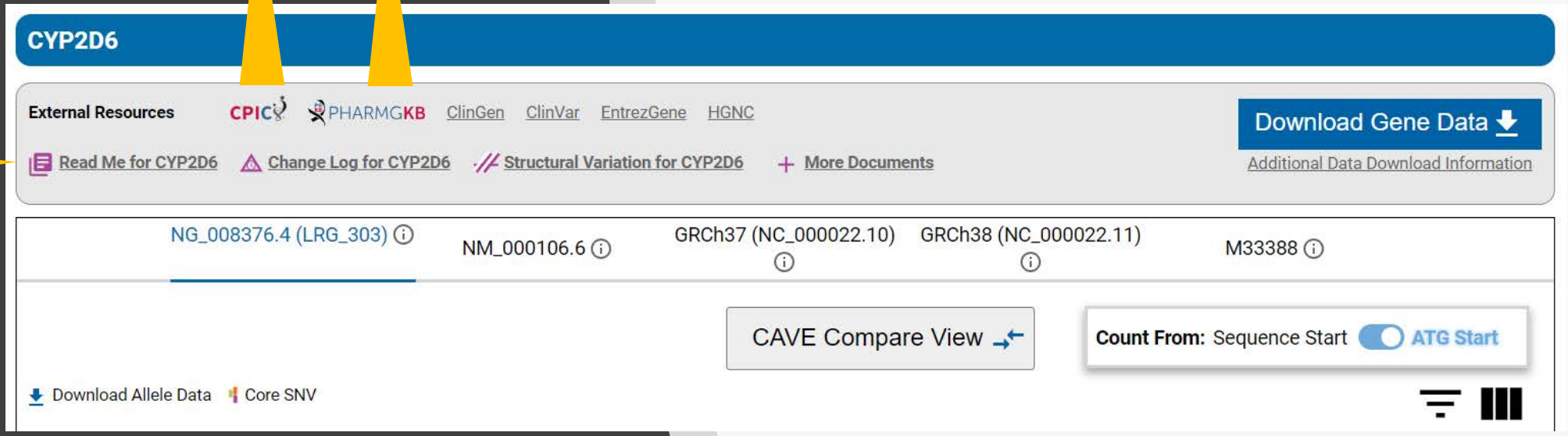
CYP2D6

- Added three novel star alleles, **173, *174* and **175*
- Added two novel suballeles, **2.034* (found as duplication) and **4.034*. In contrast to all other **4* suballeles, **4.034* is unique by having only the splice defect causing variant 1847G>A

PharmVar gene pages



RefSeq	5' limit Counting from the sequence start	5' limit Counting from the ATG translation start	3' limit Counting from the sequence start	3' limit Counting from the ATG translation start
NG_008376.4	3436	-1584	9501	4482
All SNVs within the 5' and 3' limits must be submitted for haplotype (star allele) definitions. This includes 5' flanking sequence, the 5' UTR, exons 1-9, introns 1-8, the 3' UTR, and the 3' flanking sequence.				



PharmVar

deposited by now has “year” the allele was posted

citations

CYP2D6*27		PV00451		CPIC Clinical Function →
CYP2D6*27.001	CYP2D6*27	PV00130	Def	Marez et al. 1997 Sakuyama et al. 2008 deposited by Gelineau-Morel/PharmVar Team 2024 deposited by Nofziger et al 2024
CYP2D6*27.002		PV02496	Def	deposited by Nofziger et al 2024
CYP2D6*27.003		PV02497	Def	deposited by Nofziger et al 2024

Coming: more info about depositing author(s) in Change Log document

PharmVar
Variant Frequencies

CYP2D6*10 | 100C>T (rs1065852, P34S) | 4181G>C (rs1...

Variant Positions

Gene	NG_008376.4:g.5119C>T
Transcript	NM_000106.6:c.100C>T
GRCh37	NC_000022.10:g.42526694G>A
GRCh38	NC_000022.11:g.42130692G>A

Reference Sequence	Position	Reference		Variant
NG_008376.4				
Sequence Start	5119	C	>	T
ATG Start	100	C	>	T
NM_000106.6				
Sequence Start	119	C	>	T
ATG Start	100	C	>	T
GRCh37 (NC_000022.10)				

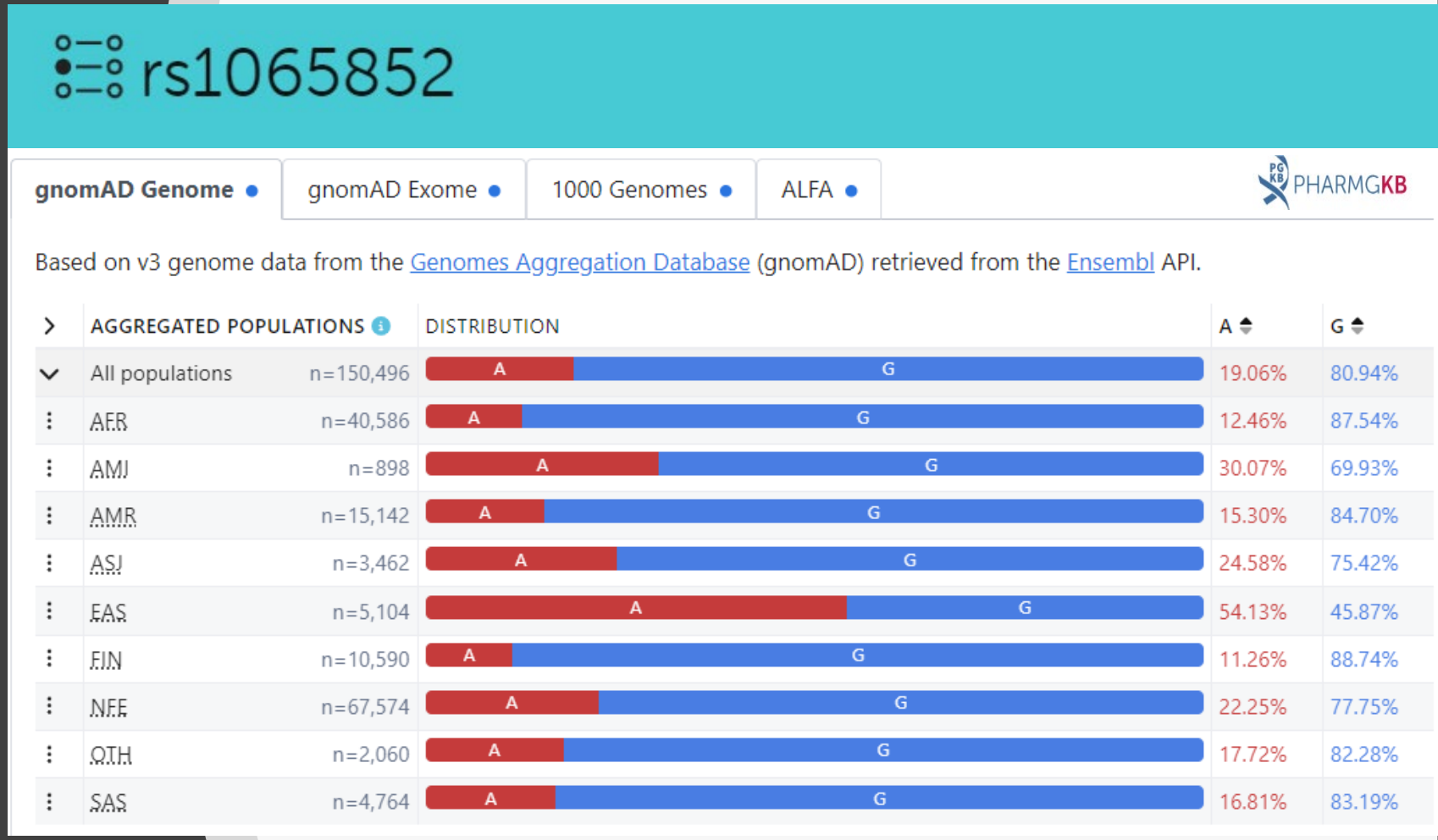
Show Haplotypes With This Variant

External Resources: dbSNP:rs1065852, PharmGKB:PA166156062, GnomAD:rs1065852

Variant Frequency: 0.212157 (GnomAD)

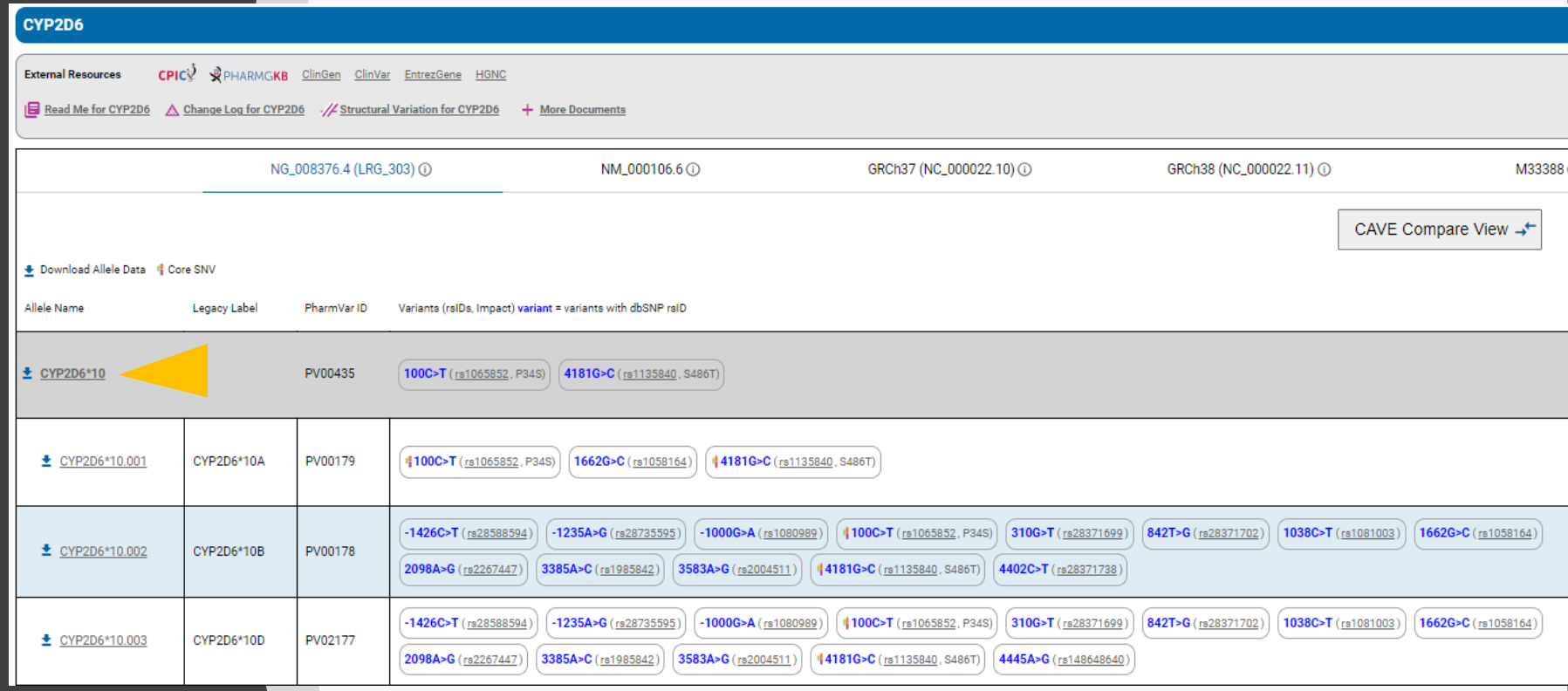
PharmVar
Variant Frequencies

link to PharmGKB variant/SNP page

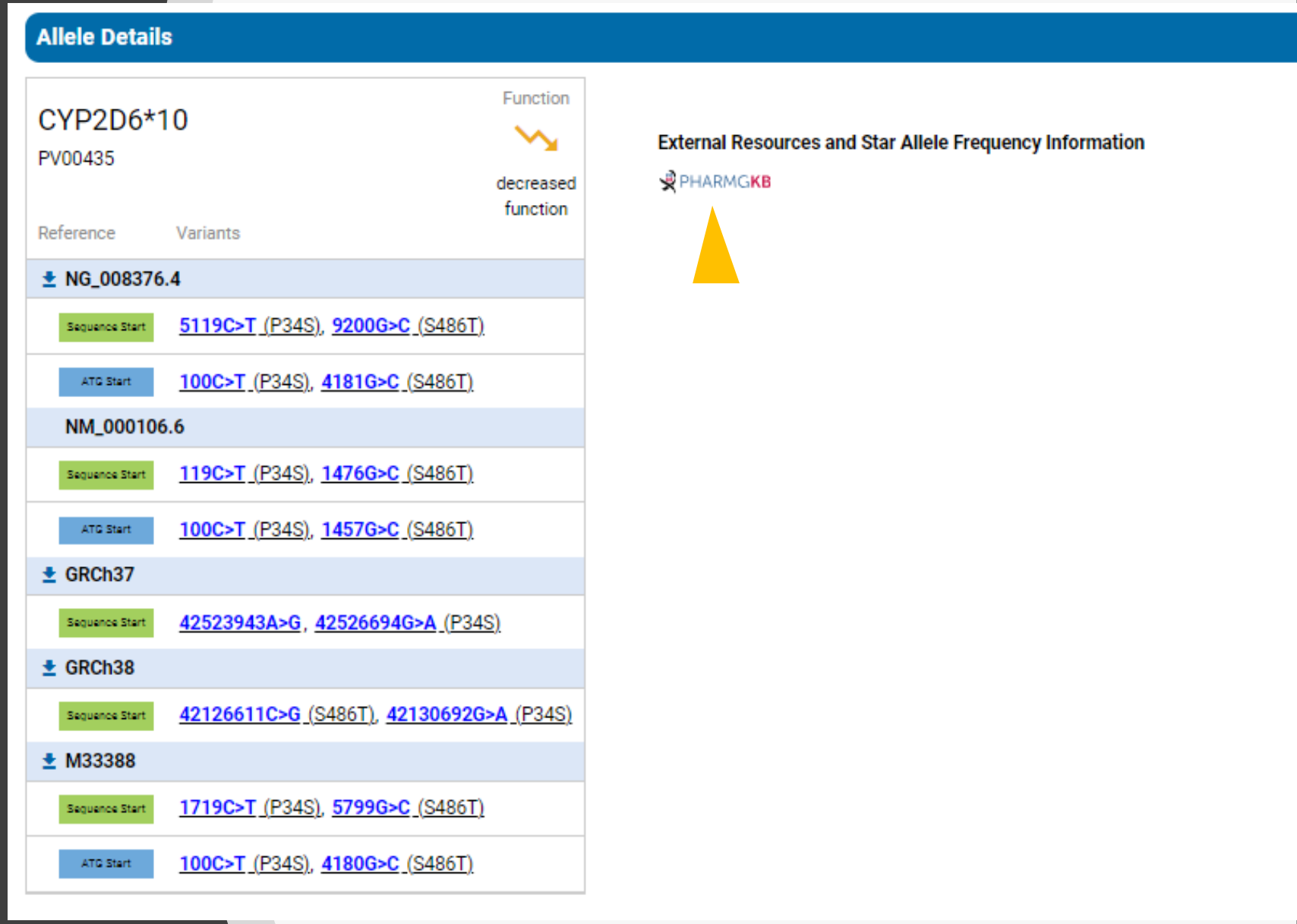


This SNP is presents the frequency of *ALL* star alleles including **4* and **10*

PharmVar
Allele Window



PharmVar
Allele Window



PharmVar Allele Window

CYP2D6*10

Frequencies

CPIC | All of Us | UK Biobank

Based on CPIC Frequency Tables.

POPULATION	CYP2D6*10 OBSERVED	ALLELES TOTAL	FREQUENCY
African American/Afro-Caribbean	777	20368	3.82%
American	127	8768	1.45%
Central/South Asian	339	4488	7.56%
East Asian	16973	39616	42.84%
European	1750	111390	1.57%
Latino	423	16098	2.63%
Near Eastern	313	4626	6.77%
Oceanian	114	1998	5.71%
Sub-Saharan African	220	4518	4.87%

DPYD

Get-RM study

Reference Materials

AMP

Clinical testing recommendations

Characterization of Reference Materials for *DPYD* – A GeT-RM Collaborative Project

Gaedigk, Turner, Moyer, Zubiaur, Boone, Wang, Broeckel and Kalman

J Mol Diag (Epub July 18, 2024)

DPYD Genotyping Recommendations: A Joint Consensus Recommendation of the AMP, ACMG, CPIC, American Pathologists, DPWG, ESPG, PharmGKV and PharmVar

Pratt, Cavallari, Fulmer, Gaedigk, Hachad, Ji, Kalman, Ly, Moyer, Scott, Turner, van Scaik, Whirl-Carrillo and Weck

J Mol Diag (Epub July 18, 2024)

DPYD

GeT-RM study revealed samples with an exon 4 and an exon 11 deletion, respectively

An exon 4 deletion has been reported in cases with 5-FU toxicity

The exon 4 deletion has been found at a frequency of 2.4% in a Finnish cohort

Other intragenic deletions have also been described in the literature

New Structural Variation document

PharmVar now lists six intragenic exon deletion events

DPYD

External Resources CPIC PHARMGKB ClinGen ClinVar EntrezGene HGNC

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

NG_008807.2 (LRG_722) | NM_000110.4

Download Allele Data

Allele Name	Legacy Label	PharmVar ID	Variants (rsIDs, Impact) variant = variants with dbSNP rsID
exon 4 del		PV02506	DPYD intragenic deletion of exon 4; see Structural Variation for DPYD
exon 6 del		PV02507	DPYD intragenic deletion of exon 6; see Structural Variation for DPYD
exon 9+10 del		PV02508	DPYD intragenic deletion of exons 9 and 10; see Structural Variation for DPYD
exon 12 del		PV02509	DPYD intragenic deletion of exon 12; see Structural Variation for DPYD
exon 14-16 del		PV02510	DPYD intragenic deletion of exons 14-16; see Structural Variation for DPYD
exon 11 del		PV02511	DPYD intragenic deletion of exon 11; see Structural Variation for DPYD

PharmVar publications

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]

Please cite!

PharmVar Tutorial on *CYP2D6* Structural Variation Testing and Recommendations on Reporting

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 114 NUMBER 6 | December 2023

Amy J. Turner[1,2], Charity Nofziger[3], Bronwyn E. Ramey[4], Reynold C. Ly[5], Chad A. Bousman[6], José A. G. Agúndez[7,8], Katrin Sangkuhl[9], Michelle Whirl-Carrillo[9], Simone Vanoni[3], Henry M. Dunnenberger[10], Gualberto Ruaño[11,12], Martin A. Kennedy[13], Michael S. Phillips[14], Houda Hachad[15], Teri E. Klein[16], Ann M. Moyer[17] and Andrea Gaedigk[18,19,*]

PharmVar GeneFocus: *CYP2A6* **Epub Jul 2024**

Alec W.R. Langlois[1,2], Meghan J. Chenoweth[1,2,3], David Twesigomwe[4], Giada Scantamburlo[5], Michelle Whirl-Carrillo[6], Katrin Sangkuhl[6], Teri E. Klein[6,7], Charity Nofziger[5], Rachel F. Tyndale[1,2,3] and Andrea Gaedigk[8,9,*]

PharmVar GeneFocus: *CYP4F2* **Epub Aug 2024**

Pablo Zubiaur[1], Cristina Rodríguez-Antona[2,3], Erin C. Boone[4], Ann K. Daly[5], Evangelia Eirini Tsermpini[6], Lubna Q. Khasawneh[7], Katrin Sangkuhl[8], Jorge Duconge[9], Mariana R. Botton[10,11], Jessica Savieo[12], Charity Nofziger[13], Michelle Whirl-Carrillo[8], Teri E. Klein[8,14] and Andrea Gaedigk[4,15,*]

PharmVar GeneFocus: *NAT2* (in preparation)

CYP2D6 this panel keeps busy…

- New star alleles, suballeles and structural variants keep coming – just posted *CYP2D6*176!*
- "Clean-up" efforts
  - Looking into alleles with limited evidence that were first defined using methods we would not accept today
    - Confirmed **27*, there are now three suballeles, one found as **27.002x2*
    - *Need to confirm *20, *23, *24, *25, *26, *30, *34, *37* and some **2, *3, *4, *6, *12, *19* suballeles
  - Concerns that some of these alleles do not exist as defined
    - Retire some alleles if no evidence can be found in the literature or databases supporting the allele in question?
  - Can we identify samples with SNV(s) of interest for reanalysis?

If you have data for alleles with a "Limited" or "Moderate" evidence level, please consider submitting to PharmVar

CYP2D6 Gene Expert Panel

Role	Name	Institution	Country
Chair	Andrea Gaedigk	Children's Mercy/PharmVar	USA
Vice Chair	Houda Hachad	AccessDx	USA
PharmVar Representative	Michael Phillips	Precision Medicine Advisers	Canada
PharmGKB/CPIC Representative	Teri Klein	Stanford, PharmGKB	USA
PharmGKB/CPIC Representative	Katrin Sangkuhl	Stanford, PharmGKB	USA
PharmGKB/CPIC Representative	Michelle Whirl-Carrillo	Stanford, PharmGKB	USA
Member	Jose Agundez	Universidad de Extremadura	Spain
Member	Chad Bousman	University of Calgary	Canada
Member	Mark Dunnenberger	NorthShore University HealthSystem	USA
Member	Martin Kennedy	University of Otago	New Zealand
Member	Reynold Ly	Nationwide Children's Hospital	USA
Member	Ann Moyer	Mayo Clinic	USA
Member	Charity Nofziger	PharmGenetix GmbH	Austria
Member	Bronwyn Ramey	Let's Get Checked	USA
Member	Gualberto Ruano	Institute of Living at Hartford Hospital	USA
Member	Amy Turner	Medical College of Wisconsin; RPRD Diagnostics, LLC	USA

***CYP2D6* expert panel**

CYP1A2 curation underway

CYP1A2 Gene Expert Panel

Role	Name	Institution	Country
Chair	Andrea Gaedigk	Children's Mercy Research Institute	USA
Vice Chair	Pablo Zubiaur	Universidad Autónoma de Madrid	Spain
PharmGKB/CPIC Representative	Michelle Whirl-Carrillo	Stanford, PharmGKB	USA
PharmGKB/CPIC Representative	Teri Klein	Stanford, PharmGKB	USA
Member	Solomon Adams	Base5	USA
Member	Matthias König	Humboldt University	Germany
Member	Dora Koller	University of Barcelona	Spain
Member	Volker Lauschke	Karolinska Institutet and Institute of Clinical Pharmacology	Sweden, Germany
Member	Martin Lewis	South Australia Health & Medical Research Institute, Adelaide	Australia
Member	Katalin Monostory	HUN-REN Research Centre for Natural Sciences	Hungary
Member	Mohamed Nagy	Children's Cancer Hospital	Egypt
Member	Amy Turner	Medical College of Wisconsin; RPRD Diagnostics, LLC	USA
Member	David Twesigomwe	Brenner Institute, University of the Witwatersrand	South Africa
Trainee	Gonzalo Villapalos-García	Hospital Universitario de La Princesa and Children's Mercy Research Institute	Spain, USA
Data Specialist	Erin Boone	Children's Mercy Research Institute	USA
Ad Hoc Member	Chad Bousman	University of Calgary	Canada

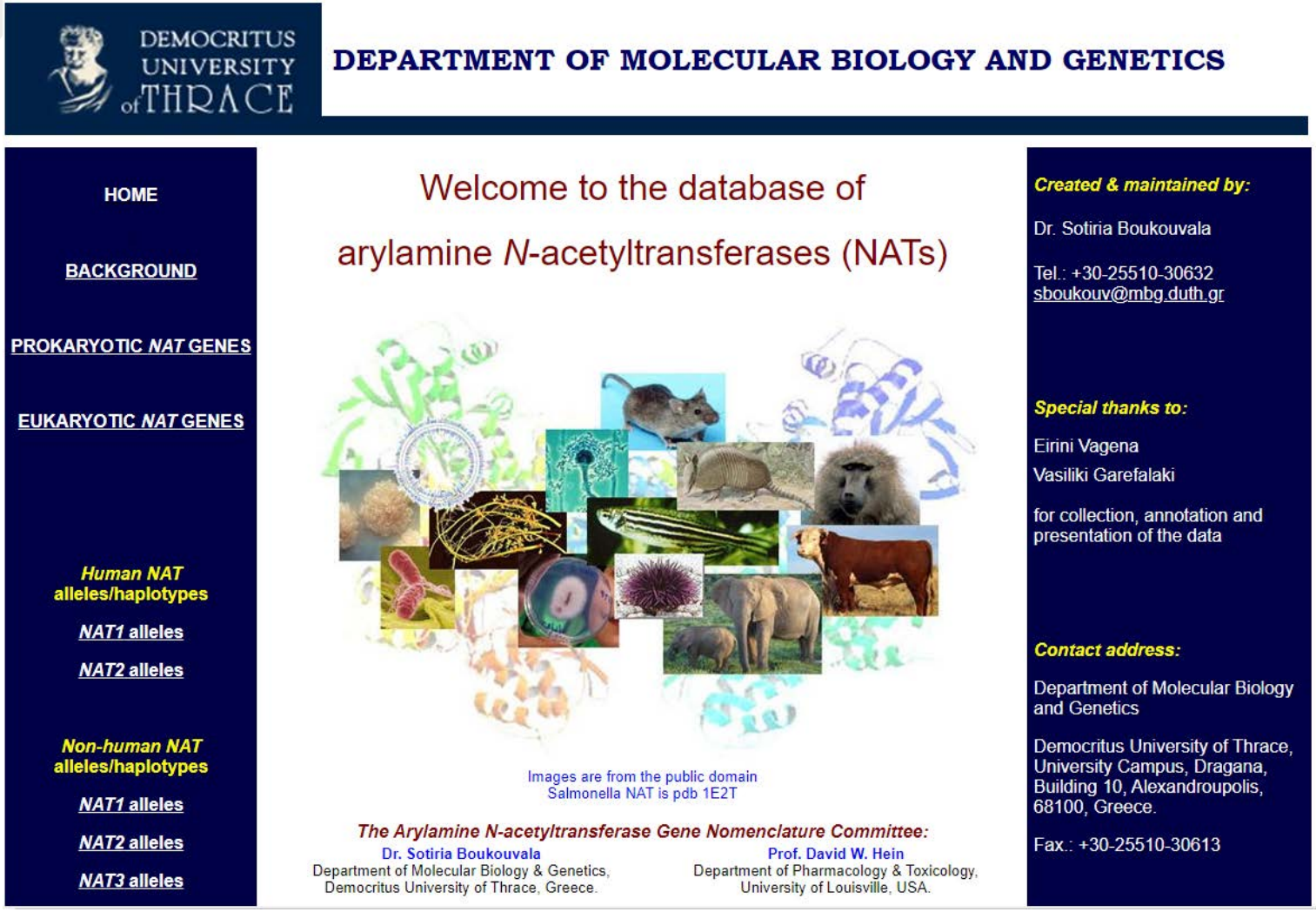
***CYP1a2* expert panel**

- No CPIC or DPWG guidelines
  - PharmGKB level 3/4
  - PharmVar Priority Level low
- Tested by many PGx panels
- Many [current] star alleles are poorly characterized
- Many common haplotypes are not defined
- **There will be major updates!**

Transition of *CYP1A2* into the PharmVar database coming soon

NAT2 was transferred from the NAT database to PharmVar!

- PharmVar *NAT2* gene page launched in March 2024
- *NAT2* “legacy” content still available at the DUTH site
- *NAT1* and non-human *NATs* will continue to be hosted by DUTH



Big “Thank You” to all who provided *NAT2* nomenclature in the past and/or served on the PharmVar expert panel to make the transition happen

NAT2
New nomenclature

used for the CPIC guideline on *NAT2* and hydralazine

- Allele definitions include the 5’ and 3’ untranslated regions
- Star allele definitions use NG_012246.1
- The “new” *NAT2*1* allele matches NG_012246.1 and GRCh38 (and the “old” **12A*)
- Used 1000 Genomes 30X WGS data to confirm existing allele definitions (and discover some new ones)
- Not all previously defined star alleles were transferred to PharmVar
- Many alleles received a new star allele number to conform with PharmVar rules

NAT2 Gene Expert Panel

Role	Name	Institution	Country
Chair	Andrea Gaedigk	Children's Mercy Research Institute	USA
Chair	Sotiria (Rea) Boukouvala	Democritus University of Thrace	Greece
PharmGKB/CPIC Representative	Michelle Whirl-Carrillo	Stanford, PharmGKB	USA
PharmGKB/CPIC Representative	Katrin Sangkuhl	Stanford, PharmGKB	USA
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Member	Jose Agundez	Universidad de Extremadura	Spain
Member	Giannoulis Fakis	Democritus University of Thrace	Greece
Member	Mariam Habil	University of Louisville	USA
Member	David Hein	University of Louisville	USA
Member	Rod Minchin	University of Queensland	Australia
Trainee	Georgia Papanikolaou	Democritus University of Thrace	Greece
Member	Estella Poloni	University of Geneva	Switzerland
Member	Adalberto Rezende Santos	Oswaldo Cruz Foundation	Brazil
Member	Raquel Teixeira	Laboratório de Biologia Molecular Aplicada a Micobactérias	Brazil
Data Specialist	Erin Boone	Children's Mercy Research Institute	USA

***NAT2* expert panel**

NAT2

Alleles not transferred

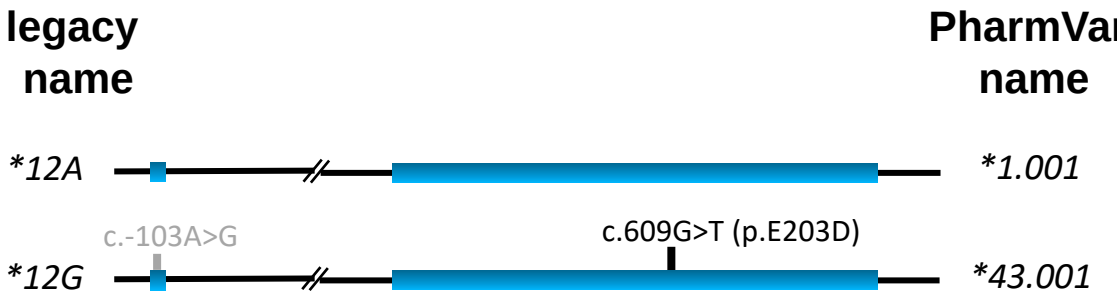
to PharmVar

- Numerous alleles defined based on computational inference
- Papers provide limited/no information about
  - about method
  - SNPs present in subjects(s) with “new” haplotype
  - Possible/alternate diplotype
  - Inferred to be present in one/few subjects
- Concerns about whether these exist
- Efforts underway by panel experts to reanalyze samples, if available
- Experts concurred that experimental validation is needed before transfer to PharmVar to ensure high-quality content of *NAT2* star alleles in PharmVar

NAT2

Renamed alleles

to conform to PharmVar rules



NAT2

Renamed alleles

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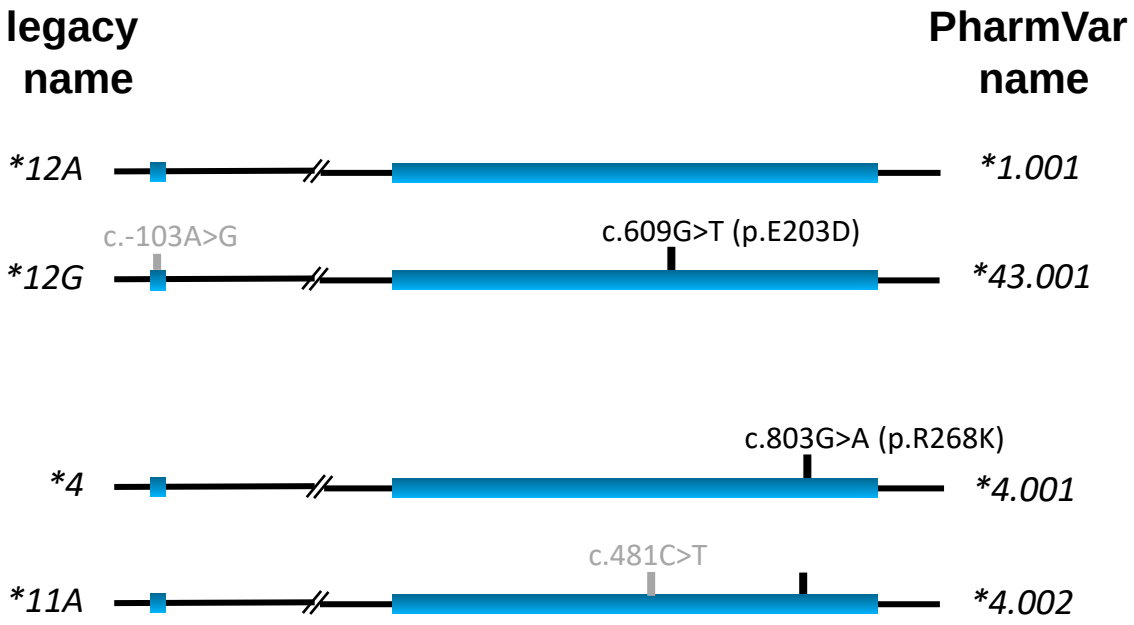
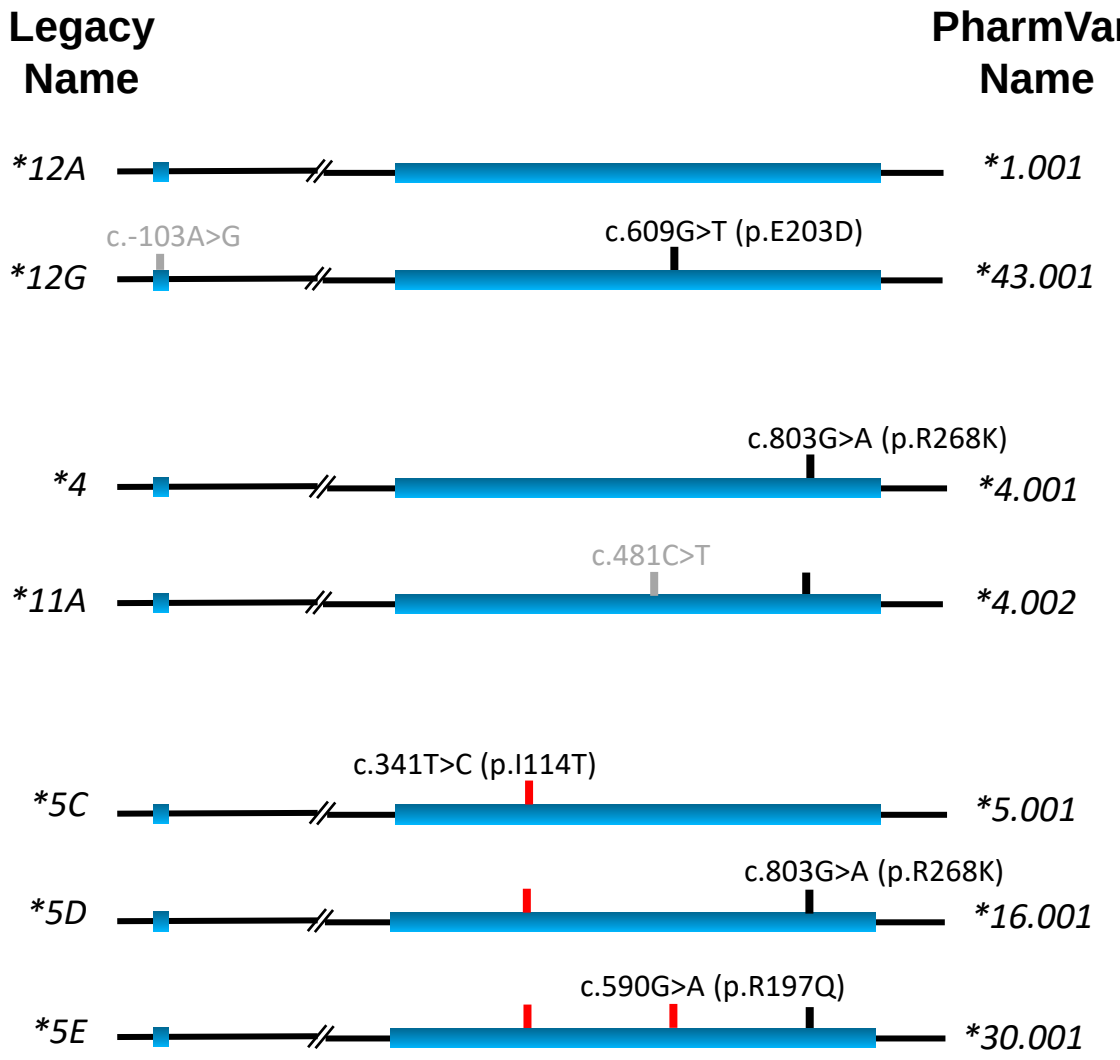


NAT2

Renamed alleles

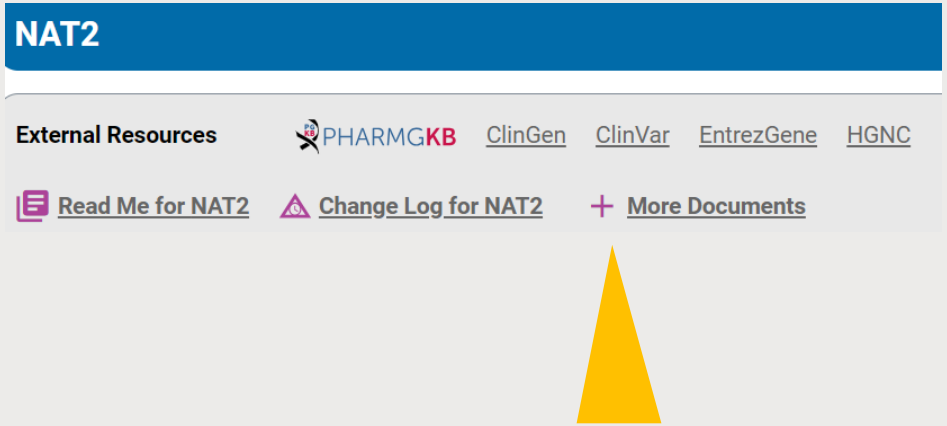
to conform to PharmVar rules



NAT2

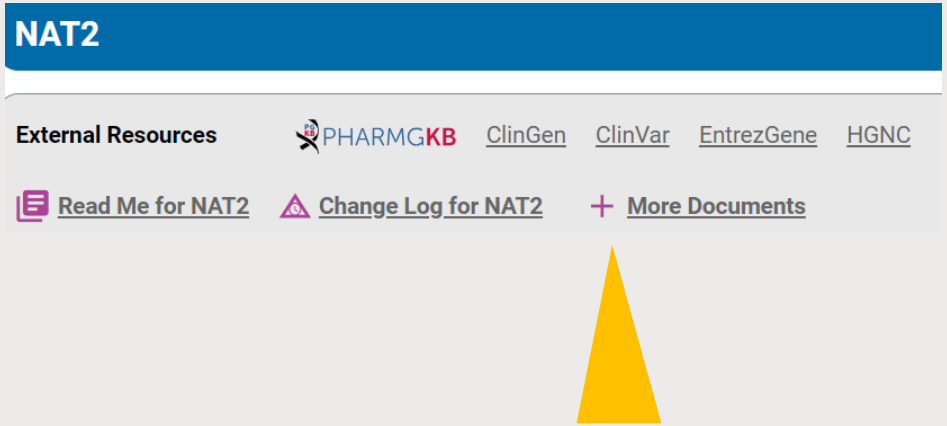
New nomenclature

Look it up!



NAT2

New nomenclature



Look-up table

Legacy name	PharmVar Name[1]	Transferred Yes/No	PharmVar data base version if transferred OR why allele was not transferred
**10*	**10.001*	yes	6.1 (March 11, 2024)
**11A*	**4.002*	yes	6.1 (March 11, 2024)
**12A*	**1.001*	yes	6.1 (March 11, 2024)
**12B*	**1.002*	yes	6.1 (March 11, 2024)
**12C*	**1.003*	yes	6.1 (March 11, 2024)
**12D*	**48.001*	yes	6.1 (March 11, 2024)
**12E*	**41.001*	yes	6.1 (March 11, 2024)
**11B*	n/a	no	allele retired from NAT nomenclature site
**12K*	n/a	no	computationally inferred; experimental evidence needed to confirm haplotype and transfer to PharmVar
**12L*	n/a	no	computationally inferred; experimental evidence needed to confirm haplotype and transfer to PharmVar
**12M*	n/a	no	computationally inferred; experimental evidence needed to confirm haplotype and transfer to PharmVar
**13B*	**13* reserved	no	evidence review in progress; if transferred, allele will keep its original star number
**13C*	n/a	no	computationally inferred; experimental evidence needed to confirm haplotype and transfer to PharmVar

NAT2

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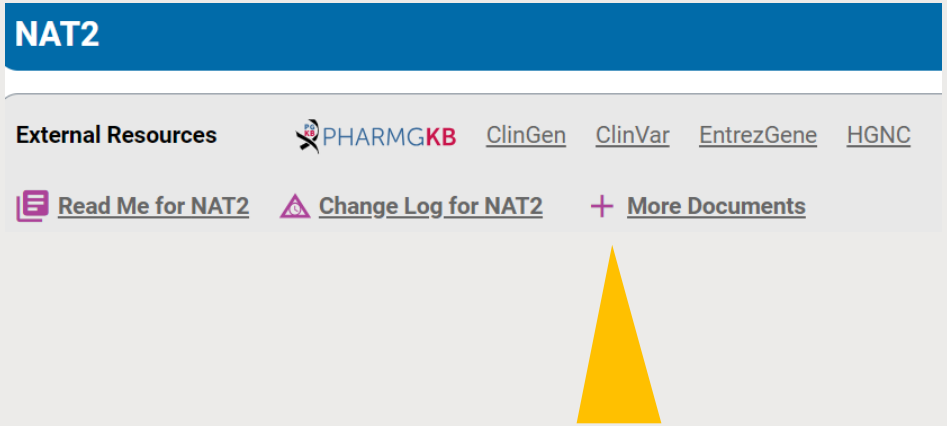

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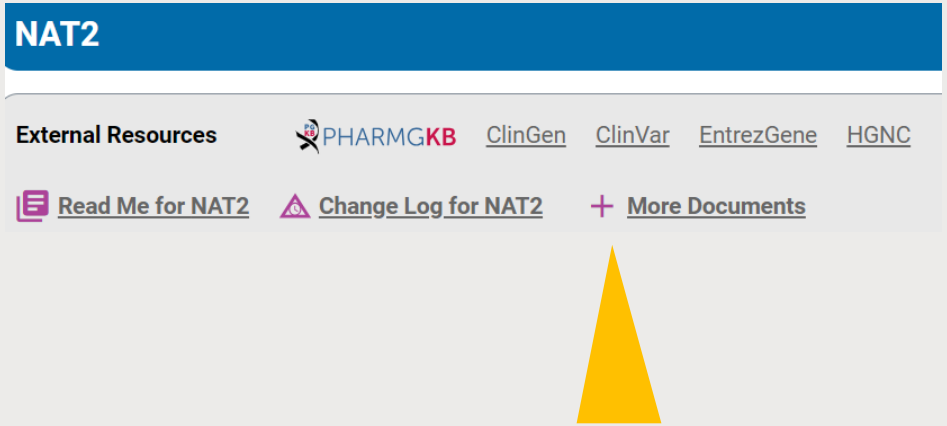

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**13C*	n/a	no	computationally inferred; experimental evidence needed to confirm haplotype and transfer to PharmVar

TPMT?
ABCG2?
VCORC1?
UGT1A1?
Other?

Can’t do this without

Gene Champions and Experts

Supported by the Children's Mercy Research Institute
NIH NIGMS R24GM123930 (2017-2021)

PharmVar

Scott Casey (website developer)
Erin Boone (data)
Wendy Wang (lab, submissions)
Expert Panelists
Submitters

PharmGKB
CPIC

Teri Klein
Michelle Whirl-Carrillo
Kelly Caudle
and all curators