

Important Information

CYP2C9 has been transitioned from the original “Nomenclature Website” (www.cypalleles.ki.se/) to PharmVar on Sept 26, 2017 (the last posted version of the CYP2C9 page is available through the ‘Archive’ link). Current gene information can be accessed through the ‘genes’ tab on the ‘menu’ bar.

A number of allelic variants may not have been sequenced for intronic flanking regions, some variants may have very limited information for up and downstream sequences and exons may not have been sequenced, but screened with other methods. Also, for many alleles, the defined haplotype is inferred. Such alleles may carry single nucleotide variants (SNVs) in exons, flanking intronic and/or up- and downstream regions that have not been captured.

Gene Region Mapped

Allele definitions contain variants positioned between -2665 and 50341 of the NG_008385.1 RefSeq. Note that new submissions will need to include sequence covering a minimum of -1800 bp of upstream (including -1766T>C) and 250 bp of downstream region. Intronic variants are not shown as part of haplotype definitions unless the variant impacts function.

Coordinates

Coordinates in the PharmVar database are available in reference to a number of sequences including Human Genome Assemblies GRCh37 and GRCh38, NG_008385.1 and NM_000771.3. The following table summarizes important information regarding differences among respective sequences.

In this ReadMe document coordinates are counted from the “A” in the ATG translation start codon as +1 for NG_008385.1 unless otherwise stated.

 **PharmVar feature:** No more counting. Get coordinates from the sequence start or the ATG start codon with one click! The default setting is NG_008385.1 counting the “A” in the ATG start codon as +1. The  buttons link out GenBank to access respective sequences.

Table 1

sequence	notes
CYP2C9	Encoded on the positive strand
NG_008385.1	The <i>CYP2C9</i> Reference Sequence (RefSeq) matches the <i>CYP2C9</i> *1 reference allele. PharmVar submissions must be annotated using the RefSeq.
LRG_1195	Locus Reference Genomic (LRG) sequence. LRGs never change once defined. The pending LRG matches NG_008385.1
NM_000771.3	transcript RefSeq
GRCh37	The <i>CYP2C9</i> sequence matches the <i>CYP2C9</i> *1 allele.
GRCh38	The <i>CYP2C9</i> sequence matches the <i>CYP2C9</i> *1 allele.

Sequence variants

Sequence variants detailed in the PharmVar database comprise single nucleotide polymorphisms (SNPs) and insertions and deletions of a single or multiple nucleotides (indels), all of which are referred to as single nucleotide variants (SNVs).

Some SNVs are unique to an allele and only occur on a single haplotype, e.g. 3608C>T is unique to the *2 haplotype. Other SNVs can occur on numerous alleles, e.g. 42614A>C is found on *3 and *18 and -1188T>C in part of numerous haplotypes including *2 and *18.

 **PharmVar feature:** By clicking on a SNV, the variation view window will slide in. This view provides SNV positions across all sequences in both count modes and the link to the NCBI dbSNP identifier (rs number; note that some SNVs may not have been allocated a dbSNP identifier). There is also a bar providing the option to display all haplotypes with the selected variant.

Core allele definitions

For many star alleles there are a growing number of so-called suballeles all sharing one or more 'key' defining sequence variant(s) (see ALLELE DESIGNATION AND EVIDENCE LEVEL CRITERIA document for details). Although suballele information is valuable for e.g. the design (sequence or SNP-panel based) and interpretation of test results, the distinction of suballeles is not necessary for phenotype prediction because **all alleles under a star number are believed to be functionally equal**. Thus, even if a test is capable of distinguishing suballeles, these are generally simply reported as e.g. *CYP2C9**2 or *8, etc.

PharmVar has developed core allele definitions in collaboration with the PharmGKB. **Only** sequence variations which change an amino acid or impact function by changing expression levels or interfere with splicing and are present in all suballeles within an allele group, are part of the **core allele definition**. With this rule-based system suballeles are collapsed into a single 'core' definition representing all suballeles categorized under a star (*) number.

Core alleles have their own unique PVID.

A core SNV is a sequence variation that is part of a core allele definition.

Core allele definitions are highlighted by a gray background in the *CYP2C9* gene page 'Table View'. Suballeles are labeled as e.g. *CYP2C9**2.001, *CYP2C9**2.002, etc. and are shown under an allele's core definition with alternating white and blue backgrounds. Function is shown in the core allele bar representing all alleles listed under that core allele definition.

For example, there are a number of *CYP2C9**2 suballeles listed. Of all the SNVs found on these suballeles, only one fulfills the rules and is shared among all suballeles namely 3608C>T (R144C). Therefore, this SNV constitutes the *CYP2C9**2 core allele definition. The *CYP2C9**2 core allele definition is shown below along all currently defined suballeles.

CYP2C9*2		PV00565	3608C>T (R144C)	decreased function
CYP2C9*2.001	CYP2C9*2A	PV00044	-1188T>C, -1096A>G, -620G>T, -485T>A, -484C>A, 3608C>T (R144C)	Deposited by Gaedigk et al. 1994, Rettie et al. 1997, Takahashi et al. 2004, King et al. 2004
CYP2C9*2.002	CYP2C9*2B	PV00046	-2663delTG, -1188T>C, -1096A>G, -620G>T, -485T>A, -484C>A, 3608C>T (R144C)	deposited by Gaedigk et al. 2004, King et al. 2004
CYP2C9*2.003	CYP2C9*2C	PV00045	-1096A>G, -620G>T, -485T>A, -484C>A, 3608C>T (R144C)	King et al. 2004
CYP2C9*2.004		PV00417	-1188T>C, -1096A>G, -620G>T, 3608C>T (R144C), 50454C>G	deposited by Campos et al.

For *CYP2C9**8, there are two SNVs that are shared among all subvariants, 1766T>C (impacting expression levels) and 3627G>A (R150H) and thus both are part of the *CYP2C9**8 core allele definition.

CYP2C9*8		PV00552	-1766T>C, 3627G>A (R150H)	possibly decreased
CYP2C9*8.001	CYP2C9*8	PV00017	-1766T>C, -1188T>C, 3627G>A (R150H), 50413C>T	deposited by Campos, Blaisdell et al. 2004, Allabi et al. 2004, Allabi et al. 2005, Liu et al. 2012
CYP2C9*8.002		PV00418	-1766T>C, -1188T>C, 3627G>A (R150H), 50413C>T, 50501C>T	deposited by Gaedigk et al.
CYP2C9*8.003		PV00416	-1766T>C, -1188T>C, 3627G>A (R150H), 50434C>T	deposited by Gaedigk et al.

 The PharmVar Comparative Allele ViewEr (CAVE)

PharmVar has developed the CAVE tool to easily compare core alleles, visualize which core SNVs are present in alleles of interest and to identify SNVs that are unique to selected alleles.

To access CAVE switch from Table View to Compare View



A sequence variation that is part of a core allele definition may be unique or occur in two or more core alleles. It may, however, also be found in some other suballeles. In contrast, some non-core SNVs may be unique and can tentatively be utilized to identify an allele of interest or discriminate it from others. As mentioned above, the CAVE tool uses core allele definitions, and hence unique SNVs that are not part of any core definition are not displayed.

One prime example is 3608C>T (R144C) which is part of the *CYP2C9**2 and *35 definitions. Therefore, to accurately discriminate these alleles from each other, additional SNVs must be tested and interpreted together.

Examples:

Select core alleles for comparison in the **selection pad**. To illustrate the example given above and show how these compare with other core alleles we have selected *CYP2C9**2, *3, *8, *18, *35 and *36.

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	*16	*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									

[Close](#) [Compare Haplotypes](#)

 Click compare haplotypes

CAVE graphically displays the core SNVs that are found in the selected alleles

- 3608C>T (R144C) is shown in **blue** for *2 and *35 indicating that it is part of their respective core allele definitions (highlighted by yellow frame). In order to discriminate these two alleles, 3552G>T, a SNV unique for *35 must be interrogated.
- Similarly, 4261A>C is shown in **blue** for *3 and *18 indicating that it is part of their respective core allele definitions (highlighted by orange frame). In order to discriminate these two alleles, 4739A>C, a SNV unique for *18 must be interrogated.

	*2	*3	*8	*18	*35	*36
-1766T>C						
1A>G						
3552G>T						
3608C>T						
3627G>A						
4261A>C						
4739A>C						

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

Function

The function of an allele is shown according to the information curated by the PharmGKB and Clinical Pharmacogenetic Implementation Consortium (CPIC) available at <https://www.pharmgkb.org/page/cyp2c9RefMaterials>. Allele functionality tables are created as part of a more formalized CPIC guideline process and are periodically updated. Additional information may have become available since the functionality table has been created. For some alleles, the assigned activity may differ from that shown on the archived Nomenclature pages. Extrapolation of the activity of a particular allele to particular substrates should be done with caution due to potential unknown substrate-specific activities of the allele.

References

The references provided in the PharmVar database include the citation in which an allele was first published. For some alleles additional reference(s) describe important updates and/or function. The reference list is not intended to provide a complete bibliography for an allele. Haplotypes not published elsewhere are listed as “deposited by”.

Allele frequencies

CYP2C9 allele frequency tables have been developed for CPIC guidelines and are available through the PharmGKB at <https://www.pharmgkb.org/page/cyp2c9RefMaterials>. A comprehensive list of frequencies and references can be found in the CYP2C9 allele frequency Table in the source tab. These tables are periodically updated.

Changes and Edits

A number of changes and edits have been made to the annotations on the original P450 Nomenclature site to standardize annotations across genes and correct errors. Please see the **CHANGE Log** document for details.