**Important Information**

*SLCO1B1 is the first drug transporter gene introduced to PharmVar. Current gene information can be accessed through the ‘genes’ tab on the ‘menu’ bar.*

In the absence of a centralized resource for *SLCO1B1* nomenclature, a star allele number may have been self-assigned by authors when an allele was first published. Not all published alleles were named, however. PharmVar is now providing nomenclature for this important pharmacogene. Published haplotypes/star alleles were systematically assessed and updated and/or revised per PharmVar allele definition criteria. Please see the [Change Log](#) document for more information.

Some of the defined alleles may not have been fully sequenced over the entire region PharmVar requires for allele definition or have only been screened for selected single nucleotide variants (SNVs) of interest. Such alleles may have additional SNVs that may alter function. There are also several fully sequenced alleles, for which only nonsynonymous SNVs have been reported; these alleles may thus harbor SNVs in addition to those listed. Each allele has been assigned a ‘haplotype evidence level’ to indicate whether the listed haplotype is based on limited (Lim), moderate (Mod) or definitive (Def) information. Please see “[Allele Designation Criteria and Evidence Level](#)” for details and examples.

**Gene Region Mapped**

*SLCO1B1* allele definitions contain exons 2-15 and 250 bp of the 3’ UTR. Note that exon 1 is untranslated (is part of the 5’UTR) - the ATG start codon is located in exon 2. Thus, haplotype definitions do not contain ‘upstream’ regions. PharmVar submissions must include sequence covering these regions. 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 several sequences including Human Genome Assemblies GRCh37 and GRCh38, NG_011745.1 and NM_006446.5. **Table 1** summarizes important information regarding these reference sequences.

In this ReadMe document coordinates are counted from the “A” in the ATG translation start codon as +1 for NM_006446.5 unless otherwise stated.

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**PharmVar Feature:** Get coordinates from the sequence start or the ATG start codon with one click! The default setting is NG_011745.1 counting the “A” in the ATG start codon as +1. The info buttons link out to GenBank to access respective sequences.
Table 1

<table>
<thead>
<tr>
<th>sequence</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLCO1B1</strong></td>
<td>Encoded on the positive strand</td>
</tr>
<tr>
<td>NG_011745.1</td>
<td>Genomic RefSeq&lt;br&gt;This sequence matches SLCO1B1*1&lt;br&gt;&lt;strong&gt;PharmVar submissions must be annotated using this RefSeq**</td>
</tr>
<tr>
<td>LRG_1022</td>
<td>Locus Reference Genomic (LRG) sequence. LRGs never change once defined.&lt;br&gt;The LRG matches NG_011745.1</td>
</tr>
<tr>
<td>NM_006446.5</td>
<td>transcript RefSeq&lt;br&gt;The MANE Select represents the gene’s transcript that is representative of biology, well-supported, expressed and is highly conserved. This transcript matches GRCh38 and is 100% identical with its RefSeq for 5’UTR, CDS, splicing and 3’UTR</td>
</tr>
<tr>
<td>GRCh37</td>
<td>The SLCO1B1 sequence matches the SLCO1B1*1 allele</td>
</tr>
<tr>
<td>GRCh38</td>
<td>The SLCO1B1 sequence matches the SLCO1B1*1 allele</td>
</tr>
</tbody>
</table>

**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) to which PharmVar collectively refers to as single nucleotide variants, or SNVs.

Some SNVs are unique to an allele and only occur on a single haplotype, e.g., c.1058T>C (p.I353T) is unique to the SLCO1B1*6 haplotype. Other SNVs can occur on several alleles, e.g., c.521T>C (p.V174A) is found on SLCO1B1*5, *15, *40, *46 and *47 and c.217T>C (p.F73L) is part of the *2 and *12 allele definitions. Indeed, many SNVs are found on numerous star alleles. An additional example is c.388A>G (p.N130D) which is also present on numerous haplotypes.

**Variation View**

By clicking on a SNV, the variation view window will slide in (the example shows c.521T>C). This view provides SNV positions across all sequences, the link to the NCBI dbSNP identifier (rs number; note that some SNVs may not have been allocated a dbSNP identifier) as well as SNV frequency. There is also a bar providing the option to display all haplotypes with the selected variant.
The top portion of the variation window displays SNV coordinates according to Human Gene Variation Society (HGVS) nomenclature on the gene, transcript and genome (GRCh37 and GRCh38) levels. Coordinates are displayed as obtained through the NCBI Variation Services and are only manually curated if no results are returned. For additional details on HGVS nomenclature see https://varnomen.hgvs.org/recommendations/DNA/.

The middle portion of the variation window displays SNV positions ‘PharmVar-style’ on the gene, transcript and genome (GRCh37 and GRCh38) levels giving positions for both count modes and detailing the reference and variant nucleotides.

Note that PharmVar consistently uses the 3’ Rule to determine the positions of inserted or deleted nucleotide(s). HGVS and ‘PharmVar-style’ positions may differ for indels in some instances which is most likely explained by differences in sequence alignments. Also, PharmVar displays single nucleotide insertions as ‘ins’ while HGVS displays them as duplications or ‘dup’. Additional details and examples are provided under ‘Standards’ at https://www.pharmvar.org/genes.

The bottom portion of the variation window provides a filter option to display all variants with the selected SNV, the link to dbSNP (if rs exists for SNV), as well as SNV frequency information.

🎉 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 Criteria and Evidence Level” for details). Although suballele information is valuable, for example test design (sequence or SNV-panel based) and the interpretation of test results, the distinction of suballeles is not necessary for phenotype prediction because all alleles under a star number are assumed to be functionally equivalent. Thus, even if a test is capable of distinguishing suballeles, these are generally simply reported as e.g., SLCO1B1*1, *14 or *15.
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 grey background on the SLCO1B1 gene page ‘Table View’. Suballeles are labeled as e.g., SLCO1B1*1.001, SLCO1B1*5.001, etc. and are shown under an allele’s core definition with alternating white and blue backgrounds. CPIC clinical allele function is shown in the core allele bar representing all alleles listed under that core allele definition.

The common SLCO1B1*5 allele has a single core SNV, c.521T>C (p.V174A) and only one defined suballele, SLCO1B1*5.001.

In contrast, for SLCO1B1*15 there are two suballeles listed to date. Of all the SNVs found on these suballeles, two qualify as core SNVs, c.388A>G (p.N130D) and c.521T>C (p.V174A). Therefore, these SNVs constitute the SLCO1B1*15 core allele definition as shown below.

SLCO1B1*25 is an example of all variants of the haplotype being core SNVs
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 c.521T>C (p.V174A) which is part of the $SLCO1B1^*5, *15, *40, *46, and *47$ allele definitions. Therefore, to accurately discriminate these alleles from each other, additional SNVs must be tested and interpreted together.

Examples:

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

- c.521T>C (p.V174A) is shown in blue for *5, *15, *40, *46 and *47 indicating that it is part of their respective core allele definitions (highlighted by orange frame). Since *5 and *15 are believed to be functionally similar, these alleles may not need to be discriminated; to determine whether a *40 allele (no function) is present, c.1929A>C (p.L643F) must be tested; the latter, however, is also present in *19 and *20 (highlighted by yellow frame) highlighting the complexity and challenges of star allele calling. C.521T>C is shown with the function symbol indicating that this variant has altered function.

- c.388A>G (p.N130D) is shown in blue for SLCO1B1*14, *15, *20, *37, *39, *46 and *47. This variant does not appear to alter function in a clinically meaningful way, and therefore does not have the PharmVar function symbol. This variant is present on numerous alleles including, but not limited to those selected for illustration. The SLCO1B1*4 and *14 core allele definitions only differ by c.388A>G and unless tested, *14 alleles are defaulted as *4. Likewise, without testing for c.388A>G, SLCO1B1*15 is defaulted as *5 and *37 is defaulted as *1.

- In contrast, c.481+1 (splice defect), c.757C>T (p.R253X) and c.1007C>G (p.P336R) are unique core SNVs for SLCO1B1*41, and *39 and *47, respectively, as indicated by the PharmVar symbol. In addition, c.481+1 (splice defect) and c.757C>T (p.R253X) are predicted to impact function and are thus shown with the function symbol.

- Also, SLCO1B1*45 (not shown in Figure above) and *46 share c.1738C>T which introduces a stop codon (p.R580X). The latter also has c.521T>C (p.V174A) which is found on several other alleles as described above. It is uncertain at this time to which
degree the premature stop codon (p.R580X) impacts function and therefore, activity of \textit{SLCO1B1}*45 and *46 may not be equivalent.

**Variant Groupings**

This feature allows PharmVar to display amino acid changes that are caused by two SNVs or a series of SNVs within a defined region that cause multiple amino acid changes.

There are no examples for this feature for \textit{SLCO1B1}.

**Function**

The function of an allele is shown according to the information curated by the PharmGKB and Clinical Pharmacogenetics Implementation Consortium (CPIC) available at [https://www.pharmgkb.org/page/slco1b1RefMaterials](https://www.pharmgkb.org/page/slco1b1RefMaterials).

‘CPIC Clinical Function’ denotes clinical allele function assignments.

It is noted that an allele’s CPIC clinical allele function may differ from its biochemical function. Examples are \textit{SLCO1B1}*5 and *15 which are classified by CPIC as ‘no function’ alleles; these alleles do retain some measurable function in vitro, however, compared to the *1 reference and may therefore be classified biochemically as decreased function.

Allele functionality tables are created following the CPIC Pharmacogene Curation SOP which is part of the CPIC guideline process; this table is periodically updated. Additional information may have become available since the functionality table has been created. Extrapolation of the function of a particular allele to particular substrates should be done with caution due to potential unknown substrate-specific function of the allele.

**Allele Frequencies**

\textit{SLCO1B1} allele frequency tables have been developed for CPIC guidelines and are available through the PharmGKB at [https://www.pharmgkb.org/page/slco1b1RefMaterials](https://www.pharmgkb.org/page/slco1b1RefMaterials). A comprehensive list of frequencies including population-specific information and references can be found in the \textit{SLCO1B1} allele frequency Table in the ‘references’ tab. These tables are periodically updated.
Variant Frequencies

PharmVar displays the frequency of a sequence variation in the **Variation Window** next to its link to dbSNP. The frequency of the SNV is provided for the GnomAD database ([https://gnomad.broadinstitute.org/](https://gnomad.broadinstitute.org/)) and the 1000 Genomes Project ([https://www.internationalgenome.org/](https://www.internationalgenome.org/)). In some cases, information may only be available for one or the other or neither. These frequencies represent the global frequency of the SNV in each of these databases.

For example, the **Variation Window** for  c.521T>C (p.V174A) indicates that the frequency of this SNV is 0.121061 (12.11%) in the GnomAD and 0.0877 (8.77%) in the 1000 Genomes Project.

Of note: the frequency of the variant DOES NOT necessarily correspond to that of a particular haplotype (or star allele) as exemplified by c.521T>C (p.V174A). As shown above, this SNV is part of several haplotypes, **SLCO1B1*5, *15, *40, *46 and *47**. Thus, the frequency of c.521T>C represents the cumulative frequency of these haplotypes.

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 supporting the haplotype. The reference list is not intended to provide a complete bibliography for an allele. Haplotypes not published elsewhere are listed as “deposited by”.

Changes and Corrections

Several changes and edits have been made to a number of previously published haplotypes to standardize annotations per PharmVar rules, correct errors and/or complement them with additional new information. These and all other changes made after the launch of the gene page are detailed in the **Change Log** document.