Pharmacogene Variation Consortium Gene Introduction: _NUDT15_

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The Pharmacogene Variation (PharmVar) Consortium is the successor of the Human Cytochrome P450 (_CYP_) Allele Nomenclature website that served the pharmacogenetics community by designating _CYP_ star (*) alleles. The aim of PharmVar is to continue the mission of serving as an official allele designation authority for the global pharmacogenetics community.[1] Herein, we describe the introduction of the first non-_CYP_ gene to PharmVar. Pharmacogenetic variation of _NUDT15_ plays a significant role in thiopurine response variability and toxicity.

THE _NUDT15_ GENE

NUDT15 is a member of a large phosphatase protein family that shares a common NUDIX catalytic domain and metabolizes a wide range of nucleotide substrates (**Table 1**). Originally characterized as a pyrophosphatase, NUDT15 converts oxidized GTP to its monophosphate form, preventing the integration of the damaged purine nucleotides into DNA and subsequent mismatch repair. However, 8-oxo-GTP is a weak substrate for NUDT15 compared with its main metabolizer NUDT1; thus, the physiological functions of NUDT15 remain unclear. NUDT15 has been linked to xenobiotic drug metabolism in genome-wide association studies of drug toxicity, and subsequent mechanistic studies have demonstrated that it plays a key role in the conversion of the active thiopurine metabolite thioguanosine triphosphate to thioguanosine monophosphate.[2] _NUDT15_ variants encoding no or severely decreased function predispose patients to excessive thiopurine activation and hematopoietic toxicities when receiving this class of drugs for either benign (e.g., inflammatory bowel diseases) or malignant (e.g., acute lymphoblastic leukemia) conditions. Given the compelling underlying biology and clinical relevance of this pharmacogenetic association, there is a growing interest in preemptive _NUDT15_-guided thiopurine dosing to avoid severe adverse events. The importance of including _NUDT15_ genetic information in dosing recommendations for preventing thiopurine toxicity is further evidenced by the updated Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline on _TPMT_-guided thiopurine dosing recommendation that includes _NUDT15_ in addition to _TPMT_.[3]

The initial genome-wide studies associated only a single nonsynonymous single-nucleotide polymorphism in exon 3 of _NUDT15_ with thiopurine toxicity.[4] There is, however, growing evidence that additional functional variants exist. A total of 16 coding region variants have been reported to date (**Figure 1**), most of which affect function and/or thermal stability of the NUDT15 protein. On the basis of NUDT15 pyrophosphatase activity with thioguanosine triphosphate as the substrate, haplotypes containing p.R139C (c.414C>T, _rs116855232_) or the p.G17_V18del (c.55_56insGAGTCG, _rs869320766_) variant showed a severe decrease in activity[2] and were thus classified as "no function" alleles by CPIC.[3]

There are substantial racial and ethnic differences in the population frequencies of _NUDT15_ variants. For example, alleles containing p.R139C (_NUDT15*2_ and _NUDT153_) are predominantly found among Asians, but have also been detected in US Hispanics, especially those with high Native American ancestry. In contrast, the allele containing a five-nucleotide deletion in exon 1 (_NUDT15*9_) is almost exclusively found in patients with European ancestry.[4]

WHY NOMENCLATURE IS NEEDED

Clinical pharmacogenetic testing can be performed by numerous platforms and approaches, including targeted genotyping, sequencing, and array-based technologies. Molecular genetic testing results typically use the Human Genome Variation Society (HGVS) nomenclature system for reporting sequence variants and the International System for Human Cytogenetic Nomenclature system for reporting copy number variants. Although haplotype nomenclature is available within the HGVS framework, results of pharmacogenetic testing for genes involved in drug metabolism, such as _CYPs_, are most commonly reported using the star allele (*) nomenclature system. In addition to the identified variants and/or haplotypes, the interpretation of these results includes variant

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allele function and inferred phenotype, which can vary between testing laboratories. As such, it is imperative to establish clearly defined haplotype nomenclature as new pharmacogenes are discovered and subsequently offered by clinical testing laboratories and included in dosing guidelines.

Because of its pivotal role in thiopurine metabolism, clinical laboratories will likely incorporate preemptive *NUDT15* genotyping in concert with *TPMT* to avoid potentially life-threatening toxicity in patients carrying *TPMT* and/or *NUDT15* risk alleles. Although nomenclature databases focusing on haplotype definitions exist for *TPMT*, *UGTs*, and *NATs*, there are no centralized resources for other important pharmacogenes, including *NUDT15*, *DPYD*, or drug transporters. Standardized allele nomenclature will allow all professionals "to speak the same language" and facilitate the communication and dissemination of allelic variation. As discussed by Kalman *et al.*,[5] there is a need to increase transparency and standardization of clinical pharmacogenetic result reporting as well as the dissemination of research findings. To that end, PharmVar is now developing nomenclature for important non-*CYP* pharmacogenes, such as *NUDT15*, with an initial focus on genes with available CPIC guidelines.

Some of the *NUDT15* allelic variants were assigned star allele numbers when published (*NUDT15*1-NUDT15*6*, *NUDT15*10*, and *NUDT15*11*), whereas others were reported without a star allele designation or designations were assigned *post hoc* (*NUDT15*7- NUDT15*9*) (**Figure 1**). The absence of a centralized and widely accepted naming system not only makes it difficult to facilitate standardized test reporting, but also to interpret test results and compare research findings. Furthermore, reports from different clinical laboratories may not be consistent and may lead to confusion regarding dosing recommendations. Consequently, standardized nomenclature, ideally established when allelic variation is first described, and subsequent consistent use of agreed-on terminology are pivotal for clinical reporting of test results to reduce potential errors in drug selection and dosing.

PHARMVAR NOMENCLATURE FOR *NUDT15*

Experts representing global research, clinical testing, and implementation interests were recruited from PharmVar members to serve on the *NUDT15* expert panel and tasked to establish a formal nomenclature, according to PharmVar allele designation principles. The panel also included a Pharmacogenomics Knowledge Base/CPIC representative to ensure that the nomenclature is consistent with CPIC guidelines and to facilitate dissemination to a greater audience through the PharmGKB knowledgebase as well as other databases, such as ClinGen. The panel met via teleconferences and communicated by email. A literature search was performed on the PubMed database (beginning of PubMed to July 13, 2018, keyword "NUDT15") to compile records for published allelic variants. Most of the 38 articles only tested for p.R139C; there were only three articles describing allelic variants (**Figure S1**).

Because of the relatively few known allelic variants and the fact that most haplotypes are characterized by a single defining nucleotide variant, the review of haplotypes with star allele names was straightforward. Discussions centered mostly on the alleles initially published as *NUDT15*2* and *NUDT15*3*, carrying either p.R139C alone or p.R139C and p.G17-V18ins in *cis*. *NUDT15*2* and *NUDT15*3* share c.415C>T (p.R139C), which causes a severe decrease in *in vitro* function assays and predisposes carriers to a high risk of developing toxicity when exposed to thiopurines. Hence, the question was raised whether c.415C>T dictates the function of both alleles and, therefore, the allele published as *NUDT15*2* should be designated as a suballele of *NUDT15*3* to be consistent with PharmVar criteria for allele designation. According to those criteria, all haplotypes/alleles that carry a sequence variation causing no function are listed under the same star number (see ALLELE DESIGNATION CRITERIA under the SUBMISSIONS menu tab). The panel also discussed concerns regarding a potential merge of the two alleles into a single star allele and suballele designation because this may cause confusion with existing literature and among the clinical laboratories that already offer *NUDT15* testing, an argument that ultimately drove the decision to keep these two designations separate. More important, this issue of *NUDT15* star allele revision underscores the need to develop systematic haplotype nomenclature when variants are initially reported.

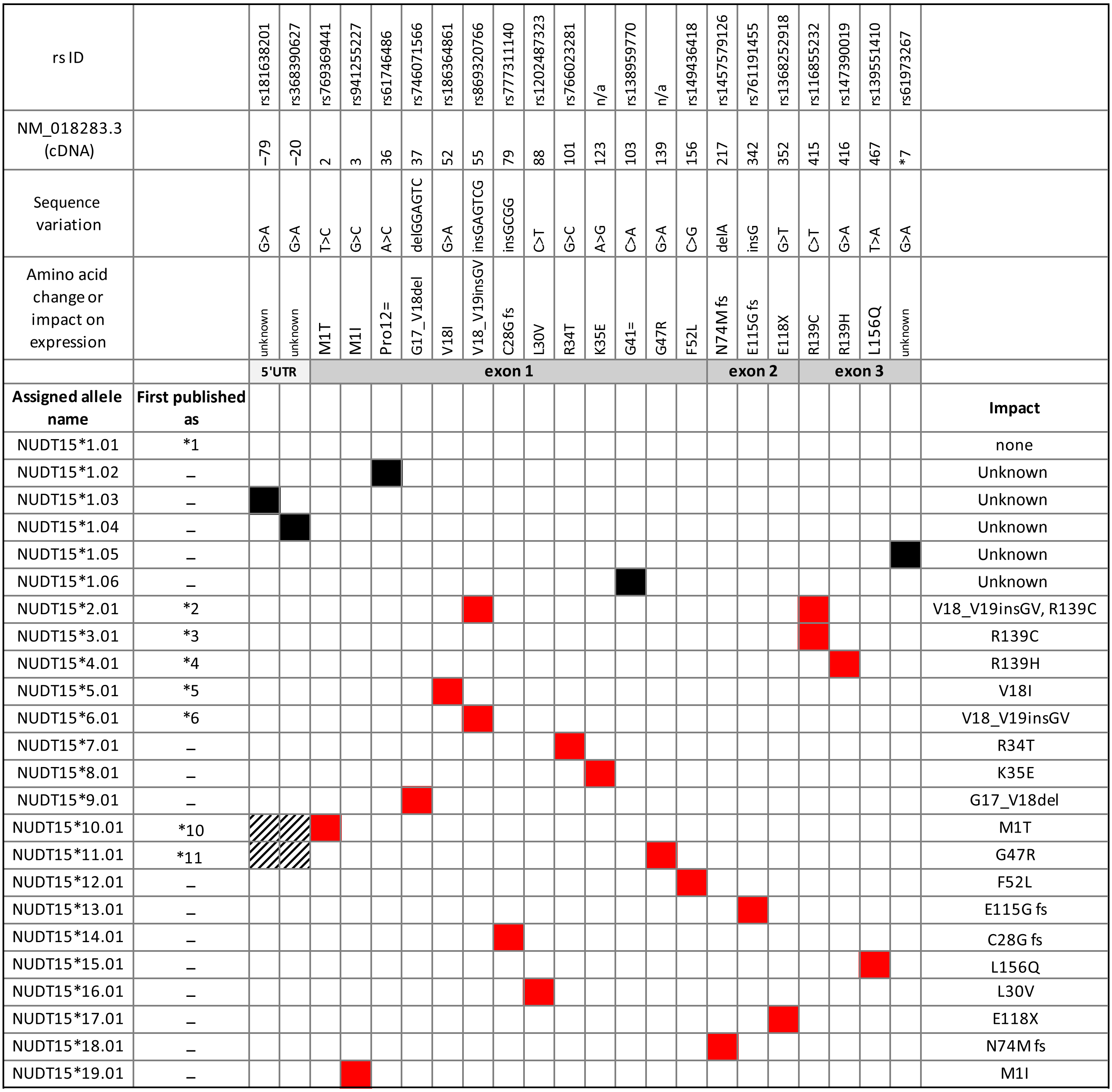
Table 1 Gene summary

Gene data	Description
Alias	NUDT15D (nudix nucleoside diphosphate linked moiety X–type motif 15), MTH2, MutT homolog 2
Gene IDs	HGNC: 23063 Entrez gene: 55270 Ensembl: ENSG00000136159 OMIM: 615792 UniProtKB: Q9NV35 PharmGKB accession ID: PA134963132
Genomic RefSeq	NG_047021.1
Transcript RefSeq	NM_018283.3
Protein RefSeq	NP_060753.1
LRG	NA

NA, not applicable; LRG, Locus Reference Genomic record

Figure 1 provides an overview of all variants published or submitted to PharmVar at the time this report was prepared. Allele frequencies can be accessed on the PharmGKB website at http://www.pharmgkb.org/page/nudt15RefMaterials. Function is assigned on the basis of *in vitro* activity data and/or thermal stability (details are available through the *NUDT15* READ ME document on the PharmVar *NUDT15* gene page and **Figure S1**). Allelic variants containing a frameshift or premature stop codon are predicted to be nonfunctional. The panel's recommendation was reviewed and approved by the PharmVar Steering Committee.

PharmVar maps all coordinates of *NUDT15* allelic variation to the most recent genomic and transcript reference sequences, GRCh37 and GRCh38 (**Table 1**). The *NUDT15* gene page which was released in September 2018 includes READ ME and CHANGE LOG documents that provide important information,



rs ID		rs181638201	rs368390627	rs769369441	rs941255227	rs61746486	rs746071566	rs186364861	rs869320766	rs777311140	rs1202487323	rs766023281	n/a	rs138959770	n/a	rs149436418	rs1457579126	rs761191455	rs1368252918	rs116855232	rs147390019	rs139551410	rs61973267	
NM_018283.3 (cDNA)		–79	–20	2	3	36	37	52	55	79	88	101	123	103	139	156	217	342	352	415	416	467	*7	
Sequence variation		G>A	G>A	T>C	G>C	A>C	delGGAGTC	G>A	insGAGTCG	insGCGG	C>T	G>C	A>G	C>A	G>A	C>G	delA	insG	G>T	C>T	G>A	T>A	G>A	
Amino acid change or impact on expression		unknown	unknown	M1T	M1I	Pro12=	G17_V18del	V18I	V18_V19insGV	C28G fs	L30V	R34T	K35E	G41=	G47R	F52L	N74M fs	E115G fs	E118X	R139C	R139H	L156Q	unknown	
		5'UTR		exon 1													exon 2			exon 3				
Assigned allele name	**First published as**																							**Impact**
NUDT15*1.01	*1																							none
NUDT15*1.02	–					⬛																		Unknown
NUDT15*1.03	–	⬛																						Unknown
NUDT15*1.04	–		⬛																					Unknown
NUDT15*1.05	–																						⬛	Unknown
NUDT15*1.06	–													⬛										Unknown
NUDT15*2.01	*2								🟥											🟥				V18_V19insGV, R139C
NUDT15*3.01	*3																			🟥				R139C
NUDT15*4.01	*4																				🟥			R139H
NUDT15*5.01	*5							🟥																V18I
NUDT15*6.01	*6								🟥															V18_V19insGV
NUDT15*7.01	–											🟥												R34T
NUDT15*8.01	–												🟥											K35E
NUDT15*9.01	–						🟥																	G17_V18del
NUDT15*10.01	*10	▨	▨	🟥																				M1T
NUDT15*11.01	*11	▨	▨												🟥									G47R
NUDT15*12.01	–															🟥								F52L
NUDT15*13.01	–																	🟥						E115G fs
NUDT15*14.01	–									🟥														C28G fs
NUDT15*15.01	–																					🟥		L156Q
NUDT15*16.01	–										🟥													L30V
NUDT15*17.01	–																		🟥					E118X
NUDT15*18.01	–																🟥							N74M fs
NUDT15*19.01	–				🟥																			M1I

Figure 1 Allele nomenclature summary. The graph contains a graphical summary of all *NUDT*15 allelic variants described to date. Of the published variants now designated *NUDT*1* through *NUDT*19*, eight have been published using star nomenclature (**1*-**6*, **10*, and **11*); those designated **7* to **9* were named as such *post hoc*. Six novel haplotypes were designated **14* to **19*. Red boxes indicate SNVs that confer an amino acid change; black boxes indicate SNVs in noncoding regions of unknown functional consequence or synonymous SNPs in coding regions. Gray shaded boxes indicate the gene regions not covered by sequencing. SNV *rs* IDs, their positions on the cDNA reference sequence, nucleotide changes, and impact (amino acid change, frameshift (fs), or stop codon (X)) within a haplotype are shown in the top panels and the right-hand column. An extended figure with additional information, including references, and PharmVar IDs is provided as **Supplemental Material**.

including details regarding allele functionality; these documents will be updated as new information becomes available. All updates will also be coordinated with PharmGKB to provide unified information to the pharmacogenomics community. Furthermore, PharmVar will be announcing the incorporation of standardized *NUDT15* nomenclature to stakeholders via blogs, social media, and targeted announcements/email communications to promote the use of standardized nomenclature because testing is being offered by an increasing number of laboratories.

NOVEL *NUDT15* ALLELIC VARIANTS

Since the inception of the *NUDT15* expert panel in April 2018, six novel previously unpublished allelic variants containing nonsynonymous sequence variations were submitted, reviewed, and

Legend to Supplemental Figure

The provided excel file provides additional information not displayed in Figure 1 of the main text.

Red boxes indicate SNVs that confer an amino acid change; black boxes indicate SNVs in noncoding regions of unknown functional consequence or synonymous SNVs in coding regions. Gray-shaded boxes indicate the gene regions not covered by NGS-based sequencing. It remains unknown whether these haplotypes harbor SNVs in these regions. Nucleotide positions are shown in reference to the genomic RefSeq NG_047021.1 (counting from the sequence start) and cDNA RefSeq NM_018283.3 (counting from ATG = +1) as well as the two genome builds currently in use (GRCh37 and 38). The nature of the sequence variation and their locations within the gene region (upstream, exon or intron) is also provided. The impact of a SNV (amino acid change, frameshift (fs) or stop codon (X)) within a haplotype is listed to the right of the graph (column Z).

Of the variants now designated *NUDT*1* through **19,* six have been published using star nomenclature (**1-*6, *10* and **11*) (1-3); PMID numbers are shown in column AA and are fully referenced below). Haplotypes designated **7-*9* were named as such post-hoc. Six novel haplotypes designated **14-*19* represent recent submissions to PharmVar (submitting author is provided in column AB. Some haplotypes are based on direct submissions only, i.e. have not been formally published elsewhere.

Per PharmVar allele designation criteria (available through the SUBMISSIONS menu tab on www.PharmVar.org), haplotypes carrying a synonymous SNV and/or a SNV in noncoding regions and are not known to impact function are designated as suballeles. Consequently, five variants have been designated as *NUDT15*1* suballeles.

PharmVar is implementing an updated haplotype versioning system that allows tracking of suballeles. As described (4), each haplotype now receives a numeric extension, signifying that e.g. *NUDT15*1.005* is a subvariant of *NUDT15*1*. All variants listed under the same star (*) number are deemed to have the same or comparable function. To date, no suballeles have been identified for *NUDT15*2* through **19*.

The figure provides information regarding allele function based on *in-vitro* activity towards two substrates, TGTP and TdTP (2, 3, 5). Reduced thermostability has been shown to be an indicator of enzyme function and is also provided, if available. For some allelic variants there is no or very limited information and therefore, it remains unknown whether these alleles cause toxicity *in-vivo*. For *NUDT*2* and **3* a clear association with 6MP intolerance has been reported but not for others. "Yes' in column AE indicates that some clinical data exist supporting that an allele contributes to toxicity regardless of the strength of evidence. Note that a number of allelic variants are categorized by PharmVar as 'severely decreased function' based on *in-vitro* activity while CPIC categorized these alleles as 'no function' in their guideline (6). No function assignments have been made by CPIC for *NUDT*10-*19* (tbd, to be determined). This information is also available in the READ ME document posted on the PharmVar gene page and the PharmGKB where updated information will be available.

References

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(5) Moriyama, T. *et al.* Novel variants in NUDT15 and thiopurine intolerance in children with acute lymphoblastic leukemia from diverse ancestry. *Blood* **130**, 1209-12 (2017). PMID: 28659275

(6) Relling, M.V. *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update. *Clin Pharm Ther,* accepted

designated *NUDT15*14* through *NUDT15*19* (**Figure 1**). An additional five haplotypes were designated as *NUDT15*1* sub-alleles because of the presence of single-nucleotide variants in noncoding regions or harboring synonymous single-nucleotide variants. It remains unknown whether these variants have any functional consequences.

PharmVar strongly encourages submissions by investigators before publication (submission requirements and details of how to submit are provided at http://www.PharmVar.org). All information is regarded as confidential and will not be shared outside of the expert panel and Steering Committee. Designated haplotypes can be held for up to 6 months to allow timing of release on PharmVar and through article publication. PharmVar also welcomes direct submissions to make information available to the public independent of a publication.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. NUDT15 nomenclature.

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CONFLICT OF INTEREST

A.J.T.'s efforts are supported in part by RPRD Diagnostics, an independent clinical laboratory offering pharmacogenetic testing services, including *NUDT15*; and S.A.S. is a paid employee of Sema4, a clinical laboratory that performs pharmacogenetic testing, including *NUDT15*. None of the other authors declare any conflicts of interest.

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***NUDT15* nomenclature as of 09-06-2018**

rs ID		rs18163820	rs368390627	rs769369441	rs941255227	rs61746486	rs746071566	rs186364861	rs869320766	rs777311140	rs1202487323	rs766023281	n/a	rs138959770	n/a	rs149436418	rs1457579126	rs761191455	rs1368252918	rs116855232	rs147390019	rs139551410	rs61973267							
NM_018283.3 (cDNA)		-79	-20	2	3	36	37	52	55	79	88	101	103	123	139	156	217	342	352	415	416	467	*7							
NG_047021.1 (genomic)		5102	5161	5182	5183	5216	5217	5232	5235	5259	5268	5281	5283	5303	5319	5336	5337	8537	8547	13153	13154	13205	13240							
NC_000013.11 (GRCh38.p7)		48037668	48037727	48037748	48037749	48037782	48037783	48037798	48037801	48037825	48037834	48037847	48037849	48037869	48037885	48037902	48040978	48041103	48041113	48045719	48045720	48045771	48045806							
NC_000013.11 (GRCh37.p13)		48611804	48611863	48611884	48611885	48611918	48611919	48611934	48611937	48611961	48611970	48611983	48611985	48612005	48612021	48612038	48615114	48615239	48615249	48619855	48619856	48619907	48619942							
sequence variation		G>A	G>A	T>C	G>C	A>C	delGGAGTC	G>A	insGAGTCG	insGCGG	C>T	G>C	A>G	C>A	G>A	C>G	delA	insG	G>T	C>T	G>A	T>A	G>A							
amino acid change or impact on expression		unknown	unknown	M1T	M1I	Pro12=	G17_V18del	V18I	V18_V19insGV	C28G fs	L30V	R34T	K35E	G41=	G47R	F52L	N74M fs	E115G fs	E118X	R139C	R139H	L156Q	unknown							
		5'		exon 1													E2			exon 3			3'							
Assigned PharmVar ID	**first published as**																							**Impact**	**Reference (PMID)**	**Direct PharmVar submission by**	**in vitro function/predicted activity**	**thermal stability**	**thiopurine toxicity clinically observed**	**CPIC function assignment**
NUDT15*1.01	*1																							none	RefSeq		normal function	-	-	Normal function
NUDT15*1.02	-					■																		none	-	Gaedigk et al; Schwab et al	normal function	-	-	tbd
NUDT15*1.03	-	■																						none	-	Gaedigk et al	normal function	-	-	tbd
NUDT15*1.04	-		■																					none	-	Gaedigk et al	normal function	-	-	tbd
NUDT15*1.05	-																						■	none	-	Schwab et al	unknown	-	-	tbd
NUDT15*1.06	-													■										none	-	Schwab et al	unknown	-	-	tbd
NUDT15*2.01	*2								🟥											🟥				V18_V19insGV, R139C	26878724	Gaedigk et al	severely decreased activity with TGTP or TdTP as substrate	reduced	yes	no function
NUDT15*3.01	*3																			🟥				R139C	26878724	Gaedigk et al; Schwab et al	severely decreased activity with TGTP or TdTP as substrate	reduced	yes	no function
NUDT15*4.01	*4																				🟥			R139H	26878724	Gaedigk et al	severely decreased activity with TGTP or TdTP as substrate	reduced	yes	uncertain function
NUDT15*5.01	*5							🟥																V18I	26878724	Gaedigk et al	severely decreased activity with TGTP or TdTP as substrate	reduced	yes	uncertain function
NUDT15*6.01	*6								🟥															V18_V19insGV	26878724	Gaedigk et al; Schwab et al	severely decreased function with TGTP; decrease more pronounced with TdTP as substrate	reduced	yes	uncertain function
NUDT15*7.01	-											🟥												R34T	28659275	-	severely decreased function with TGTP as substrate	reduced	yes	uncertain function
NUDT15*8.01	-												🟥											K35E	28659275	-	severely decreased function with TGTP as substrate	reduced	yes	uncertain function
NUDT15*9.01	-						🟥																	G17_V18del	28659275	Gaedigk et al; Schwab et al	severely decreased function with TGTP as substrate	reduced	yes	uncertain function
NUDT15*10.01	*10	▨	▨	🟥																				M1T	29923122	Kakuta et al	no function (loss of start codon)	unknown	no information	tbd
NUDT15*11.01	*11	▨	▨												🟥									G47R	29923122	Kakuta et al	unknown	unknown	no information	tbd
NUDT15*12.01	-															🟥								F52L	29519865	He et al	unknown	reduced	no information	tbd
NUDT15*13.01	-																	🟥						E115G fs	29519865	He et al	no function (frame shift)	unknown	no information	tbd
NUDT15*14.01	-									🟥														C28G fs	-	Gaedigk et al	no function (frame shift)	unknown	no information	tbd
NUDT15*15.01	-																					🟥		L156Q	-	Gaedigk et al	unknown	unknown	no information	tbd
NUDT15*16.01	-										🟥													L30V	-	Gaedigk et al	unknown (probabaly damaging per in-silico prediction)	unknown	no information	tbd
NUDT15*17.01	-																		🟥					E118X	-	Gaedigk et al	no function (premature stop codon)	unknown	no information	tbd
NUDT15*18.01	-																🟥							N74M fs	-	Schwab et al	no function (frame shift)	unknown	yes	tbd
NUDT15*19.01	-				🟥																			M1I	-	Schwab et al	no function (premature stop codon)	unknown	yes	tbd