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Strategically aligning a mandala of competencies to advance a transformative vision

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APPENDIX B

Knowledge Management and Eskind Biomedical Library Clinical and Translational Science Award (CTSA) support

CYP3A5 *3 and *6 allele characterization

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Question. Please characterize CYP3A5 poor performer alleles *3 and *6, including functional significance and frequency and indicate other potential target drugs.

Summary. The hepatic cytochrome P450 (CYP450) proteins are a superfamily of monooxygenase enzymes, which catalyze the endogenous synthesis of cholesterol, steroids, and other lipids; bioactivate some prodrugs; and biotransform other drugs and toxic chemicals [1]. Many compounds are metabolized by more than 1 cytochrome P450. The cytochrome P450 3A family is responsible for metabolizing approximately 37% of the 200 most commonly prescribed drugs, with cytochromes P450 3A4 (CYP3A4) and 3A5 (CYP3A5) accounting for the majority [2]. CYP3A4 and CYP3A5 are both expressed in liver and intestine, but CYP3A5 is the predominant form expressed in extrahepatic tissues [3] and may account for up to 50% of the total CYP3A activity in liver [4]. CYP3A5 is involved in the metabolism of vasodilators, immunosuppressants, benzodiazepines, and taxanes as well as the steroid hormones testosterone, progesterone, and androstenedione [1, 3]. A list of common substrates, inhibitors, and inducers can be found in the table at the end of this document (CYP3A5 drug table). A more comprehensive list can be found in the summary chapter by Rendic [5].

The CYP3A5 gene is located in a cluster of cytochrome P450 genes on chromosome 7q21.1. The cluster also includes several pseudogenes, one of which, CYP3A5P1, is very similar to CYP3A5 and is known to cause difficulty in cloning this gene [1]. Additionally, CYP3A5 and CYP3A4 share 84% sequence homology [6]. Genetic polymorphisms in metabolizing enzymes are a principal contributor to interindividual variation in the response to numerous drugs. More than 30 polymorphisms in the CYP3A5 gene have been described, many of which affect enzyme

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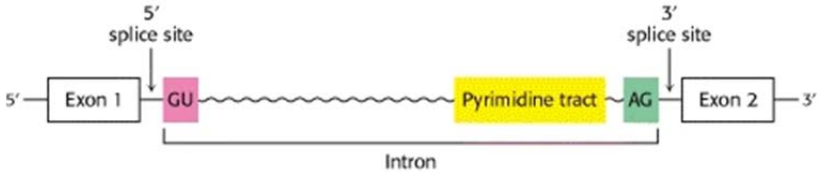
activity [7]. The table below summarizes the functional significance and frequency information from ALFRED (the Allele Frequency Database) [8] and the National Center for Biotechnology Information (NCBI) short genetic variations database dbSNP [9] for the *3 and *6 alleles across all populations. For this gene, the nucleotide change indicated below is based on current knowledge of the sequence that produces a functional CYP3A5 protein. Please see the additional material included on page 10 for information about the reference sequence discrepancy [RefSeq summary].

Allele	SNP(s)	Δ NT	aa change	functional effect	Fst	Ave Het	# Pop	~frequency of SNP
*03	rs776746	A>G	-	Severely decreased/ no activity	0.296	0.285	51	A=.3313; G=.6687
*06	rs10264272	G>A	Lys208=	Severely decreased/ no activity	—	—	—	C=.9427; T=.0573

It is important to note that the frequency of CYP3A5*3 is population dependent (see CYP3A5*3 below). What follows is a detailed synopsis of the information for the *3 [CYP3A5*3] and *6 [CYP3A5*6] alleles, including a breakdown of the frequency in different populations.

CYP3A5*3

Functional characterization. Twelve forms of this variant exist, CYP3A5*3A-*3L, but the root single nucleotide polymorphism (SNP) common to all (rs776746) is in the 3rd intron of the CYP3A5 gene [7, 9]. The thymine (T) at chromosomal position 99,270,539 is replaced by a cytosine (C), which corresponds to an adenine (A) at genomic position 12,083 being replaced by a guanine (G) as this gene is on the negative DNA strand [9, 10]. Splice sites are located at the intron-exon junctions in mRNA and are recognized by a ribonuclear complex of proteins and RNA that control genetic splicing called the spliceosome. The spliceosome recognizes specific signals in the nascent RNA, part of which is the consensus splice sequence at the splice junctions and a pyrimidine (cytosine and thymine or uracil) rich tract [11]. Although the final base of the previous exon and initial base of the next exon can vary, the first and last two nucleotides of the intron in the mRNA are always GU and AG. This is illustrated in the image below [11].



In the CYP3A5 gene, the bases immediately surrounding the position where this mutation (in brackets, red) occurs in the 3rd intron are:

TCTTTAAAGAGCTCTTTTGTCTTTCA[A/G]TATCTCTTCCCTGTTTGGACCACAT

As the intron begins with GU, and a pyrimidine rich region (the green bases above) exists prior to the AG that occurs in the CYP3A5*3 allele, Kuehl et al. concluded that by changing the

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adenine to a guanine at this location, a cryptic splice site is created [4]. The calculated individual weight matrix (R_i)* value increases from -3.2 to 8.2 bits at this position as a result of this mutation, whereas the natural acceptor site remains unchanged at 4.6 bits [12]. Thus, this new stronger cryptic acceptor splice site promotes the insertion of an intronic exon-like sequence into the mature mRNA and as a result, a premature stop codon is introduced upstream [4, 12]. Consequently, the majority of the mRNA is aberrantly spliced, so very little functional protein, if any, is produced [4, 13]. Lamba et al. [14] state that individuals homozygous for the *3 allele are considered CYP3A5 nonexpressors.

Relatively few groups have performed pharmacokinetic studies. One group found for the reconstituted CYP3A5*3L allele, the Vmax was reduced by 39%; the Km increased 2.7 fold, and the overall enzyme activity was 4.3 fold less than wild type [15]. However, as this allele also contains the cryptic splice site, the residual activity observed is a sole result of the Tyr53Cys mutation in what little CY3A5 protein is generated, rather than the defective splicing [15]. Others have investigated dosing requirements of tacrolimus with respect to genotype and independently observed that at least one wild type (CYP3A5*1) allele is sufficient for optimal CYP3A5 activity [4, 13, 16]. However, studies in kidney, liver, lung, heart, and renal transplant recipients have demonstrated that patients homozygous for the CYP3A5*3 allele required significantly less tacrolimus to reach target concentrations than those with at least 1 CYP3A5*1 allele [16]. Haufroid et al. [16], in data from renal transplant patients, observed that the pharmacokinetic parameter that gave the most realistic idea of the global exposure to tacrolimus is the total area under the curve ($AUC_{0\rightarrow\infty}$). They determined that the median $AUC_{0\rightarrow\infty}$ was 2.1–2.6 fold higher (depending on statistical method used) in non-expressers (individuals homozygous for *3) [16]. As a result, Haufroid et al. [16] conclude that at least a minimum 2-fold higher tacrolimus loading dose could theoretically be administered to those that have at least 1 functional CYP3A5 allele (*1/*1 or *1/*3) as compared with those that do not (*3/*3), and propose lowering the loading dose in the latter category.

As mentioned above, at least twelve variations of the CYP3A5*3 allele have been identified and classified [7]. The table below summarizes these alternative versions of the CYP3A5*3 allele [4, 7, 9, 10, 13, 15, 17, 18].

* Nucleic acid binding sites are analyzed based on information theory weight matrices derived from a comprehensive set of aligned functional sites. The frequencies of nucleotides at each position are used to calculate an individual information weight matrix, ($R_i(b, l)$, where b is the base, and l is the location of the base. Individual information weight matrices are calculated for wild type and mutant sequences and compared to evaluate the effect of splicing mutations. Functional binding sites have R_i values greater than zero.

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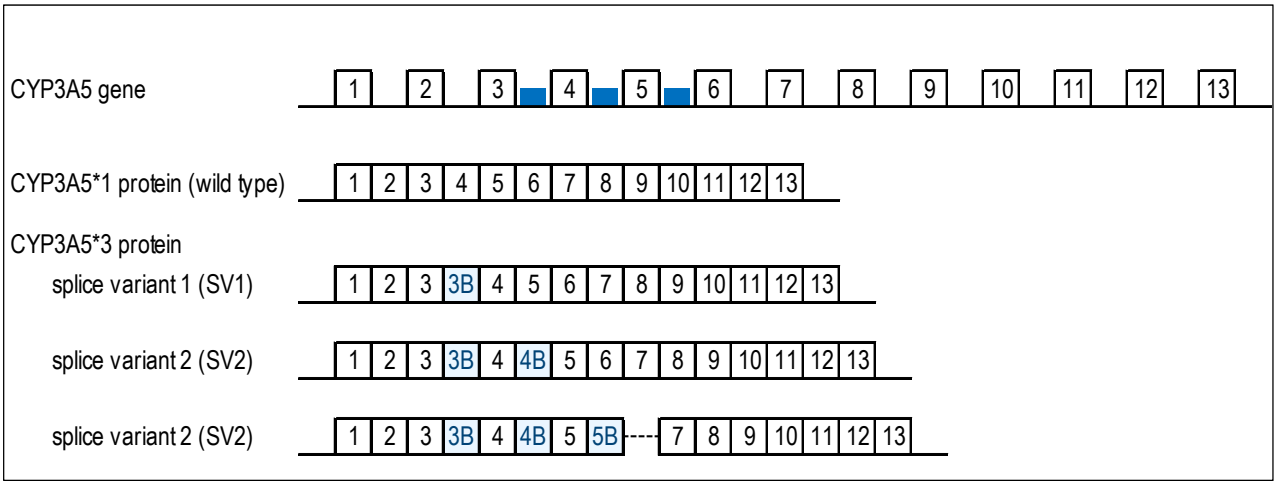
*To produce the normal CYP3A5 protein, a T is found at chromosomal position 99,720,539, corresponding to an A at position 12,083 in the genomic sequence, and a G is found at chromosomal position 99,245,914, corresponding to a C at position 36,708 in the genomic sequence

Allele	*Nucleotide changes*		*dbSNP ID (if available)*	*Effect*	*Enzyme activity*		*Reference*
	Gene changes	*Additional changes*			*In vivo*	*In vitro*	
*CYP3A5*3A*	NG_007938.1:g.12083A>G	g.36708C>T	rs776746, rs15524	Splicing defect	Decreased	Severely decreased	4
*CYP3A5*3B*	NG_007938.1:g.12083A>G	g.36708C>T, His30Tyr, Lys34X[1]	rs776746, rs15524, rs28383468	Splicing defect; H30Y		Severely decreased	13
*CYP3A5*3C*	NG_007938.1:g.12083A>G		rs776746	Splicing defect		Severely decreased	13
*CYP3A5*3D*	NG_007938.1:g.12083A>G	Leu82Arg	rs776746, rs56244447	Splicing defect; L82R		Severely decreased	17
*CYP3A5*3E*	NG_007938.1:g.12083A>G	g.36708C>T, g.32147A>G	rs776746, rs15524, rs28365094	Splicing defect		Severely decreased	17
*CYP3A5*3F*	NG_007938.1:g.12083A>G	g.36708C>T, Ile488Thr	rs776746, rs15524, rs28365085	Splicing defect; I488T		Severely decreased	18
*CYP3A5*3G*	NG_007938.1:g.12083A>G	g.36708C>T, g.18049T>C	rs776746, rs15524, rs55965422	Splicing defect		Severely decreased	18
*CYP3A5*3H*	NG_007938.1:g.12083A>G	g.36708C>T, g.18205T>C	rs776746, rs15524, n/a	Splicing defect		Severely decreased	18
*CYP3A5*3I*	NG_007938.1:g.12083A>G	g.36708C>T, g.22000A>G	rs776746, rs15524, rs72552790	Splicing defect		Severely decreased	18
*CYP3A5*3J*	NG_007938.1:g.12083A>G	g.36708C>T, Ile456Val	rs776746, rs15524, n/a	Splicing defect; I456V		Severely decreased	18
*CYP3A5*3K*	NG_007938.1:g.12083A>G	g.36708C>T, Phe446Ser	rs776746, rs15524, rs41279854	Splicing defect; F446S		Decreased	17
*CYP3A5*3L*	NG_007938.1:g.12083A>G	Tyr53Cys	rs776746, rs72552791	Splicing defect; Y53C		Decreased	15

[1]Variant results in a frameshift, ultimately leading to premature termination

Despite the additional mutations found in many of these versions of the CYP3A5*3 allele, the critical mutation common to all the CYP3A5*3 alleles is the aberrant splicing caused by the rs776746 mutation in intron 3 [4, 13, 15, 17, 18].

Kuehl et al. discovered two other alternatively spliced versions of CYP3A5*3 that include not only part of intron 3, but also introns 4 and 5 (the included pseudo exons are labeled 3B, 4B, and 5B respectively) [4].



Alternatively spliced versions of CYP3A5*3 [4].

The additional SNP (rs6977165) that results in SV2 is a substitution of adenine with a guanine base at genomic position 13,225 (chromosomal position 99,269,397T>C) [9, 12]. This creates a 3.5 bit donor site (wild type donor site is 0.1 bits), which in combination with a preexisting 5.4 bit acceptor site results in inclusion of the cryptic exon 4B in the final transcript [12]. The incorporation of exon 5B occurs concomitantly with the skipping of exon 6 as a result of the overlapping stronger 5B donor site (3.8 bits) with the weaker downstream acceptor site (3.4 bits) of the adjacent exon 6 [12].

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Not only do the CYP3A5*3 alleles yield little to no protein, but the transcribed alternatively spliced RNAs are degraded faster than wild type mRNA [19]. Busi and Cresteil note that splice variants that contain exon 3B are more unstable than wild type CYP3A5 mRNA [19].

Allele frequency. As CYP3A5*3 is the most common form of CYP3A5 in several populations (table below), many have reported frequency information. Below is a breakdown of the frequency distribution for this allele.

CYP3A5*3 (A>G); rs776746

	Hustert et al. [13]		Makeeva et al. [20]		DPDR* [21]		HapMap [22]	
Population	Sample size	Frequency	Sample size	Frequency	Sample size	Frequency	Sample size	Frequency
European/Caucasian	366	95.1%	3,538	92.3%	88	97.7%	796	95.7%
African-American	90–100	27%			60	36.7%	768	44.8%
Japanese	90–100	71%	1,304	75.5%			344	73.3%
Chinese	90–100	73%	576	76.0%			672	73.2%
Koreans	90–100	70%	—	78.0%				
Asian					96	68.8%		
African					48	12.5%	812	14.3%
Hispanic/Mexican					88	75.0%	200	74.0%
American Indian							352	75.6%

* DNA Polymorphism Discovery Resource.

From the table, the CYP3A5*3 allele appears to be the dominant form of the gene in most populations, with most groups reporting the frequency in European and Caucasian populations to be over 90%. The groups with the lowest frequencies are from African origin. Park et al. [23], in determining SNP frequencies in a Korean population, found that the overall frequency of the *3 allele was 76.5% in the 194 Koreans genotyped, 185 (95.3%) of which had at least 1 CYP3A5*3 allele. Of those, 112 of the 185 individuals (60.5%) were homozygous for the allele, and the other 73 (39.5%) were heterozygous. In addition, when examining diplotype, Park et al. [23] discovered 4 of the 12 versions of the *3 allele in the Korean population, the most common being CYP3A5*3A (94.6% of *3 alleles; 72.4% of all alleles), followed by *3C (4.4% and 3.4%, respectively), *3G (0.7% and 0.5%), and *3F (0.3% and 0.3%).

Kuehl et al. also found complete concordance between the CYP3A5*3 and CYP3AP1*3 genotypes in Caucasians [4].

CYP3A5*6

Functional characterization. The CYP3A5*6 variant (rs10264272) is a result of a single nucleotide polymorphism in the 7th exon, in which a cytosine (C) is replaced by a thymine (T) at position 99,262,835 [9]. Due to the redundancy in the genetic code, this substitution does not alter the lysine at position 208. However, as a result of this synonymous mutation, the entire exon 7 is deleted from the final mRNA, and the translated protein is found to have reduced

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catalytic activity [4]. The silent mutation may cause exon 7 skipping by disrupting an exonic splicing enhancer, as proposed by Kuehl et al. [4], but information analysis by Rogan et al. [12] with models of serine-arginine (SR) rich protein binding sites failed to reveal any difference in the strengths or distribution of the splice sites as a result of this mutation. In examining weight matrices, Rogan et al. [12] indicate that this mutation is predicted to have only a minor effect on splicing, strengthening a cryptic acceptor splice site 22 nucleotides upstream of exon 7 by 0.7 bits to 3.6 bits. Consequently, the mutation would not be expected to activate these splice sites, as they contain less information than either natural donor or acceptor sites [12]. A confirmed mechanism by which CYP3A5*6 induces exon 7 skipping has not been elucidated to date.

When determining transcript levels in *1/*6 heterozygotes, Kuehl et al. [4] found that the wild type transcript was considerably more abundant, which Rogan et al. [12] indicated may be consistent with incomplete splicing of exon 7 rather than complete exon skipping.

Allele frequency. CYP3A5*6 is rarely found in populations outside of those of African origin, as indicated in the table below.

CYP3A5*6 (G>A); rs10264272

	Hustert et al. [13]		Roy et al. [24]		DPDR* [21]		HapMap [22]	
Population	Sample size	Frequency	Sample size	Frequency	Sample size	Frequency	Sample size	Frequency
European/Caucasian	366	—	308	—	84	—	588	0.3%
African-American	90	13.0%			52	11.5%	768	13.3%
Japanese	90–100	—					340	0.6%
Chinese	90–100	—					336	0.6%
Koreans	90–100	—						
Asian			96	—	92	—		
African			400	22.0%	32	25.0%	812	20.4%
Hispanic/Mexican					84	—	196	3.1%

* DNA Polymorphism Discovery Resource.

In comparing the frequencies of the CYP3A5*3 allele with those of the CYP3A5*6 allele, one can surmise why this variant is rarely found in populations that primarily express the CYP3A5*3 allele.

CYP3A5 drug tables

The tables below summarize information from the Indiana University Clinical Pharmacology website (Flockhart table) [25] and the literature for some of the more common medicines that interact with the CYP3A proteins. Many drugs are substrates for both CYP3A4 and CYP3A5 and as such, can be metabolized by either enzyme [26]. Below, drugs are classified based on the primary CYP3A family member believed to be involved.

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CYP3A5 Substrates	Evidence
Macrolide antibiotics:	
NOT azithromycin	25
Benzodiazepines:	
alprazolam	25, 27
diazepam→3OH	5, 25
midazolam	5, 25, 26
triazolam	25, 28
Calcium Channel Blockers:	
nifedipine	15, 25, 29
verapamil	5, 25, 30
HMG CoA Reductase Inhibitors:	
atorvastatin	5, 25, 31
lovastatin	25, 31
NOT pravastatin	25, 32
NOT rosuvastatin	25, 33
simvastatin	25, 31, 34
HIV Antivirals:	
indinavir	25, 35
saquinavir	25, 36
Immune Modulators:	
cyclosporine	25, 37, 38
tacrolimus (FK506)	25, 39
Steroid 6beta-OH:	
aldosterone	40
hydrocortisone	25, 41
progesterone	5, 25, 42
testosterone	5, 25, 42
Other Substrates:	
aconitine	43
alfentanil	25, 44, 45
boceprevir	25, 46
carbamazepine	26
cilostazol	25, 47
codeine	25, 48

CYP3A5 Substrates	Evidence
Other Substrates:	
dexamethasone	5, 25, 49
dextromethorphan	5, 25, 26
irinotecan (antineoplastic)	5, 25, 50
lidocaine	25, 26
ondansetron	25, 51
oxycodone	52
quinine	25, 53
retinoic acid	5, 54
risperidone	25, 55
sildenafil (Viagra)	25, 56
sirolimus	25, 57
sunitinib	25, 58
tamoxifen→N-DMT	25, 59
taxol (paclitaxel)	25, 60
vincristine	25, 61, 62
udenafil	56
vardenafil	56

CYP3A5 Inducers	Evidence
HIV Antivirals:	
efavirenz	25, 63
nevirapine	25, 64
Glucocorticoids	
beclomethasone	5, 25, 65
budesonide	5, 25, 65
dexamethasone	5, 25, 65
dipropionate	25, 65
Unclassified Inducers:	
carbamazepine	25, 66
cyclosporin	66
oxcarbazepine	25, 67
phenobarbital	5, 25, 68
phenytoin	25, 66
rifampin	25, 66

CYP3A5 Inhibitors	Evidence
Strong Inhibitors	
HIV Antivirals:	
nelfinavir	25, 69, 70
ritonavir	25, 69, 70
saquinavir	25, 69
Other strong inhibitors	
fluconazole	25, 71
itraconazole	25, 71
voriconazole	25, 71
Moderate Inhibitors	
fluconazole	25, 72
grapefruit juice	25, 41
verapamil	25, 73
diltiazem	25, 74
Weak Inihbitors	
cimetidine	25, 75
indinavir	25, 69
amprenavir	25, 69
Unclassified Inhibitors	
NOT azithromycin	25
imatinib	25, 76
lapatinib	77

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Several groups either only tested CYP3A4, examined CYP3A or CYP3A4/5 metabolism of various compounds, or did pharmacokinetic testing in human liver microsomes without genotyping. Consequently, these drugs (listed in red) were placed on the CYP3A4/CYP3A7 list. As CYP3A5 is the predominant CYP3A expressed outside the liver, some medications metabolized outside the liver will be metabolized by CYP3A5, even if CYP3A4 is the primary enzyme involved in metabolism [78]. This is not a comprehensive list.

CYP3A4/CYP3A7 substrates	1° CYP	Evidence
Macrolide antibiotics:		
clarithromycin	3A4	5, 25, 79
Antihistamines:		
astemizole (FDA removed 1999)	3A4	25, 80
chlorpheniramine	2D6, 3A4	5, 25
terfenadine	3A4	5, 25, 26
HIV Antivirals:		
amprenavir	3A4	5, 81
nelfinavir	3A4	5, 25, 82
ritonavir		5, 25, 83, 84
Prokinetic:		
cisapride	3A4	5, 25, 85
Calcium Channel Blockers:		
amlodipine	3A4	5,25, 86, 87
diltiazem	3A4	5, 25, 88
felodipine	3A4	5, 25, 86, 89
lercanidipine	3A4, 2D6	5, 25, 86
nisoldipine	3A4	5, 25, 90
nitrendipine	3A4	5, 25, 86, 91
HMG CoA Reductase Inhibitors:		
cerivastatin	3A4	5, 25, 92, 93
Steroid 6beta-OH:		
estradiol	3A4	5, 25, 94
Kinase Inhibitors		
dasatinib	3A4	95
erlotinib	3A4	95
gefitinib	3A4	95
lapatinib	3A4	25, 95
imatinib	3A4	95
nilotinib	3A4	95
sorafenib	3A4	25, 95

Color denotes only CYP3A4 or CYP3A checked in literature

CYP3A4/CYP3A7 substrates	1° CYP	Evidence
Other Substrates:		
amiodarone	3A4	25, 96
aprepitant	3A4	25, 97
aripiprazole	3A4, 2D6	25, 98
arteether (antimalarial)	3A4	5, 99
buspirone	3A4	5, 25, 100
cafergot		25
caffeine→TMU	1A2, 3A4	5, 25, 101
Chloroquine	3A4	102
cinacalcet	3A4	25, 103
cocaine	3A4	5, 25, 104
codeine-N-demethylation	3A4	5, 25, 105
cyclosporin	3A4	5
dapsone	3A4	5, 25, 106, 107
docetaxel	3A4	5, 25, 108
domperidone	3A4	25, 109
eplerenone	3A4	25, 110
ergotamine	3A4	5, 25, 111
erythromycin	3A4	25, 26
estradiol	3A4	5, 25, 94, 112
etoposide (antineoplastic)	3A4	5, 113
ezlopitant (antiemetic)	3A4	5, 114
fentanyl	3A4	5, 25, 115, 116
finasteride	3A4	5, 25, 117
gleevec (imatinib)	3A4	25, 118
halofantrine (antimalarial)	3A4	5, 119
haloperidol	3A4	5, 25, 120, 121
levo-alpha-acetylmethadol (LAAM)	3A4	5, 25, 122
losartan (Angio II recp antagonist)	3A4	5, 123
methadone	3A4, 3A7	5, 25, 124
naphthalene	3A4	125
nateglinide	3A4	25, 126
pimozide	3A4	5, 25, 127
NOT pravastatin		25, 128
propranolol	2D6, 3A4	25, 129
quetiapine	3A4	5, 25, 130
salmeterol	3A4	5, 25, 131
telaprevir	3A4	25, 132
telithromycin	3A4	25, 133
teniposide (antineoplastic)	3A4	5, 134
terfenadine	3A4	5, 25, 26
torisel (temsirolimus)	3A4	25, 135
trazodone	3A4	5, 25, 136
zaleplon	3A4	25, 136
ziprasidone	3A4	25, 137
zolpidem	3A4	25, 138
zonisamide	3A4	5, 139
zotepine (antipsychotic)	3A4	5, 140

Color denotes only CYP3A4 or CYP3A checked in literature

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CYP3A4/CYP3A7 Inhibitors	1° CYP	Evidence
Strong Inhibitors		
HIV Antivirals:		
amprenavir	3A4	5, 69
indinavir	3A4	5, 25, 69
Other strong inhibitors		
clarithromycin	3A4	5, 141
ketoconazole	3A4	5, 25, 28, 109
telithromycin	3A4	25, 133
nefazodone	3A4	5, 25, 142
Moderate Inhibitors		
aprepitant	3A4	25, 143
erythromycin	3A4	25, 144
fluoxetine	3A4	145
fluvoxamine	3A4	25, 146
Unclassified Inhibitors		
amlodipine	3A4	5, 25, 87
boceprevir	3A4	25, 147
chloramphenicol	3A4	25, 148
ciprofloxacin	3A4	25, 149
cyclosporin	3A4	5, 150, 151
delaviridine	3A4	25, 145, 152
gestodene	3A4	25, 145
mibefradil	3A4	25, 153
mifepristone	3A4	25, 154, 155
norfloxacin	3A4	25, 156
norfluoxetine	3A4	5, 25, 157
starfruit	3A4	25, 158
telaprevir	3A4	25, 159
verapamil	3A4	160

Color denotes only CYP3A4 or CYP3A checked in literature

CYP3A4/CYP3A7 Inducers	1° CYP	Evidence
Barbiturates		
cyclobarbital		161
hexobarbital		161
mephobarbital		161
N-methylbarbital		161
phenobarbital		161
Benzimidazole derivatives		
lansoprazole	3A4	162
omeprazole	3A4	162
pantoprazole	3A4	162
rabeprazole	3A4	162
Unclassified Inducers:		
clotrimazole	3A4	5, 66
mifepristone	3A4	5, 66
modafinil	3A4	5, 163
nifedipine	3A4	66
pioglitazone	3A4	164
rifabutin	3A4	5, 165
rifampicin	3A4	5, 66
ritonavir	3A4	166
rosiglitazone	3A4	164
St. John's wort	3A4	5, 167, 168
troglitazone	3A4	164

Color denotes only CYP3A4 or CYP3A checked in literature

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Additional information about the reference sequences for CYP3A5

For the CYP3A5*3 allele, the variant (rs776746) is found in the middle of intron 3 at position g.99,270,539 [9]. The reference sequences indicate that the nucleotide at this position in the gene that produces a functional CYP3A5 enzyme is a guanine (G), and the variant is an adenine (A):

NC_000007.13:g.99270539C>T*
NG_007938.1:g.12083G>A
NM_000777.3:c.219-237G>A

* Chromosomal DNA (NC_##) always references the positive strand. The CYP3A5 gene is on the negative strand, thus the complementary bases are found in the genomic (NG_##) and cDNA (NM_##) reference sequences [169].

According to Kuehl et al. [4], the nucleotide base at position 22,893 in the CYP3A5 *3 sequence (Bacterial artificial chromosome [BAC] AC005020) is a G; it *is* the causative mutation. The authors state that a G at this position creates a cryptic splice site, which results in inclusion of the remaining portion of the intron in the final mRNA. A prematurely truncated, nonfunctional protein is translated as a result.

Given this conflicting information, a Basic Local Alignment Search Tool (BLAST) search was performed [170]. Position 22,893 in AC005020 aligned to position 12,083 in reference sequence NG_007983 (100% sequence identity in the gene region). The base is listed as a G at that position in both, further confirming the reference sequence and the *3 variant sequence as reported by Kuehl et al. are the same.

After contacting several experts, a final clarification email to a reference sequence curator resulted in a resolution. An adenine at this position results in a fully functional protein; the guanine creates the cryptic splice site responsible for the nonfunctional protein. The Genome Research Consortium was contacted by the curator to make them aware of this issue and suggest that the reference genome sequence represent the CYP3A5 *1 allele (A present at this position).

As this variant is found in approximately 80% of Europeans and Asians and only roughly 5%–20% of individuals of African origin, the majority non-African populations will test positive for this SNP [171].

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