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Aripiprazole Therapy and *CYP2D6* Genotype

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Introduction

Aripiprazole (brand names Abilify or Aristada) is an atypical antipsychotic used to manage schizophrenia, bipolar disorder, major depressive disorder, irritability associated with autistic disorder, and in the treatment of Tourette syndrome. (1)

The metabolism and elimination of aripiprazole is mainly mediated through 2 enzymes, CYP2D6 and CYP3A4. Approximately 8% of Caucasians, 3–8% of Black/African Americans and up to 2% of Asians cannot metabolize CYP2D6 substrates and are classified as "poor metabolizers." (2)

The FDA-approved drug label for aripiprazole states that in CYP2D6 poor metabolizers, half of the usual dose should be administered. In CYP2D6 poor metabolizers who are taking concomitant strong CYP3A4 inhibitors (for example, itraconazole, clarithromycin), a quarter of the usual dose should be used (Table 1) (1). The dosage reduction is the same regardless of the administration route (oral or long-acting injectable). (3)

The Dutch Pharmacogenetics Working group (DPWG) also recommends a reduced dosage for CYP2D6 poor metabolizers, "no more than 10 mg/day or 300 mg/month" (Table 2). No action is recommended for intermediate or ultrarapid metabolizers. While both of these metabolic variations alter the plasma concentrations of aripiprazole, there is no evidence that this increases the risk of reduced effectiveness or risk of side effects. (4)

In contrast to the recommendations by the FDA and DPWG, some recent studies have suggested CYP2D6 intermediate metabolizers may also require a dose decrease, but this was only based on aripiprazole clearance. (5, 6, 7, 8)

Table 1. The FDA Dosing Recommendations for Aripiprazole and CYP2D6 Metabolizer Status and Comedications (2020)

Factors	Dosage adjustments for aripiprazole tablets
Known CYP2D6 poor metabolizers	Administer half of usual dose
Known CYP2D6 poor metabolizers taking concomitant strong CYP3A4 inhibitors (for example, itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (for example, quinidine, fluoxetine, paroxetine) or CYP3A4 inhibitors (for example, itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose

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Table 1. continued from previous page.

Factors	Dosage adjustments for aripiprazole tablets
Strong CYP3A4 inducers (for example, carbamazepine, rifampin)	Double usual dose over 1–2 weeks

This FDA table is adapted from (1).

Table 2. The DPWG Dosing Recommendations for Aripiprazole and CYP2D6 Metabolizer Status (2018)

CYP2D6 metabolizer type	Action needed	Background
Poor metabolizer	Administer no more than 10 mg/day or 300 mg/month (67–75% of the standard maximum dose of aripiprazole)[1]	The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite.
Intermediate metabolizer (IM)	NO action is needed for this gene-drug interaction	The genetic variation alters the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is no evidence that this increases the risk of reduced effectiveness for UM or risk of side effects for IM.
Ultrarapid metabolizer (UM)		

DPWG: Dutch Pharmacogenetics Working Group
1 Drug labeling within the European Union states that 15 mg/day is the starting maximum dose (9).
This DPWG table is adapted from (4) .

Drug: Aripiprazole

Aripiprazole is an atypical antipsychotic primarily used to treat schizophrenia and bipolar disorder. Aripiprazole may also be used as part of the management of major depressive disorder, irritability associated with autism, and in the treatment of Tourette syndrome. (1, 3)

The first antipsychotics to be discovered in the 1950s were haloperidol and chlorpromazine. Known as "first-generation" or "typical" antipsychotics, these drugs are used to treat psychosis (regardless of the cause), chronic psychotic disorders (for example, schizophrenia), and other psychiatric conditions. However, prominent adverse effects included extrapyramidal side effects such as tardive dyskinesia, muscle rigidity, tremors, and Parkinsonian-like symptoms.

Newer antipsychotics, known as "second generation" or "atypical" antipsychotics, have a lower risk of extrapyramidal side effects such as tardive dyskinesia. However, many have serious metabolic effects. Aripiprazole is an atypical antipsychotic that is noted for having fewer metabolic side effects than other atypicals, such as clozapine, olanzapine, risperidone, and quetiapine. Other atypicals approved by the FDA include asenapine, brexpiprazole, cariprazine, lurasidone, paliperidone, and ziprasidone.

The main action of both first-generation and second-generation antipsychotics is thought to be the post-synaptic blockade of D2 dopamine receptors. All antipsychotics, with the exception of aripiprazole, are D2 antagonists.

Aripiprazole is a partial D2 agonist. Aripiprazole binds to the D2 receptor with a high affinity similar to dopamine. However, because it has low intrinsic activity, it causes much lower activation of the receptor compared with dopamine.

The combination of a high affinity for the D2 receptor and its partial agonist activity may result in aripiprazole reducing the high-frequency firing of dopamine neurons in the brain's mesolimbic system. Overactivity in this region is thought to underlie psychosis and other positive symptoms of schizophrenia. In addition, the preservation of some D2 receptor activity in other dopamine-rich pathways in the brain (mesocortical and nigrostriatal areas) may provide more protection against extrapyramidal side effects. (10, 11)

Aripiprazole also has a high affinity for the serotonin 5-HT_{2A} receptors, where it acts as an antagonist and it moderately blocks the alpha 1 adrenergic and histamine H1 receptors, which may account for the lower incidence of orthostatic hypotension and sedation compared with other antipsychotics. (12)

Adverse events with aripiprazole therapy include increased mortality in elderly individuals with psychosis caused by dementia, suicidal thoughts and behavior in children and young adults, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes including hyperglycemia, pathological gambling, and other compulsive behaviors. Additionally, orthostatic hypotension, leukopenia, neutropenia, and agranulocytosis, seizures/convulsions and potential cognitive and motor impairment have been reported. Commonly observed adverse reactions in adult schizophrenic individuals that should be reported to the FDA include akathisia. Adverse events in pediatric individuals (13–17 years old) that should be reported are extrapyramidal disorder, somnolence, and tremor. (1)

Aripiprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) superfamily of enzymes, mainly CYP2D6 and CYP3A4. Aripiprazole activity is thought to be primarily due to the parent drug, and to a lesser extent its major metabolite, dehydroaripiprazole. The mean elimination half-life is approximately 75 hours for aripiprazole, but in individuals who have no appreciable CYP2D6 activity (poor metabolizers), the mean elimination half-life for aripiprazole is around 146 hours. (1) The mean aripiprazole exposure for CYP2D6 poor and intermediate metabolizers is increased 1.5-fold compared with normal metabolizers (6).

While aripiprazole has been reported to have a minimal effect on prolactin levels (13), more recent studies have found a correlation between reduced CYP2D6 enzyme activity and increases in prolactin. (14, 15) These increases in prolactin levels were more pronounced in females and individuals with no functional CYP2D6, raising the possibility of a higher risk for hyperprolactinemia adverse reactions. Hyperprolactinemia can have significant effect in the pediatric population during growth and development and may warrant additional monitoring. (14)

Rare cardiac adverse reactions have also been observed in clinical trials with aripiprazole. (3) Two recent case reports suggest that CYP2D6 activity may play a role in predisposing an individual to atrial fibrillation or abnormal heart electrophysiology. (16, 17) One small study reported that palpitations were more commonly experienced by females versus males taking aripiprazole and more often with aripiprazole versus olanzapine treatment. (18)

The FDA-approved drug label warns that "neonates exposed to antipsychotic drugs, including aripiprazole, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery." (1) These exposures should be considered in light of the disease-associated maternal or embryo/fetal, or both, risks of untreated schizophrenia or bipolar I disorder. The FDA-approved label states that neonates who are exposed to aripiprazole during pregnancy should be closely monitored, as symptoms vary in severity and duration (hours to days) and may require prolonged hospitalization. The FDA encourages healthcare providers to register individuals who have aripiprazole exposure while pregnant to monitor pregnancy outcomes. For more information see (1, 3).

Limited data from scientific literature suggests a low level of aripiprazole can be present in breast milk. The literature reports the relative infant dose ranges between 0.7% and 8.3% of the maternal weight-adjusted dosage. (1) Though aripiprazole has a minimal effect on prolactin levels compared with the phenothiazines, case reports have documented both decreased lactation and hyperprolactinemia in nursing mothers taking aripiprazole, and other medications may be considered, as needed. (19)

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are very polymorphic and can result in decreased, absent, or increased enzyme activity.

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

CYP2D6 Alleles

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 3) (20). The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6*4/*4*). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (for example, CYP2D6 poor metabolizer). When duplicated alleles are detected, both copies are assigned an activity score for phenotyping. However, the activity score system is not standardized across clinical laboratories or CYP2D6 genotyping platforms. CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The CYP2D6 phenotype is defined by the sum of the allele activity scores, which is usually in the range of 0–3.0: (21)

- An ultrarapid metabolizer (UM) has an activity score greater than 2.25
- A normal metabolizer phenotype (NM) has an activity score of 1.25 to 2.25
- An intermediate metabolizer (IM) has an activity score of >0 to 1.25
- A poor metabolizer (PM) has an activity score of 0

Table 3. Activity Status of Selected *CYP2D6* Alleles

Allele type	Activity score	*CYP2D6* alleles
Normal function	1.0	**1, *2, *27, *33*
Decreased function	0.25-0.5	**10, *17, *41, *49*
No function	0	**3, *4, *5, *6, *36*

For a comprehensive list of *CYP2D6* alleles, please See PharmVar. Activity scores from (22).

The *CYP2D6*1* allele is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. In addition, the *CYP2D6*2*, **27*, and **33* alleles are also considered to have near-normal activity.

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, **5*, and **6*) (23, 24, 25) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (26, 27, 28) (see Table 3). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians. (29)(30)

Allele Frequencies Vary between Populations

Among Asians and in individuals of Asian descent, only approximately 50% of *CYP2D6* alleles are normal function, and the frequency of *CYP2D6* duplications is as high as 45%, although this may have been overestimated by not accounting for tandem hybrid alleles (for example, **36+*10*) (31). Other studies of a US individual population suggested less than 50% of alleles detected within Asian-descent individuals are normal-function alleles in a single copy, with 30% of alleles arising from structural variants (duplications or deletions) (32). Common no-function variants are *CYP2D6*36* and *CYP2D6*4* (32). Both these alleles contain the variant "c.100C>T" (see Allele Nomenclature table) (29, 31, 33, 34). The *CYP2D6*36* allele is the result of a gene

conversion event with the pseudogene *CYP2D7* (35). This no-function allele is most commonly found in individuals of Asian ancestry (32).

Among Africans and African Americans, only approximately 50% of *CYP2D6* alleles are normal function (23, 28, 29, 36). African Americans also have been found to have a higher frequency of no-function structural variants or decreased-function single-copy variant alleles versus Caucasian or Hispanic Americans (32).

Middle Eastern countries show a great diversity in phenotypic and allelic distribution for *CYP2D6* (37), though on average, these individuals show a lower frequency of poor metabolizer phenotypes (0.91%) and higher ultrarapid phenotypes (11.2%) than other ethnicities (Note: Oceania and Middle Eastern ethnicities combined in this study) (2).

Among European countries, there is diversity of allelic distribution (38). Gene duplications were more common in the south-eastern countries (Greece, Turkey: 6%) and less common in north-western countries (Sweden and Denmark, <1%). Meanwhile, *CYP2D6*4* and **5* alleles were generally more common in the north and less common in the south. (38) Worldwide *CYP2D6* genotype and phenotype frequencies have been catalogued and recently published (2).

CYP2D6 Phenotype

CYP2D6 Phenotype Frequencies Vary between Populations

Normal metabolizers: Approximately 77–92% of individuals have 2 normal-function alleles (**1* or **2*), or one normal-function allele and one decreased-function allele. These individuals are "normal metabolizers" and are most likely to have a phenotypically normal response to the drug.

Intermediate metabolizers: Approximately 2–11% of individuals are intermediate metabolizers—they have either 2 decreased-function alleles or one normal- or decreased-function and one no-function allele (2). A study of a diverse US urban population of children found that roughly 8% of subjects were intermediate metabolizers (39), Within the US, it has been observed that individuals of African or Asian descent were most likely to be classified as intermediate metabolizers (20–28% of population by ethnicity) (32).

Poor metabolizers: Approximately 5–10% of individuals are poor metabolizers—they have 2 no-function alleles (40). Poor metabolizers are more commonly found in European Caucasians and their descendants. The no-function *CYP2D6*4* and **5* alleles largely account for the poor metabolizer phenotype in these populations (27, 41, 42). It should be noted that the frequency of poor metabolizers can be much lower in certain populations including East Asian, Oceania and Middle Eastern (2). Studies of US multi-ethnic populations have estimated the prevalence of poor metabolizers to be between 1.5–5.7% (32, 39).

Ultrarapid metabolizers: Individuals who are ultrarapid metabolizers have at least 3 copies of the *CYP2D6* gene. The ultrarapid metabolizer phenotype has been estimated to be present in 1–2% of individuals, but the prevalence varies widely in different populations. It is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese (40, 43). Ultrarapid metabolizers made up 9% of subjects in an urban multi-ethnic population with a large portion of Hispanic/Latino subjects (39). A larger study of US individuals predicted an ultrarapid metabolizer phenotype in only 2.2% of individuals, regardless of ethnicity (32).

Linking Gene Variation with Treatment Response

Genetic variations in the *CYP2D6* gene have been found to impact serum levels of aripiprazole and dehydroaripiprazole. (8)(44, 45) Because standard doses of aripiprazole lead to higher plasma levels of aripiprazole and dehydroaripiprazole, the dose of aripiprazole should be adjusted for individuals that have 2 no-function *CYP2D6* alleles causing poor metabolizer status.

The FDA recommends that individuals who are known to be CYP2D6 poor metabolizers should receive half the standard dose of aripiprazole, or a quarter of the standard dose if they are also taking medicines that strongly inhibit CYP3A4 (for example, itraconazole, clarithromycin) (see Table 1). Multiple studies substantiate the FDA recommendations by concluding that poor metabolizers should receive a reduced dose of aripiprazole (30–50% reduction). (5, 6, 8, 45, 46)

One study further suggested that individuals with increased CYP2D6 activity (ultrarapid metabolizers) may need to take an alternative antipsychotic not metabolized by CYP2D6 because of reduced drug levels. (46) Additional studies have suggested that intermediate metabolizers should also have a reduced dosage, in contrast with the current FDA-approved drug labeling. (5, 6, 7, 47) This is particularly relevant among individuals of Asian descent, where the intermediate metabolizer phenotype is highly prevalent. (7) One study reported that females and poor metabolizers are at an elevated risk for adverse events. (8)

Phenoconversion from a CYP2D6 normal metabolizer status to reduced metabolic activity has also been suggested due to drug-drug interactions in individuals with one or more wild-type *CYP2D6*1* allele. (47) The drugs observed by this study to have an effect on CYP2D6 activity were risperidone, metoprolol and propranolol. (47) Additionally, phenoconversion has been associated with a higher rate of aripiprazole discontinuation (48). Aripiprazole can lead to drug-drug interactions with other CYP2D6 substrates, particularly those with weaker affinity for the CYP2D6 enzyme—for example, the antidepressant mirtazapine—resulting in an increase in plasma concentration for the co-medication (49). The FDA drug label recommends reducing the aripiprazole dosage with concomitant use of strong CYP2D6 inhibitors (for example quinidine, fluoxetine and paroxetine) or CYP3A4 inhibitors. (1)

Genetic Testing

The NIH Genetic Testing Registry provides examples of the genetic tests that are available for aripiprazole response and for the *CYP2D6* gene.

CYP2D6 is a particularly complex gene that is difficult to genotype because of the large number of variants and the presence of gene deletions, duplications, multiplications, and pseudogenes. The complexity of genetic variation complicates making a correct determination of *CYP2D6* genotype.

Targeted genotyping typically includes up to 30 variant *CYP2D6* alleles (over 100 alleles have been identified so far). Test results are reported as a diplotype, such as *CYP2D6 *1/*1*. However, it is important to note that the number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories. (50)

A result for copy number, if available, is also important when interpreting *CYP2D6* genotyping results. Gene duplications and multiplications are denoted by "xN" for example, *CYP2D6*1xN* with *xN* representing the number of *CYP2D6* gene copies. The functional status of the duplicated allele is also critical in interpretation of the test results, as duplication of a no-function versus a normal-function allele would result in a different total activity score and potentially different metabolizer phenotype.

If the test results include an interpretation of the individual's predicted metabolizer phenotype, such as "*CYP2D6 *1/*1*, normal metabolizer", this can be confirmed by checking the diplotype and assigning an activity score to each allele (for example, 0 for no function, 0.5 for decreased function, and 1.0 for each copy of a normal-function allele, Table 3). See the *CYP2D6* alleles section above for more information.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2020 Statement from the US Food and Drug Administration (FDA):

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, aripiprazole dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

[…]

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3% to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM).

Please review the complete therapeutic recommendations that are located here:(1).

2018 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 PM: aripiprazol [aripiprazole]

The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite.

administer no more than 10 mg/day or 300 mg/month (67-75% of the standard maximum dose of aripiprazole).

CYP2D6 IM: aripiprazol [aripiprazole]

NO action is needed for this gene-drug interaction.

The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.

CYP2D6 UM: aripiprazol [aripiprazole]

NO action is needed for this gene-drug interaction.

The genetic variation decreases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is no evidence that this increases the risk of reduced effectiveness.

Please review the complete therapeutic recommendations that are located here: (4).

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
*CYP2D6*3*	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly CYP2D6T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A (Glu410Lys)	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
*CYP2D6*31*	2851C>T (Arg296Cys)	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[3]	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*41*	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*49*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2850C>T is also referred to as 2938C>T
[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from the Pharmacogene Variation Consortium.
Alleles described in this table are selected based on discussion in the text above. This is not intended to be an exhaustive description of known alleles.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (51).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation (PharmVar) Consortium.

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Version History

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