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Primaquine Therapy and *G6PD* and *CYP2D6* Genotype

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Introduction

Primaquine is a potent antimalarial medication indicated for the radical cure of malaria caused by *Plasmodium vivax (P. vivax)* and *Plasmodium ovale (P. ovale)* species (1, 2). Malaria is a blood borne infection caused by infection of *Plasmodium* parasites that is spread by mosquitos. The *P. vivax* and *P. ovale* species present a particular challenge to treat because the parasitic life cycle includes a dormant, liver-specific stage that is not susceptible to other antimalarial medications. Thus, primaquine is often used with other therapies such as chloroquine or artemisinin-based medicines that target the reproductive, active forms of the parasite. Primaquine is also used to prevent transmission of malaria caused by *Plasmodium falciparum* (*P. falciparum)* species. A single, low dose (SLD) of primaquine has gametocidal activity, which does not cure the individual but does provide malaria transmission control.

Primaquine is a pro-drug that must be activated by the cytochrome P450 (CYP) enzyme system. Metabolism by the cytochrome P450 member 2D6 (CYP2D6) and cytochrome P450 nicotinamide adenine dinucleotide phosphate (NADPH):oxidoreductase (CPR) generates 2 hydroxylated active metabolites that generate hydrogen peroxide (H_2O_2). This causes significant oxidative stress to the malarial parasite and the host human cells. Individuals who are glucose-6-phosphate dehydrogenase (G6PD) deficient are particularly susceptible to oxidative stress and may experience acute hemolytic anemia (AHA). Before starting a course of primaquine, individuals should be tested for G6PD deficiency to ensure safe administration (1, 2). According to the FDA-approved drug label, individuals with severe G6PD deficiency should not take primaquine (Table 1) (1).

The World Health Organization (WHO) recommends that individuals with G6PD deficiency should be treated with a modified course of primaquine therapy. The recommended course for individuals with G6PD deficiency is a single dose once per week for 8 weeks, while the standard course is daily administration for 14 days (Table 2) (2). The Clinical Pharmacogenetics Implementation Consortium (CPIC) reports that the risk of adverse effects of primaquine therapy for G6PD-deficient individuals is dose-dependent, with the SLD regimen presenting the least risk (Table 3) (3).

Primaquine is contraindicated during pregnancy and is not recommended for breastfeeding individuals when the G6PD status of the baby is unknown (1, 2). Primaquine is not approved for individuals under 6 months of age. Individuals with acute illness that are prone to granulocytopenia or individuals taking another hemolytic medication are also contraindicated from taking primaquine. (1)

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Table 1. The FDA Drug Label for Primaquine Phosphate (2021)

G6PD status	Risk	Recommendation
Deficient	Hemolytic anemia	G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis
Severe deficiency	Hemolytic anemia	Primaquine should not be prescribed
Mild to moderate deficiency	Hemolytic anemia	A decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (for example, at day 3 and 8) is required
Unknown, testing unavailable	Hemolytic anemia	A decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (for example, at day 3 and 8) is required

This table is adapted from (1). G6PD - glucose-6-phosphate dehydrogenase

Table 2. The WHO Recommended Dosing Regimen for Primaquine Phosphate and G6PD Deficiency

Dosing regimen	G6PD testing	Recommendation strength, evidence certainty	G6PD status	Therapeutic goal and recommendations
Single low dose (0.25 mg/kg bw)	Not required	Strong, low	All	Reducing the transmissibility of treated *P. falciparum* infections in low-transmission areas. Recommended course does not apply to pregnant women, infants aged <6 months, women breastfeeding infants aged <6 months
14-day course (0.25–0.5[a] mg/kg bw per day)	Recommended to guide administration	Strong, high	Known G6PD normal	Treating uncomplicated malaria caused by *P. vivax, P. ovale, P. malariae* or *P. knowlesi*, preventing relapse. Excludes pregnant women, infants aged <6 months, women breastfeeding infants aged <6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency
0.75 mg/kg bw once weekly for 8 weeks	Recommended to guide administration	Conditional, very low	G6PD deficient	Treating uncomplicated malaria caused by *P. vivax, P. ovale, P. malariae* or *P. knowlesi*, preventing relapse. When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine

This table adapted from (2). Mg/kg bw - milligrams per kilogram of body weight. G6PD - glucose-6-phosphate dehydrogenase
[a] The WHO advises that "temperate" strains be treated with 0.25 mg/kg bw dose, while tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania may require the higher 0.5 mg/kg bw daily dose. *P. falciparum - Plasmodium falciparum, P. vivax – Plasmodium vivax, P. ovale – Plasmodium ovale, P. malariae - Plasmodium malariae, P. knowlesi – Plasmodium knowlesi*

Table 3. The CPIC Guidelines for Primaquine based on G6PD Phenotype

G6PD status (predicted from genotype)[a]	Dosing recommendation	Risk	Classification of recommendation
Normal	No reason to avoid primaquine based on G6PD status	Low	Strong
Deficient	Avoid primaquine at ≥ standard dose (0.25–0.5 mg/kg daily for 14 days)	High	Strong
Deficient	Medium dose (0.75 mg/kg or 45 mg, once weekly for 8 weeks) for *P. vivax* malaria; monitor individuals closely for hemolysis	Medium	Strong
Deficient	Single low dose (0.25 mg/kg) for *P. falciparum* malaria	Low to no	Strong
Deficient with CNSHA	Avoid primaquine	High	Strong
Variable or indeterminant	Ascertain G6PD status by enzyme activity; drug use should be guided by activity-based phenotype.[b]	Variable or unknown	Moderate

This table is adapted from (3). Mg/kg - milligram per kilogram of the individual's body weight. CNSHA - chronic non-spherocytic hemolytic anemia, G6PD - glucose-6-phosephate dehydrogenase, *P. vivax - Plasmodium vivax, P. falciparum - Plasmodium falciparum*
[a] Definition of G6PD status based on data from the World Health Organization and US Centers for Disease Control.
[b] X-linked mosaicism in individuals with more than one X chromosome (who are heterozygous for *G6PD* alleles of different functional status) can lead to variable G6PD function, enzyme-based assays should be used to determine G6PD activity and guide dosing. An enzyme activity-based test is also recommended for individuals with any allele of unknown function.

Drug: Primaquine

Primaquine is an 8-aminoquinoline antimalarial medication, indicated for the radical cure of *P. vivax* and *P. ovale* caused malaria (1, 4). Primaquine is approved by the WHO to prevent relapse of *P. vivax* and *P. ovale* malaria, often with chloroquine (in areas with chloroquine-sensitive *P. vivax*) (2). Though once not recommended in high-transmission settings, the WHO 2022 Malaria Guidelines state that "given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the [WHO Global Malaria Programme] group now recommends that primaquine be used in all settings" (2). In severe *P. vivax* malaria, primaquine therapy should be administered after the completion of other antimalarial therapies that target the active parasites, such as artesunate or chloroquine (2).

The standard administration of primaquine is a daily dose of 0.25 mg base per kg of body weight (mg/kg bw) for 14 days (1, 2). However, some sources recommend a standard adult dose of 15 mg base daily for 14 days, with increased dosing based on either weight over 70 kg or known infection with a frequently relapsing strain of *Plasmodium* (5, 6). In individuals with G6PD deficiency, either standard dosage presents a significant risk of life-threatening hemolysis, so an adjusted regimen of 0.75 mg/kg bw once a week for 8 weeks with close medical supervision is conditionally recommended by the WHO (2). Primaquine may also be administered as a SLD (0.25 mg/kg bw) in addition to artemisinin combination therapy (ACT) to eliminate malaria caused by *P. falciparum* in low-transmission areas (2). The benefit of SLD primaquine is primarily targeted to the community level as a means to reduce transmission, as this dose causes sterilization of the mature *P. falciparum* parasite, rather than curing the infected individual (2, 7, 8).

Primaquine is a pro-drug that needs to be metabolized to exert the desired antimalarial effect. Primaquine is metabolized by 2 different pathways: monoamine oxidase-A (MAO-A) generates the inactive metabolite carboxyprimaquine, while CYP2D6 and CPR generates the 2 active metabolites 5-hydroxyprimaquine and 5-hydroxy-6-desmethylprimaquine (9, 10). Spontaneous oxidation of the active metabolites generates

quinoneimine and H_2O_2 that contribute to the antiparasitic activity of primaquine. The enzyme CPR then mediates redox cycling of quinoneimine to the primaquine active metabolites (9, 10). Primaquine has an estimated systemic half-life of 6 hours, necessitating multiple doses for effective radical cure of *P. vivax* malaria (11).

Primaquine can cause significant oxidative stress due to the accumulation of H_2O_2 in red blood cells, leading to AHA. Under normal homeostatic conditions, NADPH protects cells from oxidative stress. The enzyme G6PD generates NADPH and is particularly critical in red blood cells where it is the only source of NADPH. Individuals who G6PD deficient are especially sensitive to oxidative stress, whether due to endogenous or exogenous sources. As a result, primaquine is contraindicated at standard doses in individuals with G6PD deficiency (1). As discussed below, the residual amount of G6PD activity can vary based on the specific underlying genotype of an individual, so the risk of AHA varies based on the degree of deficiency. The FDA-approved drug label for primaquine advises monitoring blood cell counts and hemoglobin routinely during therapy even in individuals with normal levels of G6PD activity (1).

Contraindications for primaquine treatment include pregnancy, acute illness with a predisposition to granulocytopenia (often seen in rheumatoid arthritis or systemic lupus erythematosus), and medication with other potentially hemolytic drugs (1). The WHO further advise to avoid primaquine therapy in breastfeeding women unless the G6PD status of the breastfed infant is known to be within the normal range (2). One small study found that the estimated primaquine dose that a nursing infant receives following maternal dosing with 0.5 mg/kg/day primaquine was estimated to be 0.6% of the infant daily dose (0.5 mg/day) (12). The amount of primaquine excreted into breastmilk is low, and some sources suggest that G6PD-deficient infants over 28 days of age have a low risk of hemolysis due to primaquine exposure in breastmilk (13); however avoidance of primaquine by nursing mothers when the infants G6PD status is unknown is recommended by WHO, FDA, the US Centers for Disease Control and Prevention, as well as the United Kingdom malaria treatment guidelines (1, 2, 6, 14).

Primaquine is not approved for use in children younger than 6 months of age (2), though one study of infants in Indonesia found that severe clinical outcomes following primaquine treatment in infants under 12 months of age were rare (15). On-going studies suggest that younger children (14 years of age and younger) may require a higher weight-adjusted dose due to lower exposure primaquine and its metabolites (16, 17, 18). The FDA-approved label recommends caution with dose selection for geriatric individuals, as this population has a higher frequency of decreased hepatic, renal, and cardiac function. Initiating therapy at the low end of recommended dosing range is recommended (1). However, both the FDA and the Health Canada approved drug labels clearly state that efficacy and safety of primaquine has not been assessed in individuals over age 65 (1, 5).

In addition to the hemolysis risks, primaquine therapy may also trigger QT prolongation. As such, it should be avoided in conjunction with other medications that prolong the QT interval, in individuals with cardiac conditions such as long QT syndrome, ventricular arrhythmias or bradycardia (1). Other adverse reactions to primaquine can include nausea, vomiting, epigastric distress, abdominal cramps, dizziness, rash, and pruritus. Overdosage of primaquine phosphate can cause these adverse reactions as well as central nervous system and cardiovascular disturbances, cyanosis, granulocytopenia and AHA, among others (1).

Disease: Malaria

Malaria is a serious tropical disease caused by a parasite (*Plasmodium*) that spreads to humans by infected mosquitos. The only available vaccine is moderately effective and acts only against *P. falciparum* species (19). Widely recommended antimalarial drugs such as mefloquine or atovaquone-proguanil can be used for prevention –– this is known as chemoprophylaxis. The type of chemoprophylaxis recommended depends upon the individual taking the prophylaxis (namely, age, pregnancy status, and medical comorbidities) and the nature of their exposure –– specifically, the country of residence or traveled to, the length of stay, the species of

Plasmodium that are most prevalent, and the level of drug resistance. For individuals residing in malaria-endemic regions, the WHO recommends a variety of preventative chemotherapies that can be used in infants, children, during pregnancy or collectively for the population of endemic areas (2).

Despite chemoprophylaxis, travel to malaria-endemic areas is not without risk. Individuals at elevated risk for malaria complications include pregnant women (20) and adults who have had their spleen removed (21). If travel cannot be avoided, chemoprophylaxis should be combined with additional precautions to avoid mosquito bites, such as bed nets and repellents. In 2021, the WHO estimated 247 million cases of malaria occurred worldwide, and malaria was responsible for 619,000 deaths. (22)

Malaria is found in over 100 countries and occurs throughout most tropical regions in the world. These regions include large parts of Africa, Asia, Central and South America, and parts of the Middle East and Pacific islands (22, 23). Individuals who are heterozygous carriers for sickle cell disease and G6PD deficiency have a protective advantage against malaria, and as a result, the frequency of such genetic conditions is higher in countries where malaria is endemic (24).

Malaria is transmitted to humans by the bite of an infected *Anopheles* mosquito. Only female mosquitos spread the infection (females feed on human blood, males feed on nectar). Although malaria can also be spread by sharing contaminated needles or via a contaminated blood transfusion, these are rare means of transmission.

There are several different *Plasmodium* species, but only a few species cause the most malaria cases:

- *P. falciparum*
  - The most common cause of malaria, and death from malaria
  - Predominates in sub-Saharan Africa
  - Also found in regions of Australasia (Papua New Guinea, Southeast Asia), and the Caribbean (Haiti and the Dominican Republic)
- *P. vivax*
  - A common cause of malaria outside of Africa
  - Most frequent species found in Central and South America
  - Parasite has a dormant, hypnozoite stage
  - Early gametocytes that infect mosquitos
- *Plasmodium malariae*
  - Less common
  - Found in most areas where malaria is endemic
- *P. ovale*
  - Less common
  - Parasite has a dormant, hypnozoite stage
- *Plasmodium knowlesi*
  - Less common
  - Found in some Southeast Asia areas

The first stage of malaria infection begins when an infected mosquito bites the human host. Typically, mosquitos bite at dusk, or during the night. As the mosquito feeds, infective parasite sporozoites (the motile spore-like stage in the life cycle of this parasitic sporozoan, which is the infective agent) are inoculated into humans. The sporozoites travel to the liver, where they invade liver cells and asexually reproduce to form schizonts. The liver schizonts contain daughter merozoites. This process is asymptomatic, and because it occurs outside of the red blood cell (erythrocyte), it is known as the exoerythrocytic stage.

Some species of the parasite (*P. vivax* and *P. ovale*) have an additional dormant stage in the liver. The parasite exists as hypnozoites, which can stay in the liver for weeks or months without causing any clinical symptoms.

The second stage of malaria infection is the erythrocytic stage. It begins when the liver schizonts rupture and release the daughter merozoites into the bloodstream. The merozoites invade red blood cells, digest hemoglobin, produce a toxic metabolite (hemozoin), and damage red blood cell membranes. Infected, brittle red blood cells are rapidly broken down (hemolysis) and if too many damaged red blood cells get trapped in the spleen, the spleen can rapidly enlarge (splenic sequestration).

Some of the daughter merozoites differentiate into male or female gametocytes (sexual forms). When they are ingested by a mosquito, they mature, fertilize, reproduce, and develop into sporozoites. When the mosquito feeds again, the sporozoites are inoculated into another human host and the cycle of malaria transmission is complete.

The erythrocytic stage of malaria is usually associated with fever, and malaria should always be suspected in anyone with a fever who has recently returned from a malaria-endemic region, even if antimalarial chemoprophylaxis was correctly followed. Other symptoms and signs include nausea, vomiting, abdominal pain, tachycardia (fast heart rate), diaphoresis (sweating), chills, and myalgia (muscle pain). The complications of malaria infection include severe anemia, cerebral malaria, and multi-organ failure. Without correct diagnosis and prompt treatment, malaria can be fatal.

Gene: *G6PD*

The G6PD enzyme is encoded by the *G6PD* gene, which is located on the long arm of X chromosome (Xq28). Variants in the *G6PD* gene that result in a complete loss of enzymatic activity are not viable; variants observed in living humans generally impact the stability of the enzyme. As such, males can only be hemizygous (have one *G6PD* allele) while females randomly inactivate one X chromosome during development, resulting in a mosaic expression of either one X chromosome or the other in their somatic cells. This mosaicism can occur in the hematopoietic progenitor cells that give rise to red blood cells, resulting in mixed expression of *G6PD* alleles. Females with Turner syndrome (45, X) have only one X chromosome and thus are also hemizygous for the *G6PD* gene. Males with Klinefelter syndrome have an additional X chromosome (47, XXY) and thus 2 *G6PD* alleles. Thus, it is important to consider the number of X chromosomes for an individual when determining *G6PD* genotype or phenotype.

Glucose-6-phosphate dehydrogenase deficiency affects 400 million people worldwide, with a worldwide prevalence of approximately 5% (25). Glucose-6-phosphate dehydrogenase deficiency appears to be protective against malaria infection leading to a higher prevalence (more than 25%) in countries where malaria is, or once was, endemic; for example, tropical Africa, tropical and subtropical Asia, the Middle East, and some parts of the Mediterranean (26, 27, 28). In the US, G6PD deficiency is more common among African Americans, affecting approximately 12% (29).

The G6PD enzyme catalyzes the first step in the hexose monophosphate shunt (HMP) pathway, which converts glucose to pentose sugars for nucleic acid synthesis. In this step NADP+ is reduced to NADPH, which protects cells from oxidative stress. In mature red blood cells, the HMP pathway is the only source of NADPH. This promotes the generation of reduced glutathione that protects the sulfhydryl groups of hemoglobin, which are susceptible to oxidation by H_2O_2 and oxygen radicals. Red blood cells that lack G6PD also have a deficiency of NADPH. (30)

Red blood cells that are G6PD deficient have a normal function but are more susceptible to increased oxidative stress (for example, by reactive oxygen species and H_2O_2). Oxidative stress occurs naturally, but is increased during illnesses, such as infections and diabetic ketoacidosis. Oxidative stress can also follow the ingestion of fresh fava beans (favism), and is an adverse effect of several drugs, for example, the antimalarial drugs primaquine and tafenoquine, the antibacterials dapsone and sulfamethoxazole, the skin cancer drug dabrafenib, and the uric acid lowering drugs pegloticase and rasburicase.

While some reports estimate the frequency of G6PD deficiency to be <0.3% in individuals of European, Finish, or Amish descent, other more targeted population analyses have estimated the frequency of G6PD deficiency to be 0.5% in Portuguese males, 6.4% in males from Cyprus, and 8.3% in newborn males in Greece (31, 32, 33, 34). Among Asian populations, estimates broadly range from 2.7–3.5% of individuals will be G6PD deficient (31). However, a study in Cambodia observed 16% of their male study participants were G6PD deficient (<30% activity) while 32% of their female study participants demonstrated an intermediate level of G6PD activity (30–80%) and 4% were deficient (35). Other studies in Asia report the frequency of G6PD deficiency to be approximately 9–31% in Thailand, almost 30% among the Kachin ethnic group from Myanmar and China, 8% in Lao PDR, 9% in Vietnam, and 15.8% in Myanmar (36, 37, 38, 39, 40). Thus, it is difficult to predict the likelihood of an individual being G6PD deficient based solely on their geographic ancestry, as it can vary significantly within commonly used ancestral designations.

Most individuals with G6PD deficiency are asymptomatic –– they have a normal lifespan and may not know they have G6PD deficiency. However, at birth, they may be predisposed to neonatal jaundice, and throughout life, they will be sensitive to oxidizing agents. All individuals with G6PD deficiency should avoid exposure to oxidizing agents when possible, including drugs such as primaquine.

Symptomatic individuals with G6PD deficiency may suffer from episodes of AHA or, the more severe condition, chronic non-spherocytic hemolytic anemia (CNSHA). The management of hemolytic episodes depends on the severity of hemolysis, with more severe cases requiring blood transfusions. Folic acid may be given to prevent the worsening of anemia in individuals with folate deficiency and to induce formation of new red blood cells.

More than 200 genetic variants of the *G6PD* gene have been identified so far (41), with approximately 400 biochemical and enzyme variants (42). Most known *G6PD* variants are missense, which can also be inherited as haplotypes that are comprised of more than one variant allele (43). Large deletions are rare, and a complete lack of G6PD activity is thought to be fatal in utero.

The normal (wild-type) copy of the *G6PD* gene is known as *G6PD* B, and is found in most Caucasians, Asians, and Africans. Common *G6PD* variants include:

- *G6PD* A+ (p.Asn126Asp) has normal enzyme activity and is not associated with hemolysis, and is found in up to 30% of individuals of African descent and approximately 1.5% of Latinos (44, 45)
- *G6PD* A- (p.Asn126Asp with p.Val68Met) is associated with mild to moderate hemolysis and is found in up to 15% of African Americans (46). Additional *A-* haplotypes have also been identified, both with the A+ variant with a second variant (p.Asn126Asp with p.Arg227Leu; and p.Asn126Asp with p.Leu323Pro. See Nomenclature table below for additional information) (47)
- *G6PD* Mediterranean (p.Ser218Phe) can cause severe hemolysis, and is a common pathogenic variant in Caucasians (48)
- *G6PD* Canton (p.Arg489Leu) can cause severe hemolysis, and is found in Asians (49)
- *G6PD* Viangchan (p.Val291Met) is the most common *G6PD* variant among Thais, Laotians, Cambodians, and Malaysians (50, 51)

The WHO recently updated its categorization of *G6PD* variants into 4 classes based on the median residual enzyme activity in males (expressed as a percentage of normal activity) (52). Class A variants have <20% activity and are associated with CNSHA.

Most individuals with G6PD deficiency have variants that belong to class B (enzyme activity less than 45%). Class B variants are associated with intermittent hemolysis, usually triggered by infection or drugs, but most of the time, affected individuals are asymptomatic. Class C variants show median G6PD activity from 60–150% and are not associated with hemolysis. In class U are all the variants with unknown clinical significance, regardless of activity level. The CPIC has assigned G6PD phenotypes based on *G6PD* genotypes; the updated WHO categories are provided in Table 4 for completeness (3).

Table 4. Assignment of likely G6PD Phenotype based on Genotype/Diplotype (CPIC, 2022)

Likely phenotype	Definition[a]	Genotype	WHO class for *G6PD* variants[b]	Example of diplotype[c]
Normal	Very mild or no enzyme deficiency (no less than 60% of normal enzyme levels) (60–150% of normal activity)	An X chromosome hemizygote who has a nondeficient (class IV) allele	IV (C)	B, Sao Borja
		An individual who has 2 nondeficient (class IV) alleles	IV/IV (C)	B/B, B/Sao Borja
Deficient	Less than 10–60% of normal enzyme activity (20–45% of normal activity)	An X chromosome hemizygote who has a deficient (class II–III) allele	II, III (B)	A–, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham
		An individual who has 2 deficient (class II–III variants) alleles	II/II, II/III, III/III (B)	A–/A–, A–/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan
Deficient with CNSHA	Severe enzyme deficiency (<10% activity) and associated with CNSHA (<20% of normal activity)	An X chromosome hemizygote who has a class I allele	I (A)	Bangkok, Villeurbanne
		An individual who has 2 deficient (class I variants) alleles	I/I (A)	Bangkok/Bangkok, Bangkok/Villeurbanne
Variable[d]	Normal or deficient enzyme activity[c]	An individual who has one nondeficient (class IV) and one deficient (class I–III variants) allele	IV/I, IV/II, IV/III (U)	B/A–, B/Mediterranean, B/Bangkok
Indeterminant	Uncertain		(U)	

CNSHA - chronic non-spherocytic hemolytic anemia, WHO - World Health Organization, G6PD - glucose-6-phosphate dehydrogenase

[a] The traditional (Class I–IV) and updated (A, B, C, and U) activity levels are both provided, with the updated activity ranges provided in parentheses where relevant.

[b] WHO classifications were under revision at the time of Clinical Pharmacogenetics Implementation Consortium publication, updated classifications (using A, B, C, and U designations) have been proposed based on enzyme activity levels and are provided in parenthesis here (52).

Class I alleles are extremely rare; the distinction between class II and III alleles is not clear. Almost all individuals will have class II, III, or IV alleles. It should be noted that the class of a variant may have been assigned only by the clinical manifestations of an individual in which the variant was subsequently identified.

[c] Due to the large number of *G6PD* variants, many other diplotypes may be possible besides those given as examples here; see Supplementary data from(3) for a more comprehensive list of alleles with their assigned WHO class. For Human Genome Variation Society terms, please see the Nomenclature table below. The alleles and diplotypes provided here are based upon the historic class I-IV definitions and may not fit the updated WHO classification.

[d] Due to X-linked mosaicism, females heterozygous for one nondeficient (class IV) and one deficient (class I–III variants) allele may display a normal or a deficient phenotype. It is, therefore, difficult to predict the phenotype of these individuals (Supplementary Material online (*G6PD* heterozygotes)) (3).

This table is adapted from (3).

Phenoconversion of G6PD Phenotype

Increased turnover of red blood cells may lead to a temporary increase in G6PD activity as measured by enzyme activity assays. One study of 335 individuals with acute malaria infection (either *P. vivax* or *P. falciparum*) found that, on average, G6PD enzyme activity was 10.4% lower in the convalescent, post-infection state than during acute malarial infection. Furthermore, 66–87% of individuals who, following resolution of their malarial infection, had intermediate to severe G6PD deficiency yet they had presented with normal levels of G6PD activity during the acute infection stage (53).

Gene: *CYP2D6*

The CYP450 superfamily 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. One prominent member, CYP2D6, is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers (54).

The *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 5). (55) Star alleles are defined by the variants detected on one chromosome (haplotype).

The combination of *CYP2D6* haplotypes that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on their impact on enzyme function, each allele can be assigned an activity score from 0 to 1, which in turn is then used to assign a phenotype (for example, CYP2D6 PM). However, the activity score system is not standardized across all clinical laboratories or *CYP2D6* genotyping platforms. The CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The CYP2D6 phenotype is predicted from the diplotype activity score defined by the sum of the allele score values, which usually ranges from 0 to 3.0: (56)

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

Table 5. Activity Status of Selected *CYP2D6* Alleles

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

For a comprehensive list of *CYP2D6* alleles, please See the Pharmacogene Variation Consortium . Activity scores from (56).

The *CYP2D6*1* allele is the wild-type allele when no variants are detected and is associated with normal enzyme activity and the NM phenotype. 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*) (57, 58, 59, 60) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (61, 62, 63) (see Table 5). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more

common in individuals with European ancestry, **17* more common in Africans, and **10* more common in Asians. (64)

Larger structural variants at the *CYP2D6* locus have also been described, including gene duplications, deletions, tandem alleles, and gene conversions. As one might expect, deletions result in a no-function allele (for example, the **5* allele is a deletion). Duplications have been reported for alleles with normal function and decreased function, as well. In the case of allele duplications, the activity scores for the full complement of *CYP2D6* alleles are summed to determine the predicted metabolizer phenotype. Additional details on structural variants are available from PharmVar (65).

The frequency of the *CYP2D6* star alleles with altered function varies across global populations, resulting in different frequencies of the resulting metabolizer phenotype(s). Given CYP2D6's role in the metabolism of many drugs, the literature on allele and phenotype frequency is expansive. Most populations have a high frequency for normal-function star alleles, and thus a high proportion of the population are NMs. However, reduced-function alleles like *CYP2D6*10* are highly prevalent in East Asian populations, leading to a higher proportion of IM phenotype individuals in this ancestral group. Many groups in sub-Saharan Africa have higher frequencies of decreased-function alleles like *CYP2D6*17* and **29*, which can correlate with lower metabolizer scores in these individuals. More details regarding published allele and phenotype frequencies are available in the CYP2D6 supplemental chapter.

Phenoconversion of CYP2D6 Phenotype

Factors other than genotype can affect CYP2D6 enzyme activity and, thus the metabolizer phenotype of any individual. Administration of multiple drugs, sometimes called polypharmacy or co-medications, can lead to a phenomenon called phenoconversion, whereby an individual with one metabolizer genotype can have the enzymatic activity of a different metabolizer group (higher or lower, depending on the medications). The enzymatic activity of CYP2D6 can be inhibited or reduced by medications including duloxetine, paroxetine, fluoxetine, bupropion, and quinidine (66, 67, 68, 69). This can result in NMs or IMs responding to medications as if they were PMs. Thus, co-medication with multiple CYP2D6 strong or moderate inhibitors may result in reduced metabolism of drug substrates. In contrast, discontinuing a concomitant CYP2D6 inhibitor can then revert the individual's CYP2D6 activity back to genetically predicted phenotype baseline. Both chloroquine and primaquine are used to treat malaria in regions with chloroquine-sensitive *Plasmodium* species, however both inhibit CYP2D6 enzyme activity and co-administration was found to inhibit CYP2D6-mediated hydroxylation (70).

Other Genes of Interest

The *P450 oxidoreductase* (*POR)* gene encodes the CPR enzyme that is involved in primaquine metabolism. Deficiency of *POR* presents with a variety of phenotypes; potential clinical presentations include 21-hydroxylase deficiency, polycystic ovary syndrome, and Antley-Bixler syndrome, as well as a distinct disorder of sexual development (71, 72). Genetic variants in *POR* have been shown to affect the enzymatic activity of many members of the CYP450 family, including 3A4 and 2D6 (73).

Genetic variation in *MAO-A* (rs6323, NM_000240.4:c.891G>T) has been found to be associated with reduced metabolism of primaquine to carboxyprimaquine in healthy volunteers (74). Variation in *CYP2C19* was also shown to influence primaquine metabolism in healthy volunteers, though the clinical impact of the variation was unclear (74).

Drug transport proteins can also impact the efficacy of various medications. Notably, variations in transport proteins encoded by solute carrier organic anion transporter (*SLCO)1A2* and *SLCO1B1* (75), as well as *CYP2C8* (76) variants associated with decreased enzymatic activity, have been associated with altered clearance of *P. vivax* parasites and a higher frequency of relapse after primaquine and chloroquine therapy. It is possible that the

apparent decrease in therapeutic effect associated with these genetic variations is due to altered chloroquine transport or metabolism, particularly as chloroquine is known to be transported by SLCOs and metabolized by CYP2C8.

Linking *G6PD* and *CYP2D6* Genetic Variation with Treatment Response

Individuals with G6PD deficiency (<20% activity) or intermediate deficiency (20–45% activity) (2) are at a significant risk of hemolysis when treated with the standard primaquine course (daily for 14 days) but have shown tolerance for an extended course with a single dose of primaquine per week for 8 weeks (2). One study in Cambodia found that 95% of the individuals with reduced G6PD activity were able to complete the 8-week course of primaquine and no severe adverse events were recorded (35). A meta-analysis of 20 different trials, based in Africa or Asia, of SLD primaquine found that the proposed WHO regimen (0.25 mg/kg) was, indeed, safe, even in the context of G6PD deficiency (7). While individuals with G6PD deficiency demonstrated a more significant drop in hemoglobin concentration in the 2–3 days immediately following treatment and were more likely to experience hemoglobinuria within 72 hours of primaquine treatment, these effects were transitory and only 2 (out of 194) individuals required further intervention (7). Other risk factors for anemia following SLD primaquine, aside from G6PD deficiency, were high parasite density, young age, and the primary anemia risk factor: low baseline hemoglobin levels (7).

Based on non-clinical metabolism data and limited clinical data, the Health Canada approved drug label for primaquine advises that *CYP2D6* polymorphism may be associated with variable clinical response and suggests it may be useful to consider drug-drug interaction or CYP2D6 metabolizer status; it further states that for CYP2D6 PMs, alternative treatment should be considered (5). Several studies in the literature suggest that individuals who are CYP2D6 IM or PMs may not respond well to standard primaquine therapy for the radical cure of *P. vivax* malaria, which may result in a relapse of malaria symptoms and positive malaria tests weeks to months later (77). There are several case reports that link CYP2D6 reduced enzymatic activity or IM/PM genotypes with malaria relapse after primaquine therapy (78, 79, 80, 81, 82, 83). A study of 25 individuals found that IM or PM phenotypes were associated with malaria relapse, while individuals with CYP2D6 NM phenotype did not experience relapse following treatment with chloroquine and primaquine (84). Additionally, a case-control study of 57 individuals found that CYP2D6 IM or PM phenotype (determined either by genotype or inferred based on reduced dextromethorphan metabolism) strongly correlated with increased frequency of malaria relapse (85). A prospective cohort study with 190 individuals found *P. vivax* malaria relapse was more common among individuals with reduced *CYP2D6* activity alleles (86). A study of 260 individuals living in a *P. vivax* endemic region of the Amazon found a significant correlation between *CYP2D6* reduced-function genotype (AS<1) and risk of malaria recurrence (87). In Korea, individuals with CYP2D6 IM phenotype were more likely (an odds ratio of 2.33) to have *P. vivax* malaria relapse even after treatment with primaquine (82). Similar results were observed in a study with 120 individuals in the Yunnan Province of China, where the c.886C>T and *CYP2D6*2* variants were associated with relapse of *P. vivax* malaria after treatment with chloroquine and an 8-day course of primaquine (88). A meta-analysis of 9 studies that included a total of 970 individuals from Asia, Brazil, and Oceania found that CYP2D6 IM and PMs were nearly twice as likely to experience malaria relapse following primaquine therapy as compared to NM or UM individuals (82). In contrast, a small study of 51 individuals treated with chloroquine and primaquine combination therapy did not observe any significant enrichment for CYP2D6 IM or PMs among the relapse group, though the limited number of relapses and sample size may have left this study underpowered (89). A larger study with 157 subjects from Australia also found no association between CYP2D6 activity and malaria relapse (90).

Reduced CYP2D6 activity was found to be associated with reduced clearance of *P. falciparum* gametocytes in SLD primaquine therapy in a study of 774 individuals from Africa; however, even with reduced CYP2D6 activity, the addition of SLD primaquine was more effective to clear gametocytes than ACT alone (91). This same study

found no significant impact of CYP2D6 activity on the frequency or degree of anemia following SLD primaquine in G6PD deficient individuals (91). Similarly, a study of 157 children, aged 1–10 years, found no difference in the incidence or severity of acute hemolysis nor in efficacy against the *Plasmodium* parasites among individuals with reduced CYP2D6 or G6PD activity treated with ACT with SLD primaquine, leading the authors to conclude that this treatment regimen is both safe and sufficient to reduce *P. falciparum* transmission (7). The WHO guidelines do not require G6PD testing when administering SLD primaquine (2).

The *G6PD* and *CYP2D6* Gene Interactions with Medications Used for Additional Indications

Medications that can induce oxidative stress in red blood cells can trigger hemolysis readily in individuals with G6PD enzyme deficiency. Many of these medications are antimalarials (tafenoquine, for example) but many more medications pose a hazard for G6PD deficient individuals.

- Urate-lowering medications: both refractory gout and tumor lysis syndrome can cause systemic elevation of urate levels, medications such as rasburicase and pegloticase are uricase enzymes that aid in the breakdown of uric acid into more soluble metabolites. These reactions produce H_2O_2 as a byproduct, thus increasing oxidative stress in the body.
- Kinase inhibitors: anticancer medications such as dabrafenib may also increase oxidative stress.
- Antimicrobial medications: nitrofurantoin, often used for urinary tract infections, was determined to be a medication of moderate risk for AHA in G6PD-deficient individuals by CPIC and may call for additional monitoring. In contrast, CPIC found sulfamethoxazole to be a medication with low-to-no risk in G6PD deficient individuals. (3)

Additional information on gene-drug interactions for *G6PD* are available from PharmGKB, CPIC and the FDA (search for "G6PD").

The CYP family of enzymes is involved in the metabolism of many substances and CYP2D6 especially has been implicated in altered pharmacologic responses for many compounds. The drugs can be categorized into many different classes:

- Antipsychotics—for example, aripiprazole, risperidone, thioridazine and—to a lesser extent—clozapine is metabolized by CYP2D6. According to the FDA, aripiprazole dosage should be reduced for PMs and thioridazine is contraindicated for individuals who are known to have reduced CYP2D6 activity due to increased risk of potentially fatal side effects. The UMs may have a decreased plasma concentration of risperidone.
- Tricyclic antidepressants—for example, amitriptyline, and imipramine may require dosage adjustments, potentially guided by therapeutic drug monitoring, to achieve the desired therapeutic range in UMs or PMs. Ultimately, tricyclic antidepressants may be ineffective in CYP2D6 UMs.
- Serotonin and norepinephrine reuptake inhibitors—for example atomoxetine and venlafaxine may have reduced efficacy in UMs at standard doses while PMs are at risk of elevated plasma concentrations for both medications. The Dutch Pharmacogenetics Working Group advises against the use of venlafaxine in CYP2D6 PMs and IMs.
- Cardiovascular dysfunction—for example, carvedilol, metoprolol, and propafenone are all metabolized by CYP2D6, and PMs will have higher plasma concentrations of these medications compared with NMs resulting in potentially undesired side effects or (in the case of metoprolol) extensive slowing of the heart rate.
- Anticancer medications—for example, tamoxifen is activated by CYP2D6, and IMs or PMs may have reduced benefit from tamoxifen therapy.

- Pain management—for example, codeine and tramadol are pro-drugs that require activation by CYP2D6 to achieve the desired analgesic effect.
- Various therapies for genetic disorders—for example eliglustat used in the treatment of Gaucher disease, and deutetrabenazine used in the treatment of Huntington disease—have reduced dose recommendations for CYP2D6 PMs. The CYP2D6 UMs may not achieve adequate concentrations of eliglustat and therefore *CYP2D6* genotyping is required before initiation of eliglustat therapy.

It is important to note that *CYP2D6* is the most common biomarker in drug responses for FDA drug labels, the list provided here is by no means exhaustive. Additional information on gene-drug interactions for *CYP2D6* are available from PharmGKB, CPIC and the FDA (search for "CYP2D6").

Genetic Testing

The NIH Genetic Testing Registry (GTR) displays genetic tests that are available for primaquine response, the *G6PD* gene, and the *CYP2D6* gene. Molecular genetic testing can be used to confirm the diagnosis of G6PD deficiency, and testing may also be used to screen females with a family history of G6PD deficiency to see if they are carriers.

While many biochemical *G6PD* variants are known, the genetic underpinnings of some of these variants may still be unknown. Additionally, quantitative, or semi-quantitative tests for G6PD enzyme activity may be more readily available in some settings. Whether the clinical test is biochemical or molecular, assessment of G6PD enzyme activity is required before administering primaquine for the radical cure of *P. vivax* or *P. ovale* malaria, per the FDA (1). A number of point-of-care tests have been developed and tested (92, 93, 94) to improve the accessibility of *G6PD* genetic testing before administration of medications like primaquine, though the availability of such testing in areas with the highest malarial burden is still lacking (95).

The available *CYP2D6* tests include targeted single-gene tests as well as multi-gene panels or genome-wide sequencing tests. In addition, variant *CYP2D6* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (96). The test results may include an interpretation of the individual's predicted metabolizer phenotype, which can be confirmed by checking the diplotype and calculating the *CYP2D6* activity score, as described in the "*CYP2D6* Alleles" section above. When individuals have more than 2 copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", for example, *CYP2D6*1/*2x2*. Some laboratories also use the notation of DUP to indicate an increase in copy number, but the report does not always specify the number of duplications nor the allele that has been duplicated due to technical limitations.

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.

2021 Statement from the US Food and Drug Administration (FDA):

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available.

[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.

Primaquine should not be prescribed for patients with severe G6PD deficiency…

In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. If primaquine administration is considered, baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available.

When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine. Risk factors for G6PD deficiency or favism must be assessed. Baseline hematocrit and hemoglobin must be checked before treatment and close hematological monitoring (e.g. at day 3 and 8) is required. Adequate medical support to manage hemolytic risk should be available.

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

2022 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

It is recommended to avoid primaquine at standard (or higher) anti-relapse dosages of 0.25–0.5 mg/kg daily for 14 days for the treatment of P. vivax or *P. ovale* in G6PD deficiency. For the anti-gametocyte treatment of *Plasmodium falciparum* malaria, the single-dose regimen of 0.25 mg/kg is considered safe and effective (low to no risk in G6PD deficiency). For the treatment of *P. vivax* or *P. ovale* malaria for radical cure of liver-stage infections, 0.75 mg/kg once weekly for 8 weeks (WHO) or 45 mg for adults once weekly for 8 weeks (CDC) is considered in the medium risk category, and patients should be monitored closely for hemolysis… No dose of primaquine is considered safe in patients who are G6PD deficient with CNSHA and thus should be avoided.

Please review the complete therapeutic recommendations that are located here: (3).

2020 Statement from Health Canada:

Hemolytic anemia and G6PD deficiency

Due to the risk of hemolytic anemia in G6PD deficient patients, G6PD testing has to be performed before using primaquine. […] Due to the limitations of G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Observe particular caution in individuals with a personal or family history of hemolytic anemia.

In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of using primaquine; if primaquine administration is considered, the dosage regimen should be adapted accordingly (see DOSAGE AND ADMINISTRATION) and close hematological monitoring is required.

[….]

CYP2D6 genotype:

Based on non-clinical data, primaquine activity probably depends on the formation CYP2D6 metabolite(s). Therefore, CYP2D6 polymorphism may be associated with variability in clinical response to primaquine.

Limited clinical data reported more elevated treatment failure rates in patients with CYP2D6 poor or intermediate metabolizer status than in patients with normal/extensive metabolizer status (see ACTION AND CLINICAL PHARMACOLOGY).

In case of treatment failure, after checking patient's compliance to treatment, it may be useful to reconsider potential concomitant use of CYP2D6 inhibitors (see DRUG INTERACTIONS) and to assess the patient's CYP2D6 status if feasible. For poor CYP2D6 metabolizers, alternative treatment should be considered.

Please review the complete therapeutic recommendations that are located here: (5).

Nomenclature for Selected *G6PD* and *CYP2D6* Alleles

Nomenclature of Selected *G6PD* Alleles

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD B	WT	NM_001042351.3	NP_001035810.1	IV/ Normal	--
G6PD A+	p.Asn126Asp	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	IV/ Normal	rs1050828
G6PD Sao Borja	p.Asp113Asn	NM_001042351.3:c.337G>A	NP_001035810.1:p.Asp113Asn	IV/ Normal	rs5030870
G6PD A-	A-$^{202A/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs1050829
		NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met		
G6PD A-	A-$^{680T/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs137852328
		NM_001042351.3:c.680G>T	NP_001035810.1:p.Arg227Leu		
G6PD A-	A-$^{968C/376G}$	NM_001042351.3:c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs76723693
		NM_001042351.3:c.968T>C	NP_001035810.1:p.Leu323Pro		
G6PD Bangkok	p.Lys275Asn	NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met	III/ Deficient	
G6PD Kalyan-Kerala	p.Glu317Lys	NM_001042351.3:c.949G>A	NP_001035810.1:p.Glu317Lys	III/ Deficient	rs137852339
G6PD Orissa	p.Ala44Gly	NM_001042351.3:c.131C>G	NP_001035810.1:p.Ala44Gly	III/ Deficient	rs78478128
GP6D Canton	p.Arg459Leu	NM_001042351.3:c.1376G>T	NP_001035810.1:p.Arg459Leu	II/ Deficient	rs72554665
G6PD Chatham	p.Ala335Thr	NM_001042351.3:c.1003G>A	NP_001035810.1:p.Ala335Thr	II/ Deficient	rs5030869
G6PD Mediterranean	p.Ser188Phe	NM_001042351.3:c.563C>T	NP_001035810.1:pSer188Phe	II/ Deficient	rs5030868
G6PD Viangchan	p.Val291Met	NM_001042351.3:c.871G>A	NP_001035810.1:p.Val291Met	II/ Deficient	rs137852327
G6PD Villeurbanne	p.Thr334del	NM_001042351.3:c.1000_1002delACC	NP_001035810.1:pThr334del	I/Deficient with CNSHA	n/a

Additional allele information available from PharmGKB and CPIC's G6PD Allele Definition Table (revised 2018).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
* WHO classifications based on (97) WHO - World Health Organization; PharmGKB - Pharmacogenomics Knowledgebase; CPIC - Clinical Pharmacogenetics Implementation Consortium; CNSHA - chronic non-spherocytic hemolytic anemia, G6PD - glucose-6-phosphate dehydrogenase

Nomenclature of Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2D6*2	2851C>T	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*3	2550delA	NM_000106.6:c.775del	NP_000097.3:p.Arg259fs	rs35742686
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	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
CYP2D6*10	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*17	1022C>T	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*27	3854G>A	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
CYP2D6*31	2851C>T	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*36[1]	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C	NM_000106.6:c.1432C>T+ NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735+ rs766507177
	4159G>C	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G	NM_000106.6:c.1444G>A+ NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221+ rs75467367
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
CYP2D6*41	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2989G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

Nomenclature of Selected continued from previous page.

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

[1] *CYP2D6*36* is a gene conversion with *CYP2D7*; variants provided here are from the Pharmacogene Variation Consortium.
CYP2D6 - cytochrome P450 member 2D6, dbSNP - database of single nucleotide polymorphisms
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 (98).
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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