



## Genetic Variants Influencing Patient Response to Opioid Therapy

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Almost every nurse can relate to examples in which an individual receiving a high dose of an opioid had no analgesic effect, whereas another experienced respiratory compromise with a small dose. In many cases, variant responses can be attributed to genetic influences responsible for metabolism of the opioid through the cytochrome p450 system (CYP), including CYP2D6, CYP3A, and CYP2B6. Variants of the mu receptor can also affect the affinity of the opioid for its receptor. A discussion of some common alleles (polymorphisms) associated with variable response to opioids is included in this article.

### Phase I Metabolizing Enzymes

The CYP system is a group of more than 50 metabolizing enzymes responsible for the oxidation of endogenous and exogenous organic compounds (Cavallari, Jeong, & Bress, 2011; Eggert & Howe, 2010; Krau, 2013). Each enzyme within a given subfamily is encoded by a single gene, and polymorphisms are associated with each of these CYP enzymes (Krau, 2013). A polymorphism is a change in the gene's DNA sequence that affects the gene's protein product; each polymorphism associated with that gene is known as an allele. A person who receives the same allele from each parent is considered to be a homozygote at this gene location (locus). A person who receives a different allele from each parent is considered to be a heterozygote.

For each of the identified CYP enzymes, individuals can be placed into four functional categories known as phenotypes: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra metabolizers (UMs) (Cavallari et al., 2011; Fernandez Robles, Degnan, & Candiotti, 2012; Krau, 2013; Vuilleumier, Stamer,

& Landau, 2012). PMs have two non-functional alleles and produce virtually no functional amount of that particular CYP enzyme. IMs have reduced enzyme activity, with at least one allele producing some functional enzyme. EMs carry two functional alleles, and they are considered to have normal enzyme activity. UMs have more than two active alleles (they have inherited extra copies of the gene in question), and these individuals express high enzyme activity. Because the production of each CYP enzyme is regulated by a single gene, an individual may have the IM phenotype for CYP3A4 and the UM phenotype for CYP2D6.

**CYP2D6:** CYP2D6 is responsible for metabolizing 20%–30% of all marketed drugs, including opioids (Cavallari et al., 2011; Fernandez Robles et al., 2012; Krau, 2013). CYP2D6 is the most polymorphic of the CYP system, with more than 130 alleles identified to date (Human Cytochrome P450 [CYP] Allele Nomenclature Committee, 2014). Among the most studied alleles are CYP2D6\*1 and CYP2D6\*2, which are associated with normal enzyme production, and CYP2D6\*10, CYP2D6\*17, CYP2D6\*29, and CYP2D6\*41, which are associated with decreased enzyme activity (Cavallari et al., 2011). CYP2D6\*3, CYP2D6\*4, CYP2D6\*5, CYP2D6\*6, CYP2D6\*7, and CYP2D6\*8 are identified as nonfunctional alleles (Cavallari et al., 2011; Ma & Lu, 2011). The distribution of these alleles varies among ethnic populations, and the individual's phenotype will be determined by which two alleles have been inherited from his or her parents and if he or she inherited an extra copy of that same allele. The phenotypes with greatest implications to drug therapy are PMs and UMs. About 8%–10% of Caucasians and 50% of Asians are considered to be CYP2D6 PMs (Miaskowski, 2009), whereas 10%–16% of Saudi Arabians and Ethiopians are considered to be UMs (Cavallari

et al., 2011; Krau, 2013). The response to therapy depends on whether the opioid is an active compound or a prodrug. Table 1 lists various opioid responses based on the patient's phenotype.

Codeine, a prodrug, must be converted by CYP2D6 to morphine, which is responsible for analgesia (Vuilleumier et al., 2012). After codeine is administered, morphine's median area under the curve shows significant variability based on phenotype (PMs = 0.5 mcg h/l, EMs = 11 mcg h/l, UMs = 16 mcg h/l) (Fernandez Robles et al., 2012). The PM and UM phenotypes are most predictive of opioid response (Vuilleumier et al., 2012). Tramadol is also metabolized by CYP2D6, with its active metabolite (odesmethyltramadol) having 200-fold potency over the parent drug (Vuilleumier et al., 2012). This is why PMs who receive tramadol demonstrate significantly lower response rates than EMs (Vuilleumier et al., 2012). UMs using these drugs have a higher potential for drug intoxication and respiratory compromise (Cavallari et al., 2011; Krau, 2013; Miaskowski, 2009; Vuilleumier et al., 2012).

Hydrocodone and oxycodone also have potent active metabolites mediated by CYP2D6 (Vuilleumier et al., 2012). Andreassen et al. (2012) reported that UMs receiving oxycodone receive a 1.5- to 6-fold increase in analgesia over EMs, and that PMs have significantly lower concentrations of active metabolites (oxymorphone and noroxymorphone) than do EMs. Although phenotype has been shown to influence opioid pharmacokinetics, only a few studies validate differences in response. Vuilleumier et al. (2012) reported that analgesia with oxycodone may be weaker in CYP2D6 PMs, whereas

ONF, 42(4), 420–422.  
doi: 10.1188/15.ONF.420-422