**Supplemental Material**

# Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (*CYP2D6*) genotype and codeine therapy

Kristine R. Crews[1], Andrea Gaedigk[2], Henry M. Dunnenberger[3], Teri E. Klein[4], Danny D. Shen[5], John T. Callaghan[6], Evan D. Kharasch[7], Todd C. Skaar[6]

[1] Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN

[2] Division of Clinical Pharmacology and Medical Toxicology, Children's Mercy Hospital & Clinics, Kansas City, MO

[3] University of Tennessee College of Pharmacy, Memphis, TN

[4] Department of Genetics, Stanford University, Stanford, CA

[5] Departments of Pharmaceutics and Pharmacy, School of Pharmacy, University of Washington, Seattle, WA

[6] Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[7]Department of Veterans Affairs, RLR VA Medical Center, Indianapolis, IN

[8]Division of Clinical and Translational Research, Department of Anesthesiology, Washington University in St. Louis, Saint Louis, MO

**CPIC Updates:**

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on the PharmGKB website (www.pharmgkb.org). Relevant information will be periodically reviewed and updated guidelines will be published online.

**Literature Review:**

We searched the PubMed® database (1966 to February 2011) and Ovid MEDLINE (1950 to February 2011) for keywords (cytochrome P450 2D6) OR (CYP2D6) AND (codeine OR morphine) for the association between *CYP2D6* genotype and codeine metabolism or codeine-related adverse drug event (ADE) or outcome. For additional reviews, see references.(1,2)

To construct a *CYP2D6* minor allele frequency table based on ethnicity, the PubMed® database (1966 to February 2011) and Ovid MEDLINE (1950 to February 2011) were searched using the following criteria: ((CYP2D6 or 2D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity)). Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or minor allele percentages for *CYP2D6* genotypes were reported, (3) the method by which *CYP2D6* was genotyped was reliable and proven (no proof-of-principle experiments), (4) the sample population consisted of at least 50 patients, and (5) the study represented an original publication (no reviews or meta-analyses).

**Gene: *CYP2D6***

**Genetic Test Interpretation**

The haplotype, or star (*) allele name, is determined by the combination of single nucleotide polymorphisms (SNPs) and other sequence variations including insertions and deletions that are interrogated in the genotyping analysis. In addition, large rearrangements including an entire gene deletion (i.e. *CYP2D6*5*), duplications or multiplications of functional, reduced function and non-functional genes, e.g. *CYP2D6*1xN, *2xN, *41xN* and **4xN* can be observed. Also, non-functional hybrid genes composed of *CYP2D7* and *CYP2D6* including *CYP2D6*13, *16* and **66* have been described. A further consideration is that some genotypes may carry a combination of non-functional and functional alleles and until specifically tested for, may be misinterpreted as functional duplications. It is therefore important to know which SNPs a particular test includes and how alleles are defined. Also, not every genotyping test necessarily discriminates between functional and non-functional gene duplications, and hybrid genes are typically not tested for. Consequently, CYP2D6 activity may be over-estimated. Each star (*) allele is defined by the presence of specific sequence variations. The genotypes that constitute the most common haplotype, or star (*) alleles for *CYP2D6* and the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in Supplemental Table S2. Tools for *CYP2D6* allele calling, genotype assignment and phenotype predicting are being developed by PharmGKB and can be accessed at www.pharmgkb.org.

**Challenges of *CYP2D6* genotyping**

Because the genomic structure of the *CYP2D6* gene is complex, there are several factors that cause potential uncertainty in the genotyping results and phenotype predictions. 1) Since it is impractical to test for every variation in the *CYP2D6* gene, patients with rare variants may be assigned a default genotype; this can happen when a patient's one or two rare allele(s) are not included in the genotype test used. 2) There are multiple gene units involved in duplication and other major rearrangements. These may be functional, reduced function, or nonfunctional. If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate. 3) Some SNPs exist on multiple alleles (e.g. rs1065852 100C>T exists on *CYP2D6*4, *10* and **36* alleles; another example is *CYP2D6*69* which carries the 'key' SNPs for *CYP2D6*10* and **41*. If testing indicates heterozygosity for these 2 SNPs (in the absence of 1846G>A), a *CYP2D6*10/*41* genotype is typically assigned, because this is the most likely genotype. However, a *CYP2D6*1/*69* genotype cannot be excluded with certainty.) Therefore to unequivocally determine the presence of certain alleles, testing for multiple SNPs may be required. 4) Allele frequencies may vary considerably among patients of different populations and ethnic backgrounds. *CYP2D6*10,* for instance, is very common in Asian populations, and *CYP2D6*17* is common in people of Sub-Saharan African descent. These alleles, however, have a considerably lower prevalence, or are even absent, in other ethnic groups such as Caucasians of European ancestry. Another example is *CYP2D6*14A:* unless the *CYP2D6*14A* 'key' SNP 1758G>A is tested, heterozygosity of 100C>T and 2850G>A may lead to an assignment of *CYP2D6 *2/*10* and not the correct *CYP2D6*1/*14A* assignment. The latter allelic variant is present in Asian populations and therefore has been incorporated in Asian genotyping panels.(3) Thus, the alleles that should be tested for a given population may vary considerably. And finally, 5) certain alleles carry genes in tandem arrangements. One such example is *CYP2D6*36+*10* (one copy of the non-functional *CYP2D6*36* and one copy of the reduced function *CYP2D6*10*). This tandem can be found in Asians and is typically reported as a default assignment of *CYP2D6*10*.

**Available Genetic Test Options**

Commercially available genetic testing options change over time. Additional updated information can be found at http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp.

The following list provides a selection of different platforms that are currently available for *CYP2D6* genotyping, some of which are approved by the U.S. Food and Drug Administration (FDA). It should be noted that some platforms do not include an assessment of *CYP2D6* copy number and thus cannot adequately assign accurate *CYP2D6* diplotypes.

1. AmpliChip® CYP450 Test (Roche): http://www.roche.com/products/product-details.htm?type=product&id=17
2. xTAG® CYP2D6 (Luminex, Corporation): http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGCYP2D6/index.htm

3. INFINITI® CYP450 2D6 (AutoGenomics, Inc): http://www.autogenomics.com/pharma_2D6.php
4. DMET™ (Affymetrix): http://www.affymetrix.com/browse/products.jsp?productId=131412&navMode=34000&navAction=jump&aId=productsNav#1_1
5. VeraCode® ADME Core Panel (Illumina): http://www.illumina.com/products/veracode_adme_core_panel.ilmn
6. TaqMan® Drug Metabolism Genotyping Assay Sets (Applied Biosystems, Inc): https://products.appliedbiosystems.com/ab/en/US/adirect/ab?cmd=catNavigate2&catID=608221

Clinical genotyping services for *CYP2D6* are available from multiple companies. Several examples are listed below.

1. LabCorp: https://www.labcorp.com/wps/portal/
2. Quest Diagnostics: http://www.questdiagnostics.com/hcp/testmenu/jsp/showTestMenu.jsp?fn=10490.html&labCode=SJC
3. Mayo Medical Laboratories: http://www.mayomedicallaboratories.com/test-catalog/Overview/83180
4. ARUP: http://www.aruplab.com/guides/ug/tests/0051232.jsp
5. PGx Lab (Louisville): http://www.pgxlab.com/cyp-2d6/

**Levels of Evidence**

The evidence summarized in Supplemental Table S6 is graded using a scale based on previously published criteria(4) and applied to other CPIC guidelines:(5-7)

- **High**: Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate**: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak**: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations.

**Strength of Therapeutic Recommendations**

Multiple rating schemes for strength of recommendations in a number of clinical guidelines were evaluated. Ultimately, we chose to use a slight modification of a transparent and simple system for just three categories for recommendations: strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action.(5) CPIC's therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data for codeine, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing CYP2D6, *in vitro* CYP2D6 enzyme activity from tissues isolated from individuals of known *CYP2D6* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians.(5) They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents. **(**http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf )

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

**Supplemental Table S1. Frequencies[a] of *CYP2D6* alleles in major race/ethnic groups[b]**

| Allele | African | African American | Caucasian (European + North American) | Middle Eastern | East Asian | South/Central Asian | Americas | Oceanian |
|---|---|---|---|---|---|---|---|---|
| ***1**[c] | 39.23 | 41.70 | 48.40 | 59.46 | 33.09 | 53.7 | 60.57 | 70.15 |
| ***2**[d] | 20.12 | 12.34 | 26.93 | 24.10 | 12.29 | 31.90 | 24.12 | 1.20 |
| ***3** | 0.03 | 0.34 | 1.27 | 0.13 | 0.00 | 0.00 | 0.42 | 0.00 |
| ***4** | 3.36 | 6.03 | 18.32 | 7.60 | 0.46 | 6.56 | 11.57 | 1.13 |
| ***5** | 6.07 | 5.86 | 2.74 | 2.34 | 5.66 | 2.54 | 1.98 | 4.95 |
| ***6** | 0.00 | 0.27 | 0.96 | 0.96 | 0.03 | 0.00 | 0.74 | 0.00 |
| ***7** | 0.00 | 0.00 | 0.13 | ND | 0.00 | ND | 0.00 | 0.00 |
| ***8** | 0.00 | 0.00 | 0.03 | ND | 0.00 | ND | 0.15 | 0.00 |
| ***9** | 0.10 | 0.54 | 1.99 | 0.00 | 0.09 | 1.43 | 1.33 | 0.00 |
| ***10** | 6.77 | 4.32 | 2.76 | 3.53 | 44.58 | 19.76 | 4.14 | 1.60 |
| ***14** | 0.13 | 0.00 | 0.00 | ND | 0.95 | 0.00 | 0.47 | 0.00 |
| ***17**[e] | 19.98 | 18.32 | 0.29 | 1.40 | 0.02 | 0.38 | 2.01 | 0.05 |
| ***36** | 0.00 | 0.56 | 0.00 | ND | 2.19 | ND | ND | 0.00 |
| ***41**[f] | 10.94 | 10.31 | 8.69 | 22.95 | 2.54 | 10.50 | 6.36 | 0.00 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***1xN*** | 1.47 | 0.44 | 0.70 | 3.81 | 0.29 | 0.50 | 0.84 | 11.83 |
| ***2xN***[g] | 6.41 | 1.61 | 2.24 | 4.93 | 1.54 | 1.25 | 2.42 | 0.00 |
| ***4xN*** | 1.40 | 2.07 | 0.22 | 0.00 | 0.00 | 0.00 | 0.47 | 0.00 |

ND: not determined.

[a] Average frequencies are based on actual numbers of subjects with each allele reported in multiple studies. For full details and references please see http://www.pharmgkb.org/download.action?filename=CYP2D6_Literature_Table_and_Legend.pdf.

[b] Worldwide race/ethnic designations correspond to the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH).(8,9)

[c] Note that because *CYP2D6*1* is not genotyped directly, all alleles testing negative for a sequence variation are defaulted to a *CYP2D6*1* assignment. Likewise, sequence variations of alleles that were not tested for also default to a *CYP2D6*1* assignment and hence contribute to the frequencies reported for this allele. Its inferred frequency is calculated as: 100% - (sum of variant allele frequencies reported in %).

[d] *CYP2D6*2* is a 'default' assignment and, unless tested and discriminated, *CYP2D6*8, *11, *17, *35, *41* among others are defaulted to a *CYP2D6*2* assignment. Its frequency as shown here may therefore be over-estimated.

[e] *CYP2D6*17* is a 'default' assignment and, unless tested and discriminated, includes the rare *CYP2D6*40* and **58* variants.

[f] Note that *CYP2D6*41* has not consistently been determined by its key SNP 2988G>A across studies; some platforms still use the -1584C>G SNP to discriminate between *CYP2D6*2* and **41*. This may lead to an overestimation of the *CYP2D6*41* frequency especially in Africans and their descendents.

[g] *CYP2D6*2xN* contains alleles with confirmed *CYP2D6*2* gene duplications and/or multiplications, but also duplication events that were defaulted to a *CYP2D6*2xN* assignment, i.e. the test determined the presence of a duplication, but did not determine the nature of the duplicated gene. The actual frequency of *CYP2D6*2xN* may therefore be lower than the frequency shown.

**Supplemental Table S2. Commonly tested polymorphisms defining *CYP2D6* variant alleles and their effect on CYP2D6 protein.**

| Allele[a] | Major Nucleotide Variation[b,c] | dbSNP Number[d] | Effect on CYP2D6 Protein |
|---|---|---|---|
| ***1*** [e] | - | - | - |
| ***1xN*** | Gene duplication or multiplication | - | Increased protein expression |
| ***2*** [f] | 2850C>T<br>4180G>C[g] | rs16947,<br>rs1135840 | R296C<br>S486T |
| ***2xN*** | Gene duplication or multiplication | - | Increased protein expression |
| ***3*** | 2549delA | rs35742686 | Frameshift |
| ***4*** | 100C>T,<br>1846G>A<br>[4180G>C[g]] | rs1065852,<br>rs3892097<br>rs1135840 | P34S,<br>splicing defect<br>[S486T] |
| ***4xN*** | Gene duplication or multiplication | - | P34S,<br>splicing defect |
| ***5*** | Gene deletion | N/A | Gene deletion |
| ***6*** | 1707delT | rs5030655 | Frameshift |
| ***10*** | 100C>T<br>4180G>C[g] | rs1065852,<br>rs1135840 | P34S<br>S486T |
| ***17*** | 1023C>T<br>2850C>T<br>4180G>C[g] | rs28371706,<br>rs16947,<br>rs1135840 | T107I<br>R296C<br>S486T |
| ***41*** | 2850C>T<br>2988G>A<br>4180G>C[g] | rs16947,<br>rs28371725,<br>rs1135840 | R296C<br>Splicing defect<br>S486T |

[a] See Human Cytochrome P450 Allele Nomenclature Committee website (http://www.cypalleles.ki.se) for comprehensive haplotype definitions of *CYP2D6* variant alleles and updated allele information.

[b] Based on accession # M33388.

[c] Some of the alleles may carry multiple nucleotide variations. More specific details on the combinations of SNPs present in each allele can be found at http://www.cypalleles.ki.se or http://www.pharmgkb.org/gene/PA128#tabview=tab4. In addition, the specific SNPs included in the genotyping assays can be found in the assays' product inserts.

[d] RefSNP accession ID number (*http://www.ncbi.nlm.nih.gov/snp/*).

[e] The *CYP2D6*1* allele is characterized by the absence of any sequence variations. Consequently, this allele can not be identified by a SNP; rather *CYP2D6*1* is assigned by default when no SNPs are detected during testing.

[f] The *CYP2D6*2* allele is characterized by two amino acid changes; both, however also occur in many other alleles. Therefore, if an allele carries these two SNPs exclusively, it is designated *CYP2D6*2*. This is the only way to truly distinguish *CYP2D6*2* from other alleles (e.g., *CYP2D6*17* and **41*).

[g] This SNP is present on many allelic variants including functional and non-functional variants. Specifically, it has been found on some *CYP2D6*4* subvariants. While some tests include this SNP, it can not be utilized to identify an allelic variant with certainty.

**Supplemental Table S3. Examples of *CYP2D6* genotypes with resulting activity scores and phenotype classification.**

| Allele 1 | Allele 2 | CYP2D6 Diplotype | CYP2D6 Activity Score | Phenotype |
|---|---|---|---|---|
| **1* | **1xN*[a] | **1/*1xN* | ≥3.0 | UM |
| **2x2*[b] | **41* | **2x2/*41* | 2.5 | UM |
| **1* | **2* | **1/*2* | 2.0 | EM |
| **1* | **17* | **1/*17* | 1.5 | EM |
| **2* | **3* | **2/*3* | 1.0 | EM |
| **1* | **4x2* | **1/*4x2*[c] | 1.0 | EM |
| **10* | **10* | **10/*10* | 1.0 | EM[e] |
| **4* | **10* | **4/*10* | 0.5 | IM |
| **5* | **6* | **5/*6*[d] | 0 | PM |

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer. Extensive metabolizers with an activity score of 2.0 are expected to exhibit higher CYP2D6 enzyme activity versus individuals with activity scores of 1.5 and 1.0, respectively.

See www.pharmgkb.org and http://www.cypalleles.ki.se/cyp2d6.htm for updates on *CYP2D6* alleles and nomenclature

[a] **1xN* denotes that the allele carries 2 or more copies of a normal activity *CYP2D6*1* gene. In case of a duplication (2 copies), an activity score value of 2 will be assigned; in case of 3 gene copies, a value of 3 will be assigned, etc. Therefore, if paired with a second functional allele, the activity score is ≥3 depending on the number of genes present.

[b] **2x2* denotes an allele that carries two functional gene copies. In this example the gene duplication is paired with a *CYP2D6*41* allele that carries one copy of a reduced function allele.

[c] Regardless of the number of copies present, *CYP2D6*4* and **4xN* are always non-functional.

[d] The 1707delT variation will present as homozygous in a test due to the absence of a gene copy on the second allele. If no test is performed for the *CYP2D6*5* gene deletion, the genotype will be assigned as homozygous *CYP2D6*6/*6* which is technically inaccurate, but correctly predicts a PM phenotype. The same may occur in the presence of *CYP2D7/2D6* hybrid genes.

[e] Note that some investigators may define patients with a *CYP2D6*10/*10* genotype as intermediate metabolizers. The classification used in this guideline is based on data specific for formation of morphine from codeine.(10,11)

**Supplemental Table S4. Association between allelic variants[a] and CYP2D6 enzyme activity**

| Functional Status | Activity Score | Alleles |
|---|---|---|
| Functional / normal activity/ wild-type[b] | 1 | **1*[c], **2, *27, *33, *35, *45, *46, *39, *48, *53* |
| Reduced-function / decreased activity | 0.5 | **9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72* |
| Non-functional, variant, or mutant / no activity | 0 | **3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *57, *62* |

[a] See http://www.cypalleles.ki.se/cyp2d6.htm for updates on *CYP2D6* allelic variants and nomenclature.

[b] An important caveat for all genotyping tests is that the decision to assign an allele a "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type".

[c] *1 is defined as wild-type.

**Supplemental Table S5. Predicted metabolizer phenotypes based on *CYP2D6* diplotypes (allele combinations).**

| | | Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a]) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Allele** | ***1*** | ***2*** | ***1xN or *2xN*** | ***3*** | ***4 or *4xN*** | ***5*** | ***6*** | ***10*** | ***17*** | ***41*** |
| ***1*** | **EM** | **EM** | **UM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** |
| ***2*** | | **EM** | **UM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** | **EM** |
| ***1xN or *2xN*** | | | **UM** | **EM or UM** | **EM or UM** | **EM or UM** | **EM or UM** | **UM** | **UM** | **UM** |
| ***3*** | | | | **PM** | **PM** | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***4*** | | | | | **PM** | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***5*** | | | | | | **PM** | **PM** | **IM** | **IM** | **IM** |
| ***6*** | | | | | | | **PM** | **IM** | **IM** | **IM** |
| ***10*** | | | | | | | | **EM[b]** | **EM[b]** | **EM[b]** |
| ***17*** | | | | | | | | | **EM[b]** | **EM[b]** |
| ***41*** | | | | | | | | | | **EM[b]** |

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer

[a] Frequencies of predicted metabolizer phenotypes can be estimated based on the frequencies provided in Table S1.

[b] Note that some investigators may define patients with these diplotypes as intermediate metabolizers. The classification used in this guideline is based on data specific for formation of morphine from codeine.(10,11)

**Supplemental Table S6. Evidence linking CYP2D6 phenotype or genotype with codeine metabolism or response.**

| Type of experimental model (in vitro, in vivo preclinical, or clinical) | Major findings | References | Level of evidence* |
|---|---|---|---|
| In Vitro | Decreased Vmax and higher apparent Km for codeine *O*-demethylation to morphine in human liver microsomes with PM phenotype by dextromethorphan metabolism versus EM phenotype | Dayer *et al*. 1988(12) | High |
| In Vitro | Less morphine formation from codeine *O*-demethylation in human liver microsomes with PM phenotype by dextromethorphan versus EM phenotype | Mortimer *et al*. 1990(13) | High |
| In Vitro | Higher apparent Km for codeine *O*-demethylation to morphine in microsomes prepared from yeast cells expressing human CYP2D6 with PM genotype versus EM genotype | Oscarson *et al*. 1997(14) | High |
| In Vitro | Decreased Vmax for codeine *O*-demethylation to morphine in microsomes prepared from insect cells expressing human CYP2D6 reduced-function alleles versus *1 alleles | Yu *et al*. 2002(15); Shen *et al*. 2007(16); Zhang *et al*. 2009(17) | High |
| Preclinical | No analgesia observed in rats deficient for CYP2D1, a homolog for *CYP2D6* in humans, after codeine administration | Cleary et al. 1994(18) | High |
| Clinical | CYP2D6 phenotype by dextromethorphan metabolism correlated with morphine production following codeine administration in healthy volunteers. Metabolic ratios of *O*-demethylation of codeine were highest in EMs, intermediate in IMs and lowest in PMs | Chen *et al*. 1988(19) | High |
| Clinical | CYP2D6 PM phenotype by debrisoquine hydroxylation associated with lower formation and excretion of morphine, morphine-6-glucuronide, morphine-3-glucuronide and normorphine following codeine administration versus EM phenotype | Yue *et al*. 1989(20) | High |
| Clinical | CYP2D6 PM phenotype by sparteine | Sindrup *et al*. 1990(21) | High |

| | | | |
|---|---|---|---|
| | oxygenase associated with lower plasma concentration of morphine following codeine administration versus EM phenotype; codeine did not produce significant analgesia in response to copper vapor laser stimuli in PM phenotype | | |
| Clinical | CYP2D6 PM phenotype by dextromethorphan metabolism associated with lower partial clearance to morphine and codeine-6-glucuronide following single-dose and chronic dosing of codeine versus EM phenotype | Chen *et al*. 1991(22) | High |
| Clinical | CYP2D6 PM phenotype by debrisoquine hydroxylation and induced by drug interaction with quinidine pretreatment associated with lower formation of morphine following codeine administration versus EM phenotype; codeine resulted in no significant analgesia in response to selective transcutaneous nerve stimulation in PM phenotype | Desmeules et al. 1991(23) | High |
| Clinical | CYP2D6 PM phenotype by debrisoquine hydroxylation and induced by drug interaction with quinidine pretreatment associated with reduced *O*-demethylation to morphine, and reduced respiratory, psychomotor and pupillary effects following codeine administration versus EM phenotype | Caraco *et al*. 1996(24) | High |
| Clinical | CYP2D6 PM phenotype by sparteine oxygenase associated with lower formation of morphine and morphine-6-glucuronide following codeine administration versus EM phenotype; codeine did not produce significant analgesia during cold pressor test in PM phenotype | Poulsen *et al*. 1996(25) | High |
| Clinical | CYP2D6 PM genotype in Chinese subjects associated with lower urinary excretion of morphine and morphine-6-glucuronide following codeine administration versus EM genotype | Tseng et al. 1996(26) | High |
| Clinical | CYP2D6 PM phenotype by debrisoquine hydroxylation associated with reduced *O*-demethylation to morphine after codeine administration versus EM phenotype; rifampin induced codeine metabolism to morphine in | Caraco *et al*. 1997(27) | High |

| | | | |
|---|---|---|---|
| | EM and not PM | | |
| Clinical | CYP2D6 PM phenotype by debrisoquine metabolism associated with lower urinary excretion of morphine, morphine-3-glucuronide and morphine-6-glucuronide following codeine administration versus EM phenotype; no difference in prolongation of gastrointestinal transit time in PM versus EM following codeine administration | Hasselström *et al*. 1997(28) | High |
| Clinical | CYP2D6 PM phenotype by dextromethorphan hydroxylation associated with lower urinary excretion of morphine following codeine administration versus EM phenotype; urine opiate screening results were negative sooner for PM phenotype than for EM phenotype after codeine administration | Hedenmalm *et al.* 1997(29) | High |
| Clinical | PM phenotype by sparteine sulfate associated with reduced formation of morphine versus EM phenotype; PM associated with reduced gastrointestinal side effects (i.e., orocecal transit time) after receiving codeine versus EM phenotype | Mikus *et al*. 1997(30) | High |
| Clinical | CYP2D6 PM phenotype by sparteine oxygenase and genotype associated with lower formation of morphine, morphine-3-glucuronide and morphine-6-glucuronide and less analgesia during cold pressor test following codeine administration versus EM phenotype ; no difference in side effect profile in PM versus EM phenotype | Eckhardt *et al*. 1998(31) | High |
| Clinical | CYP2D6 PM phenotype by sparteine metabolism associated with lower urinary excretion of morphine and morphine-6-glucuronide following codeine administration versus EM phenotype | Poulsen *et al*. 1998(32) | High |
| Clinical | No association between *CYP2D6* genotype and analgesia after receiving codeine | Vree *et al*. 2000(33) | High |

| | | | |
|---|---|---|---|
| Clinical | CYP2D6 PM genotype associated with lower plasma concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide following codeine administration versus EM genotype in children; no relationship between phenotype and post-operative analgesia. No significant difference in plasma concentration of morphine or metabolites in IM genotypes versus EM genotypes | Williams *et al.* 2002(34) | High |
| Clinical | CYP2D6 PM phenotype by dextromethorphan metabolism and genotype associated with reduced plasma concentration of morphine, morphine-6-glucuronide and normorphine, and reduced miosis following codeine administration versus EM phenotype. No significant difference in plasma concentration of morphine or metabolites in IM genotype versus EM genotype | Lötsch *et al*. 2006(35) | High |
| Clinical | Higher plasma concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide following codeine administration in healthy volunteers with *CYP2D6* gene duplication (> 2 functional alleles) than in carriers of 2 functional *CYP2D6* alleles; greater incidence of sedation in UM versus EM | Kirchheiner *et al.* 2007(36) | High |
| Clinical | Low morphine formation in PMs following codeine administration predicted by *CYP2D6* genotyping or dextromethorphan-based phenotyping; high morphine formation in UMs predicted by combining dextromethorphan-based phenotyping and *CYP2D6* genotyping | Lötsch *et al.* 2009(11) | High |
| Clinical | African American patients with sickle cell disease and variant *CYP2D6* alleles (*7, *29, *41) had significantly lower excretion of morphine, morphine-6-glucuronide, and morphine-3-glucuronide after codeine dose vs those without variant alleles | Shord *et al.* 2009(37) | High |
| Clinical | Heterozygous EMs (*1/*4) associated with lower urinary excretion of morphine, morphine-3-glucuronide and morphine-6- | Vevelstad *et al.* 2009(10) | High |

| | | | |
|---|---|---|---|
| | glucuronide following codeine and paracetamol or levomepromazine with codeine and paracetamol administration versus homozygous EMs (*1/*1) | | |
| Clinical | CYP2D6 PM genotype associated with lower plasma concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide following codeine administration versus EM genotype in patients with end-stage renal disease | Molanaei *et al.* 2010(38) | High |
| Clinical | Case reports of decreased analgesia from codeine in CYP2D6 PMs by genotype | Persson *et al.* 1995(39); Fagerlund *et al.* 2001(40);Foster *et al.* 2007(41) | Moderate |
| Clinical | Sedation, unresponsiveness, nausea, dizziness, respiratory depression, blurred vision, miosis, epigastric pain in CYP2D6 UMs by genotype following normal doses of codeine | Dalen *et al.* 1997(42); Gasche *et al.* 2004(43) | Moderate |
| Clinical | Fatal neonatal opioid toxicity in an infant breastfed by a CYP2D6 UM mother | Koren *et al.* 2006(44); Madadi et al. 2009(45) | Moderate |
| Clinical | Case reports of severe or fatal respiratory depression and hypoxia in children with UM genotype after receiving codeine | Voronov *et al.* 2007(46); Ciszkowski *et al.* 2009(47) | Moderate |

EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer

References


1. Stamer, U. M., Zhang, L. & Stuber, F. Personalized therapy in pain management: where do we stand? *Pharmacogenomics* **11**, 843-864 (2010).
2. Rollason, V., Samer, C., Piguet, V., Dayer, P. & Desmeules, J. Pharmacogenetics of analgesics: toward the individualization of prescription. *Pharmacogenomics* **9**, 905-933 (2008).
3. Kim, E. Y. *et al.* Robust CYP2D6 genotype assay including copy number variation using multiplex single-base extension for Asian populations. *Clin Chim Acta* **411**, 2043-2048 (2010).
4. Valdes, R., Payne, D.A., Linder, M.W. (NACB, Washington, D.C., 2010).
5. Relling, M. V. & Klein, T. E. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther* **89**, 464-467 (2011).
6. Relling, M. V. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther* **89**, 387-391 (2011).
7. Scott, S. A. *et al.* Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy. *Clin Pharmacol Ther* (2011).
8. Rosenberg, N. A. *et al.* Genetic structure of human populations. *Science* **298**, 2381-2385 (2002).
9. Rosenberg, N. A. *et al.* Clines, clusters, and the effect of study design on the inference of human population structure. *PLoS Genet* **1**, e70 (2005).
10. Vevelstad, M., Pettersen, S., Tallaksen, C. & Brors, O. O-demethylation of codeine to morphine inhibited by low-dose levomepromazine. *Eur J Clin Pharmacol* **65**, 795-801 (2009).
11. Lotsch, J. *et al.* Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* **144**, 119-124 (2009).
12. Dayer, P., Desmeules, J., Leemann, T. & Striberni, R. Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome P-450 dbl/bufI). *Biochem Biophys Res Commun* **152**, 411-416 (1988).
13. Mortimer, O. *et al.* Polymorphic formation of morphine from codeine in poor and extensive metabolizers of dextromethorphan: relationship to the presence of immunoidentified cytochrome P-450IID1. *Clin Pharmacol Ther* **47**, 27-35 (1990).
14. Oscarson, M., Hidestrand, M., Johansson, I. & Ingelman-Sundberg, M. A combination of mutations in the CYP2D6*17 (CYP2D6Z) allele causes alterations in enzyme function. *Mol Pharmacol* **52**, 1034-1040 (1997).
15. Yu, A., Kneller, B. M., Rettie, A. E. & Haining, R. L. Expression, purification, biochemical characterization, and comparative function of human cytochrome P450 2D6.1, 2D6.2, 2D6.10, and 2D6.17 allelic isoforms. *J Pharmacol Exp Ther* **303**, 1291-1300 (2002).
16. Shen, H. *et al.* Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. *Drug Metab Dispos* **35**, 1292-1300 (2007).

17. Zhang, W. Y., Tu, Y. B., Haining, R. L. & Yu, A. M. Expression and functional analysis of CYP2D6.24, CYP2D6.26, CYP2D6.27, and CYP2D7 isozymes. *Drug Metab Dispos* **37**, 1-4 (2009).
18. Cleary, J., Mikus, G., Somogyi, A. & Bochner, F. The influence of pharmacogenetics on opioid analgesia: studies with codeine and oxycodone in the Sprague-Dawley/Dark Agouti rat model. *J Pharmacol Exp Ther* **271**, 1528-1534 (1994).
19. Chen, Z. R., Somogyi, A. A. & Bochner, F. Polymorphic O-demethylation of codeine. *Lancet* **2**, 914-915 (1988).
20. Yue, Q. Y., Svensson, J. O., Alm, C., Sjoqvist, F. & Sawe, J. Codeine O-demethylation co-segregates with polymorphic debrisoquine hydroxylation. *Br J Clin Pharmacol* **28**, 639-645 (1989).
21. Sindrup, S. H. *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* **48**, 686-693 (1990).
22. Chen, Z. R., Somogyi, A. A., Reynolds, G. & Bochner, F. Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* **31**, 381-390 (1991).
23. Desmeules, J., Gascon, M. P., Dayer, P. & Magistris, M. Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* **41**, 23-26 (1991).
24. Caraco, Y., Sheller, J. & Wood, A. J. Pharmacogenetic determination of the effects of codeine and prediction of drug interactions. *J Pharmacol Exp Ther* **278**, 1165-1174 (1996).
25. Poulsen, L. *et al.* Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol* **51**, 289-295 (1996).
26. Tseng, C. Y., Wang, S. L., Lai, M. D., Lai, M. L. & Huang, J. D. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther* **60**, 177-182 (1996).
27. Caraco, Y., Sheller, J. & Wood, A. J. Pharmacogenetic determinants of codeine induction by rifampin: the impact on codeine's respiratory, psychomotor and miotic effects. *J Pharmacol Exp Ther* **281**, 330-336 (1997).
28. Hasselstrom, J., Yue, Q. Y. & Sawe, J. The effect of codeine on gastrointestinal transit in extensive and poor metabolisers of debrisoquine. *Eur J Clin Pharmacol* **53**, 145-148 (1997).
29. Hedenmalm, K., Sundgren, M., Granberg, K., Spigset, O. & Dahlqvist, R. Urinary excretion of codeine, ethylmorphine, and their metabolites: relation to the CYP2D6 activity. *Ther Drug Monit* **19**, 643-649 (1997).
30. Mikus, G. *et al.* Effect of codeine on gastrointestinal motility in relation to CYP2D6 phenotype. *Clin Pharmacol Ther* **61**, 459-466 (1997).
31. Eckhardt, K. *et al.* Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain* **76**, 27-33 (1998).
32. Poulsen, L., Riishede, L., Brosen, K., Clemensen, S. & Sindrup, S. H. Codeine in post-operative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol* **54**, 451-454 (1998).

33. Vree, T. B., van Dongen, R. T. & Koopman-Kimenai, P. M. Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract* **54**, 395-398 (2000).
34. Williams, D. G., Patel, A. & Howard, R. F. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* **89**, 839-845 (2002).
35. Lotsch, J. *et al.* Evidence for morphine-independent central nervous opioid effects after administration of codeine: contribution of other codeine metabolites. *Clin Pharmacol Ther* **79**, 35-48 (2006).
36. Kirchheiner, J. *et al.* Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* **7**, 257-265 (2007).
37. Shord, S. S. *et al.* The pharmacokinetics of codeine and its metabolites in Blacks with sickle cell disease. *Eur J Clin Pharmacol* **65**, 651-658 (2009).
38. Molanaei, H. *et al.* Influence of the CYP2D6 polymorphism and hemodialysis on codeine disposition in patients with end-stage renal disease. *Eur J Clin Pharmacol* **66**, 269-273 (2010).
39. Persson, K. *et al.* Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* **39**, 182-186 (1995).
40. Fagerlund, T. H. & Braaten, O. No pain relief from codeine...? An introduction to pharmacogenomics. *Acta Anaesthesiol Scand* **45**, 140-149 (2001).
41. Foster, A., Mobley, E. & Wang, Z. Complicated pain management in a CYP450 2D6 poor metabolizer. *Pain Pract* **7**, 352-356 (2007).
42. Dalen, P., Frengell, C., Dahl, M. L. & Sjoqvist, F. Quick onset of severe abdominal pain after codeine in an ultrarapid metabolizer of debrisoquine. *Ther Drug Monit* **19**, 543-544 (1997).
43. Gasche, Y. *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* **351**, 2827-2831 (2004).
44. Koren, G., Cairns, J., Chitayat, D., Gaedigk, A. & Leeder, S. J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* **368**, 704 (2006).
45. Madadi, P. *et al.* Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* **85**, 31-35 (2009).
46. Voronov, P., Przybylo, H. J. & Jagannathan, N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. *Paediatr Anaesth* **17**, 684-687 (2007).
47. Ciszkowski, C., Madadi, P., Phillips, M. S., Lauwers, A. E. & Koren, G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med* **361**, 827-828 (2009).