

Supplemental Material

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

Kristine R. Crews¹, Andrea Gaedigk², Henry M. Dunnenberger³, Teri E. Klein⁴, Danny D. Shen⁵, John T. Callaghan⁶, Evan D. Kharasch⁷, Todd C. Skaar⁶

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.pgxlabs.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

<i>*1xN</i>	1.47	0.44	0.70	3.81	0.29	0.50	0.84	11.83
<i>*2xN^g</i>	6.41	1.61	2.24	4.93	1.54	1.25	2.42	0.00
<i>*4xN</i>	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
<i>*1</i> ^e	-	-	-
<i>*1xN</i>	Gene duplication or multiplication	-	Increased protein expression
<i>*2</i> ^f	2850C>T 4180G>C ^g	rs16947, rs1135840	R296C S486T
<i>*2xN</i>	Gene duplication or multiplication	-	Increased protein expression
<i>*3</i>	2549delA	rs35742686	Frameshift
<i>*4</i>	100C>T, 1846G>A [4180G>C ^g]	rs1065852, rs3892097 rs1135840	P34S, splicing defect [S486T]
<i>*4xN</i>	Gene duplication or multiplication	-	P34S, splicing defect
<i>*5</i>	Gene deletion	N/A	Gene deletion
<i>*6</i>	1707delT	rs5030655	Frameshift
<i>*10</i>	100C>T 4180G>C ^g	rs1065852, rs1135840	P34S S486T
<i>*17</i>	1023C>T 2850C>T 4180G>C ^g	rs28371706, rs16947, rs1135840	T107I R296C S486T
<i>*41</i>	2850C>T 2988G>A 4180G>C ^g	rs16947, rs28371725, rs1135840	R296C Splicing defect 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 <i>O</i> -demethylation to morphine in human liver microsomes with PM phenotype by dextromethorphan metabolism versus EM phenotype	Dayer <i>et al.</i> 1988(12)	High
In Vitro	Less morphine formation from codeine <i>O</i> -demethylation in human liver microsomes with PM phenotype by dextromethorphan versus EM phenotype	Mortimer <i>et al.</i> 1990(13)	High
In Vitro	Higher apparent Km for codeine <i>O</i> -demethylation to morphine in microsomes prepared from yeast cells expressing human CYP2D6 with PM genotype versus EM genotype	Oscarson <i>et al.</i> 1997(14)	High
In Vitro	Decreased Vmax for codeine <i>O</i> -demethylation to morphine in microsomes prepared from insect cells expressing human CYP2D6 reduced-function alleles versus *1 alleles	Yu <i>et al.</i> 2002(15); Shen <i>et al.</i> 2007(16); Zhang <i>et al.</i> 2009(17)	High
Preclinical	No analgesia observed in rats deficient for CYP2D1, a homolog for <i>CYP2D6</i> in humans, after codeine administration	Cleary <i>et al.</i> 1994(18)	High
Clinical	CYP2D6 phenotype by dextromethorphan metabolism correlated with morphine production following codeine administration in healthy volunteers. Metabolic ratios of <i>O</i> -demethylation of codeine were highest in EMs, intermediate in IMs and lowest in PMs	Chen <i>et al.</i> 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 <i>et al.</i> 1989(20)	High
Clinical	CYP2D6 PM phenotype by sparteine	Sindrup <i>et al.</i> 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 <i>et al.</i> 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 <i>O</i> -demethylation to morphine, and reduced respiratory, psychomotor and pupillary effects following codeine administration versus EM phenotype	Caraco <i>et al.</i> 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 <i>et al.</i> 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 <i>O</i> -demethylation to morphine after codeine administration versus EM phenotype; rifampin induced codeine metabolism to morphine in	Caraco <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 1998(32)	High
Clinical	No association between <i>CYP2D6</i> genotype and analgesia after receiving codeine	Vree <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 2006(35)	High
Clinical	Higher plasma concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide following codeine administration in healthy volunteers with <i>CYP2D6</i> gene duplication (> 2 functional alleles) than in carriers of 2 functional <i>CYP2D6</i> alleles; greater incidence of sedation in UM versus EM	Kirchheiner <i>et al.</i> 2007(36)	High
Clinical	Low morphine formation in PMs following codeine administration predicted by <i>CYP2D6</i> genotyping or dextromethorphan-based phenotyping; high morphine formation in UMs predicted by combining dextromethorphan-based phenotyping and <i>CYP2D6</i> genotyping	Lötsch <i>et al.</i> 2009(11)	High
Clinical	African American patients with sickle cell disease and variant <i>CYP2D6</i> 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 <i>et al.</i> 2009(37)	High
Clinical	Heterozygous EMs (*1/*4) associated with lower urinary excretion of morphine, morphine-3-glucuronide and morphine-6-	Vevelstad <i>et al.</i> 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 <i>et al.</i> 2010(38)	High
Clinical	Case reports of decreased analgesia from codeine in CYP2D6 PMs by genotype	Persson <i>et al.</i> 1995(39); Fagerlund <i>et al.</i> 2001(40); Foster <i>et al.</i> 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 <i>et al.</i> 1997(42); Gasche <i>et al.</i> 2004(43)	Moderate
Clinical	Fatal neonatal opioid toxicity in an infant breastfed by a CYP2D6 UM mother	Koren <i>et al.</i> 2006(44); Madadi <i>et al.</i> 2009(45)	Moderate
Clinical	Case reports of severe or fatal respiratory depression and hypoxia in children with UM genotype after receiving codeine	Voronov <i>et al.</i> 2007(46); Ciszkowski <i>et al.</i> 2009(47)	Moderate

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

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