

Report Contents

1. Coriell Personalized Medicine Collaborative Research Study Report. This report includes all data included in the clinical report as well as supplemental drug specific interpretations and educational material.
2. Clinical Report. This report was generated and approved by Coriell's CLIA certified genotyping laboratory.



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CPMC Research Study Report

Name:	NATALIE DEMO	Gender:	Female
Date of Birth:		Date Collected:	
Coriell ID:	DEMONAT	Date Received:	
Lab Accessioning Number:	DEMONAT	Date of Report:	07/26/2017
Ordering Physician:			

CYP2D6 and Codeine Response

These results were generated in a CLIA-approved laboratory as part of the Coriell Personalized Medicine Collaborative research study. Results take into account 20 genetic variants in the CYP2D6 gene and the total number of gene copies that are present, all of which are known to contribute to the metabolism of codeine. This report reflects this participant's predicted metabolism status based on genetic testing but does not reflect whether they are currently taking codeine.

The CPMC has a genetic counselor available to assist with report interpretation at no charge. For questions please contact us at cpmcgc@coriell.org or by phone at 888-580-8028. Participants may schedule an appointment with a board certified genetic counselor by logging into their web portal account and clicking on "request an appointment". For general information about the CPMC please visit our website cpmc.coriell.org.

This research report includes all data included in the clinical report as well as supplemental drug specific interpretations and educational material. Please see the report that follows for the official clinical report.

Your Genetic Result

The CPMC tested multiple sites of genetic variation within the CYP2D6 gene and checked the number of copies of CYP2D6 that you carry, all of which affect the way the body responds to codeine.

Your combination of genetic variant results is listed below in yellow.
Your CYP2D6* result is:

CYP2D6*1/*1 (x4)
(Codeine Ultra-Rapid Metabolizer)

VARIANTS TESTED	YOUR RESULT ¹	REFERENCE VALUE
rs35742686 (CYP2D6*3)	A/A	A/A
rs3892097 (CYP2D6*4M, CYP2D6*4)	G/G	G/G
rs5030655 (CYP2D6*6)	T/T	T/T
rs5030867 (CYP2D6*7)	A/A	A/A
rs28371720 (CYP2D6*9)	AGA/AGA	AGA/AGA
rs1065852 (CYP2D6*10, CYP2D6*4, CYP2D6*14A, CYP2D6*36, CYP2D6*56B, CYP2D6*64, CYP2D6*69)	C/C	C/C
rs5030863 (CYP2D6*11)	G/G	G/G
rs5030862 (CYP2D6*12)	G/G	G/G
rs5030865 (CYP2D6*14B, CYP2D6*14A)	G/G	G/G
rs72549357 (CYP2D6*15)	T/T	T/T
rs28371706 (CYP2D6*17, CYP2D6*40, CYP2D6*64)	C/C	C/C
rs72549353 (CYP2D6*19)	AACT/AACT	AACT/AACT
rs72549354 (CYP2D6*20)	-/-	-/-
rs72549352 (CYP2D6*21)	-/-	-/-
rs72549351 (CYP2D6*38)	GACT/GACT	GACT/GACT
rs72549356 (CYP2D6*40)	-/-	-/-
rs28371725 (CYP2D6*41, CYP2D6*69)	G/G	G/G
rs72549346 (CYP2D6*42)	-/-	-/-
rs72549349 (CYP2D6*44)	G/G	G/G
rs72549347 (CYP2D6*56, CYP2D6*56B)	C/C	C/C
EXON 9 GENE CONVERSION COPIES (CYP2D6*36)	0	0
CYP2D6 GENE COPY NUMBER ²	4	2

¹When your variant result for all CYP2D6 variants tested are the same as the reference, the combined genetic result is called CYP2D6*1/*1. In some cases your combined genetic result may be uncertain. Other variants, not currently included in this CPMC test may influence this result and interpretation.

²When a CYP2D6 copy number of greater than two copies is detected, the CPMC test cannot determine which of the two CYP2D6*numbered genes has multiple copies and both possibilities are considered in the interpretation of your metabolizer type.

Interpretation of Your Results
Codeine Ultra-Rapid Metabolizer
CYP2D6 Result: CYP2D6*1/*1 (x4)

- Your combination of genetic variants indicates that you have increased CYP2D6 activity.
- Ultra-rapid metabolizers convert codeine to morphine at a fast rate and are at risk of an adverse reaction to codeine.
- An alternative pain medication should be considered.
- If you are currently taking codeine and experiencing side effects such as drowsiness, shortness of breath and nausea, talk to your doctor about an alternative pain medication.
- This result may also affect your response to other medications.

Share this information with your healthcare providers.

Do not make any changes to any medication without talking to your healthcare provider.

How Common

The table and picture below show the different types of codeine metabolizers and how common each is in the African Ancestry population.

Reduced CYP2D6 activity	<u>Poor Metabolizer</u> 3 out of 100 people Not expected to respond to codeine.	
	<u>Intermediate Metabolizer</u> 26 out of 100 people Less likely to respond to codeine.	
Typical CYP2D6 activity	<u>Extensive Metabolizer</u> 69 out of 100 people Expected to respond to codeine.	
Increased CYP2D6 activity	<u>Ultra-Rapid Metabolizer</u> 2 out of 100 people Increased risk of an adverse reaction when taking codeine.	

What is Codeine?

Codeine is an opioid analgesic that is primarily used to treat pain.

Uses:

- Treatment of mild to moderately severe pain
- Treatment of cancer associated pain
- Treatment of diarrhea and diarrhea-predominant irritable bowel syndrome
- Suppression of cough

Risk Factors Affecting Response to Codeine

Genetic Risk Factors

Genetic variants, or changes, in a gene called CYP2D6 can affect the way your body metabolizes codeine. Some people with certain genetic variants may not benefit as much from taking codeine, while some people with another type of genetic variation may have an adverse reaction to codeine. These people are likely to benefit from using an alternative drug.

Non-Genetic Risk Factors

Many factors affect how your body responds to medications.

Non-genetic factors include: diet, lifestyle, medical history and interactions between medications.

Genetic Risk Factors

Some medications are metabolized (broken down or activated) by enzymes. Variants in the genes coding for these enzymes may cause your body to metabolize a medication more quickly or more slowly than normal. This change can affect how well the medication works, as well as the risk of side effects.

Genes Affecting Codeine Metabolism:

CYP2D6

Types of Variants in CYP2D6

There are many variants in the CYP2D6 gene. Some variants are changes in the DNA sequence and others are changes in the number of copies of the entire gene. A number system has been created to name common combinations of variants and to name the number of gene copies. Some variant combinations have not been assigned a number yet. Other combinations of variants cannot be assigned a number with certainty. When possible, you will have a CYP2D6 result with two numbers. If a copy number variation is present, this will be shown by a multiplication sign followed by the number of copies of the gene.

Example: CYP2D6 *1/*4 (× 3)

Types of Codeine Metabolizers

Each result is associated with a metabolizer status which describes how the enzyme is working.

Example: poor metabolizer

Drug-Drug Interactions

In addition to your genes, other medications that you take may affect how your body responds to codeine and may increase the risk of side effects associated with both codeine and the other medications.

The following medications, when taken with codeine, may not work as well, may reduce the benefit of taking codeine, or may increase the risk for side effects:

	Drug Class/Type	Medication
	Macrolide antibiotics	Erythromycin (Erygel [®])
CYP3A4 inhibitors	Azole-antifungal agents	Ketoconazole (Extina [®] , Nizoral [®] , Xolegel [®])
	Protease inhibitors	Ritonavir (Norvir [®])
CYP3A4 inducers		Rifampin (Rifamate [®] , Rifadin [®]), Carbamazepine (Carbatrol [®] , Equetro [®] , TEGretol [®]), Phenytoin (Dilantin [®] , Phenytek [®])
CYP2D6 inhibitors		Paroxetine (Paxil [®]), Fluoxetine (Prozac [®]), Bupropion (Aplenzin [®] , Wellbutrin [®] , Zyban [®]), Quinidine (Quinaglute [®] , Quinidex [®])
	Benzodiazepines and other sedatives/hypnotics, anxiolytics	Diazepam (Valium [®]), Alprazolam (Xanax [®]), Clonazepam (Klonopin [®]), Lorazepam (Ativan [®])

	sedatives/hypnotics, anxiolytics, tranquilizers	Clonazepam (Klonopin [™]), Lorazepam (Ativan [™]), Zolpidem (Ambien [®]), Melatonin
	Muscle relaxants	Baclofen (Gablofen [®]), Chlorzoxazone (Lorzone [®] , Parafon [®]), Carisoprodol (Soma [®]), Cyclobenzaprine (Amrix [®] , Fexmid [®]), Dantrolene (Dantrium [®] , Ryanodex [®]), Metaxalone (Skelaxin [®]), Methocarbamol (Robaxin [®]), Tizanidine (Zanaflex [®])
CNS Depressants	General anesthetics	Propofol (Diprivan [®]), Ketamine (Ketalar [®]), Isoflurane (Forane [®] , Terrell [®]), Sevoflurane (Sojourn [®] , Ultane [®]), Etomidate (Amidate [®]), Enflurane, Desflurane (Suprane [®])
	Antipsychotics	Haloperidol (Haldol [®]), Risperidone (Risperdal [®]), Aripiprazole (Abilify [®]), Clozapine (Clozaril [®] , FazaClo [®]), Iloperidone (Fanapt [®]), Olanzapine (Zyprexa [®]), Quetiapine (Seroquel [®])
	Other opioids	Morphine (MS Contin [®] , Roxanol [®] , Kadian [®]), Oxycodone (Oxycontin [®] , Roxicodone [®]), Fentanyl (Duragesic [®]), Tramadol (Conzip [®] , Ryzolt [®] , Ultram [®]), Hydrocodone (Hycodan [®] , Robidone [®])
	Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (Prozac [®]), Sertraline (Zoloft [®]), Citalopram (Celexa [®]), Escitalopram (Lexapro [®]), Fluvoxamine (Luvox [®])
	Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine (Effexor [®]), Duloxetine (Cymbalta [®])

Serotonergic Drugs	Tricyclic antidepressants (TCAs)	Amitriptyline (Elavil [®]), Imipramine (Tofranil [®]), Clomipramine (Anafranil [®]), Nortriptyline (Pamelor [®]), Desipramine (Norpramin [®]), Doxepin (Silenor [®]), Trimipramine (Surmontil [®])
	Triptans	Sumatriptan (Imitrex [®])
	5-HT ₃ receptor antagonists	Odansetron (Zofran [®] , Zuplenz [®]), Granisetron (Sancuso [®]), Palonosetron (Aloxi [®])
	Other drugs that effect the serotonin neurotransmitter system	Mirtazapine (Remeron [®]), Trazodone (Oleptro [®])
Monoamine Oxidase Inhibitors (MAOIs)		Phenelzine (Nardil [®]), Tranylcypromine (Parnate [®]), Linezolid (Zyvox [®]), Intravenous methylene blue
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics		Butorphanol (Stadol [®]), Nalbuphine (Nubain [®]), Pentazocine (Talwin [®]), Buprenorphine (Buprenex [®] , Butrans [®])
Diuretics		Hydrochlorothiazide (Microzide [®]), Furosemide (Lasix [®]), Spironolactone (Aldactone [®]), Triamterene (Dyrenium [®])
Anticholinergics		Benzatropine (Cogentin [®]), Dimenhydrinate (Dramamine [®]), Diphenhydramine (Benadryl [®]),

Dextromethorphan (Delsym[™], Robitussin[™])

If you are taking codeine now, or are prescribed it in the future, talk to your healthcare providers about other medications you are taking that may interact with codeine.

Result Limitations

- This result alone does **NOT** predict your total response to codeine.
- Other factors such as body weight, various health conditions, and other medications may impact an individual's response to codeine.
- There may be other genetic variants within the CYP2D6 gene which influence response to codeine but are not included in this test.
- There may be other genetic variants or combinations of known genetic variants in the CYP2D6 gene for which response to codeine has not been documented and/or validated in multiple studies.
- There may be genetic variants in other genes that influence response to codeine.
- This result reflects published data available at the time this gene-drug pair was approved by the CPMC Informed Cohort Oversight Board (December, 2010). The information provided may change as new scientific information becomes available.
- Although rare, it is possible that you may receive an incorrect result; 100% accuracy of reported results cannot be guaranteed.
- Occasionally, we will be unable to interpret one or more gene variants. In this case you will not receive a result for those variants and in some cases your drug response cannot be interpreted. It is expected that you will receive results for about 95% of variants approved by the Pharmacogenetics Advisory Group (PAG) and Informed Cohort Oversight Board (ICOB).
- Every effort will be made to provide you with risk information based on your reported race/ethnicity. However, data may not be available for all races/ethnicities. Please see your individual results to determine which race/ethnicity the data is based on.

Test Limitations

DNA-based testing is highly accurate, however there are many sources of potential error including: mis-identification of samples, rare technical errors, trace contamination of PCR reactions, and rare genetic variants that interfere with analysis. This test or one or more of its components was developed and its performance characteristics determined by the Coriell Institute for Medical Research. It has not been approved by the Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary. The Coriell Institute is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high-complexity testing.

Methods

References

- Brousseau DC, et al. *The Journal of Pediatrics*. 2007; 150:623-626.
- Crews KR, et al. *Clinical Pharmacology and Therapeutics*. 2012; 91(2):321-326.
- Eckhardt K, et al. *Pain*. 1998; 76:27-33.
- Gharani N, et al. *Genome Medicine*. 2013; 5(10):93.
- The Human Cytochrome P450 (CYP) Allele Nomenclature Database: <http://www.cypalleles.ki.se/cyp2d6.htm>
- Kirchheiner J, et al. *The Pharmacogenomics Journal*. 2007; 7:257-265.
- Koren G, et al. *Lancet*. 2006; 368:704.
- Lotsch J, et al. *Pain*. 2009; 144:119-124.
- Madadi P, et al. *Clinical Pharmacology and Therapeutics*. 2009; 85:31-35.

Test Methodology

Saliva samples were collected using Oragene DNA Collection Kits (DNA Genotek) and DNA was extracted manually according to the manufacturer's instructions or automatically using a DNAdvance Kit (Agencourt). Purified DNA was quantified using UV absorbance at 260 nm. One microgram of the resulting DNA from each sample was used as template in the Affymetrix DMET Plus GeneChip assay. Data analysis was performed using Affymetrix DMET Console software. Ten nanogram of DNA from each sample was used in the CYP2D6 copy number assay (Taqman Copy Number Assay, ThermoFisher, Hs00010001). Data analysis was performed using CopyCaller V2.1 software (ThermoFisher). Risk interpretation was based on Coriell's CYP2D6/Codeine Response Genotype Translation Version 1.

To view your clinical report, [click here](#). The clinical report contains the lab generated testing information and does not include all the content in the research study report.

[Risk interpretation based on Coriell's CYP2D6/Codeine Activity Genotype Translation Version 1 (January 2015)]



CYP2D6 GENE TEST FOR CODEINE RESPONSE

Name: NATALIE DEMO Sample Type: Saliva
 Date of Birth: Gender: Female
 Coriell ID: DEMONAT Date Collected:
 Lab Accessioning Number: DEMONAT Date Received:
 Ordering Physician: Date of Report: 07/26/2017

NAME OF GENE: CYP2D6	LOCATION OF GENE: 22q13	
Variants tested	RESULT	Reference Genotype
rs35742686 (CYP2D6*3)	A/A	A/A
rs3892097 (CYP2D6*4M, CYP2D6*4)	G/G	G/G
rs5030655 (CYP2D6*6)	T/T	T/T
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rs72549349 (CYP2D6*44)	G/G	G/G
rs72549347 (CYP2D6*56, CYP2D6*56B)	C/C	C/C
EXON 9 GENE CONVERSION COPIES (CYP2D6*36)	0	0
CYP2D6 GENE COPY NUMBER ²	4	2
Combined Result[^]	CYP2D6*1/*1 (x4)	

[^] When the Result for all CYP2D6 variants tested are the same as the reference, the Combined Result is called CYP2D6 *1/*1. In some cases, due to technical limitations, your Combined Result may not be able to be determined. It may still be possible to provide an interpretation for such a result based on possible genetic outcomes (for example in rare combinations of non-reference results at more than one variant, or the presence of a "result not available" at one or more variants). ²When a CYP2D6 copy number of greater than two copies is detected, the CPMC test cannot determine which of the two CYP2D6*numbered genes has multiple copies and both possibilities are considered in the interpretation of metabolizer type.

Interpretation

This individual is expected to be a **Codeine Ultra-Rapid Metabolizer** based on the Combined Genetic Result: **CYP2D6*1/*1 (x4)**

Individuals who are ultra-rapid metabolizers have increased CYP2D6 enzymatic function and are at a higher risk of experiencing an adverse reaction to codeine. An alternative pain medication, such as morphine or a non-opioid drug (e.g., acetaminophen, NSAIDs), should be considered.

Test Limitations

DNA-based testing is highly accurate, however there are many sources of potential error including: mis-identification of samples, rare technical errors, trace contamination of PCR reactions, and rare genetic variants that interfere with analysis. There may be other variants in the CYP2D6 gene that are not included in this test, that influence the response to codeine. This test or one or more of its components was developed and its performance characteristics determined by the Coriell Institute for Medical Research. It has not been approved by the Food and Drug Administration (FDA). The FDA has determined that such approval is not necessary. The Coriell Institute is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 as qualified to perform high-complexity testing.

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Electronically signed by

Owatha L. Tatum, PhD, Laboratory Director

This clinical report only includes data generated in the CLIA approved genotyping laboratory, for additional information please see the research report.

References

1. Brousseau DC, et al. *The Journal of Pediatrics*. 2007; 150:623-626.
2. Crews KR, et al. *Clinical Pharmacology and Therapeutics*. 2012; 91(2):321-326.
3. Eckhardt K, et al. *Pain*. 1998; 76:27-33.
4. Gharani N, et al. *Genome Medicine*. 2013; 5(10):93.
5. The Human Cytochrome P450 (CYP) Allele Nomenclature Database: <http://www.cypalleles.ki.se/cyp2d6.htm>
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