

Cytochrome P-450 1A2 Genotyping

The cytochrome P450 enzyme CYP1A2 acts on 5-10% of drugs in current clinical use. CYP1A2 plays a major role in the metabolism of many commonly used drugs, including clozapine, imipramine, caffeine, fluvoxamine, paracetamol, phenacetin, theophylline, tacrine and others. Furthermore, CYP1A2 activates several aromatic amines and thus is a key enzyme in chemical carcinogenesis. Several studies on the CYP1A2-dependent metabolism of caffeine or phenacetin have demonstrated that this enzyme is expressed in human livers at various levels amongst individuals, suggesting polymorphic control of enzyme activity.

Genelex CYP1A2 DNA test identifies the two major nucleotide variants by PCR-RFLP, providing increased sensitivity and quality performance. Analytical specificity and sensitivity for detection of these mutations are >99%.

Specimen Types

Please call Client Services at 800-523-6487 to obtain specimen kits.

- **Buccal Swabs:** 4 sterile Whatman OmniSwabs™
- **Blood:** 5-10 cc whole blood lavender-top EDTA or Yellow-top ACD-A tubes
- **Turnaround Time:** 10 days turnaround (5 day turnaround for STATS)

CPT Codes

CYP1A2 Mutation DNA Analysis (provided for your guidance only)
1 X 83891, 2 X 83892, 2 X 83898, 2 X 83894, 1 X 83912, 1 X 83912-26

Clinical Significance

Hyperinduction phenotype: 39 - 47% (Japanese, Egyptian, Caucasian)
Drugs metabolized by this enzyme approximately 5-10%
Low affinity/high capacity enzyme

Cytochrome P450 1A2 (CYP21A2) is a highly polymorphic liver enzyme of the cytochrome P450 super family involved with the metabolism and elimination of 5-10% of commonly prescribed drugs. CYP1A2 is also involved in the metabolic activation of carcinogens from chemical toxins such as those found in cigarette smoke. There is considerable variation in 1A2 metabolic activity due to genetic factors, environmental factors, and drug-drug interactions. CYP1A2 is both inducible and can be inhibited, “turned on or off” by many medications and food-drug interactions. Fluoroquinolones, for example, are metabolized by and inhibit the enzyme CYP1A2. This can prevent the metabolism of concomitant medications such as theophylline and caffeine, causing excess central nervous system side effects and cardiac stimulation. Conversely, smoking may induce CYP1A2, resulting in enhanced metabolism of 1A2 substrates and the potential of sub-therapeutic response. Variation in the levels of CYP1A2 activity could result in increased or decreased capacity to activate substrates.

Genetic polymorphisms in CYP21A2 are common and can affect therapeutic response to drugs. The enzyme activity is expressed at highly variable levels. Three phenotypes are identified: normal induction, diminished induction and hyperinduction.

Genetic polymorphisms in the CYP1A2 gene influence the magnitude of CYP1A2 induction. Two important polymorphisms that cause functional changes in enzymatic activity have been identified in the CYP1A2*1 the wild-type allele. The **CYP1A2*1C** allele is the result of a single point mutation (-3860 G>A) and is associated with decreased CYP1A2 metabolic activity in comparison to the normal wild-type CYP1A2*1A allele. The **CYP1A2*1F** allele is the result of a single point mutation (-163 C>A) and is associated with increased induction particularly in smokers in comparison to the wild-type CYP1A2*1A allele. The distribution of CYP1A2 genotypes is as follows: *1F/*1F (nucleotide sequence A/A) ~ 46 %; *1A/*1F (nucleotide sequence C/A) ~ 44%; and *1A/*1A (nucleotide sequence C/C) ~ 10%, indicating that high induction is the most common phenotype.

Detecting genetic variations in drug-metabolizing enzymes is useful for identifying individuals who may experience adverse drug reactions with conventional doses of certain medications. Individuals who possess CYP1A2*1F and/or CYP1A2*1C variants may exhibit different pharmacokinetics (drug levels) than normal individuals. As a result, such individuals may require non-conventional doses of medications that require CYP1A2 for biotransformation. Conversely, medications that do not require CYP1A2 biotransformation may be preferentially selected for patients with potentially impaired CYP1A2 metabolic capacity to avoid adverse drug reactions.

Laboratory Test Interpretation and Dosage Recommendations

Genelex offers improved detection rates using an extended Cytochrome P-450 1A2 DNA variant panel. This test identifies the major nucleotide variants by PCR-RFLP , providing increased sensitivity and quality performance.

Cytochrome P-450 1A2 Mutations Detected		
CYP1A2 allele	Nucleotide change	Effect on Enzyme Metabolism
*1A	None (wildtype)	Normal
*1C	-3860G>A	Decreased
*1F	-163C>A	Increased Induction

For additional information see the CYP1A2 allele nomenclature database at <http://www.imm.ki.se/CYPalleles/cyp1a2.htm>

Testing places individuals in one of three categories:

- **Normal Induction** represents the norm for induction of metabolic activity in the presence of an inducer. Genotypes consistent with the normal induction phenotype include two CYP1A2 *1A alleles.
- **Diminished Induction** represents a lower than normal level of induction in the presence of an inducer. Genotypes consistent with the diminished induction phenotype are those with either one or two CYP1A2*1C alleles.
- **Hyperinduction** represents a higher than normal level of induction in the presence of an inducer. Induction may be approximately 40% higher in these patients than in those with the normal induction phenotype. Genotypes consistent with the hyperinduction phenotype include one or two CYP1A2*1F alleles. Patients with this phenotype may require an increased dosage of CYP1A2 substrates due to higher than normal rates of drug metabolism in the presence of an inducer.

Doses of CYP1A2 substrates with a narrow therapeutic range should be decreased immediately on cessation of heavy smoking. A stepwise daily dose reduction of approximately 10% until the fourth day after smoking cessation accompanied by therapeutic drug monitoring has been proposed by Faber et al.

Direct DNA testing will not detect all the known mutations that result in decreased or inactive CYP1A2. Absence of a detectable gene mutation or polymorphism does not rule out the possibility that a patient has an intermediate or poor metabolizer phenotype. This test does not detect polymorphisms other than those listed. Other polymorphisms in the primer binding regions can affect the testing, and ultimately, the genotyping assessments made. Therapeutic drug monitoring is recommended in patients with metabolic variations.

Drug Metabolism Guide

This list is not all inclusive and is for your guidance only.

Substrates Metabolized through Cytochrome P-450 1A2

Substrates refers to drugs that are either activated or deactivated by the pathway.

Note=bold indicates major; italics indicated minor pathway

Acetaminophen	Fluphenazine	Naproxen
Amitriptyline	Flutamide	Olanzapine
Caffeine	Fluvoxamine	Ondansetron
Chlordiazepoxide	Frovatriptan	Perphenazine
Chlorpromazine	Gregafloxacin	Phenacetin
Clomipramine	Haloperidol	Propafenone
Clozapine	Imipramine	Propranolol
Cyclobenzaprine	Melatonin	Riluzole
Dacarbazine	Mesoridazine	Ropinirole
Diazepam	Mexiletine	Ropivacaine
Duloxetine	Mibefradil	<i>R</i> -Warfarin
Estrogens	Mirtazapine	Tacrine

Tamoxifen	Toremifrene	Zolmitriptan
Theophylline	Trifluoperazine	Zolpidem
Thioridazine	Verapamil	
Thiothixene	<i>Ziprasidone</i>	

Inhibitors of Cytochrome P-450 1A2

Inhibitors refers to drugs that reduce the ability of the pathway to process drugs. Co-administration will decrease the rate of metabolism of drugs through the metabolic pathway listed, increasing the possibility of toxicity.

Note=bold indicates major; italics indicated minor inhibitor

Anastrozole	Isoniazid	Phenacetin
Caffeine	Lidocaine	Propafenone
Cimetidine	Lomefloxacin	<i>Ranitidine</i>
Ciprofloxacin	Mexiletine	Rifampin
Enoxacin	Mibefradil	<i>Ropinirole</i>
Fluphenazine	Nelfinavir	Sparfloxacin
Flutamide	Norfloxacin	Tacrine
Fluvoxamine	Ofloxacin	Ticlopidine
Grafruit juice	Oral contraceptives	Verapamil
Grepafloxacin	Perphenazine	Zafirlukast

Inducers of Cytochrome P-450 1A2

Inducers refers to drugs that increase the activity of a pathway.

Co-administration increases the rate of excretion for drugs metabolized through the pathway indicated, reducing the drug's effectiveness.

Broccoli	Chronic smoking	Moricizine
Brussel spouts	Clarithromycin	Omeprazole
Cabbage	Erythromycin	Phenobarbital
Caffeine	Esomeprazole	Phenytoin
Carbamazepine	griseifulvin	Rifampin
Cauliflower	Insulin	Ritonavir
Charbroiled foods	Lansoprazole	

Methodology

DNA extraction/Polymerase Chain Reaction (PCR)/ Enzyme inactivation /Allele-specific primer extension / Hybridization using immobilized nucleic acid probes/ Fluorescent detection.

Laboratory specimens were analyzed using the Tag-It™ Mutation Detection System for P450-2C9 which detects 5 nucleotide variants in a multiplex polymerase chain reaction and allele-specific primer extension format.

References

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