CYTOCHROME P450

Cytochrome P450, abbreviated CYP450, encodes and designates a large family of hemoproteins found in many organisms.[1] These proteins are responsible for a large number of oxidative reactions in the body, many of which play integral roles in endogenous and exogenous compound metabolism; and are usually part of the metabolic pathway's multicomponent electron transfer chains. As a testament to its prevalence, more than 7700 distinct gene sequences that code for the CYP450 family of proteins have been identified through all domains of life.[2]

In regards to drug metabolism, the CYP450 proteins account for approximately 75% of all known metabolic reactions of the sort.[3] Drugs interact with the CYP450 proteins by either inducing (functioning as a substrate) or hindering (functioning as an inhibitor) or enhancing (functioning as an inducer) the normal function of the protein. These reactions are very important in terms of drug safety and toxicity, since altering the protein's functionality may adversely affect its ability to screen and process other drugs present in the system, potentially causing toxic buildup of low therapeutic index compounds in the body, eventually leading to an overdose.

Therefore gaining accurate perception of a patient's CYP450 baseline is the key to fine tuning a prescription. Only through genetic screening can such perspective be obtained, allowing for more accurate drug dosage adjustments as well as avoiding use of drugs with side effects that the patient is more systemically sensitive to due to the patient's unique CYP450 genetic profile.

CYP450 2C9

CYP450 2C9 is a major isoform in the cytochrome P450 (CYP450) family of drug metabolizing proteins. It has a major role in the oxidation of xenobiotic and endogenous compounds, and accounts for nearly 18% of CYP450 proteins found in the liver, where a majority of drug and toxic substance metabolism occurs.

The CYP450 2C9 protein functions in a vast variety of important drug reactions. These reactions then play an integral part in the way the body deals with many situations during medical treatment, such as warfarin therapy (common anti-coagulant used in surgery)[4], tolbutamide administration (oral agent used in type II diabetes treatments)[5], and non-steroidal anti-inflammatory drug use (commonly used in arthritis treatment as well as other cases that require anti-inflammatory and/or analgesic effects)[6].

CYP450 2C19

CYP450 2C19 is another important member of the cytochrome P450 (CYP450) family of enzymes. Like its counterparts in the CYP450 family it functions to metabolize various common place drugs, such as mephenytoin (anticonvulsant often prescribed for epilepsy), proguanil (leading anti-malarial drug), and many antidepressants as well.[7]

An important characteristic of CYP450 2C19 is its racial heterogeneity; where it has been found that Asian populations exhibit the highest percent (15-20%) of genetic polymorphisms, while Caucasian populations exhibited the lowest percent (3-5%).[8,9] In most of the cases evaluated, the presence of 2C19 polymorphisms resulted in the patients exhibiting no protein function and thus made them poor metabolisers of 2C19 regulated drugs.

CYP450 2D6

CYP450 2D6 is the member of the cytochrome P450 (CYP450) family that is responsible for the metabolism of most xenobiotics found in the body. This class of compounds is variable in nature but include common products such as antibodies, which are used by young and old alike for many ailments, ranging from the flu to other more serious maladies like cancers.

However while it has such a wide variety of substrates, it also has a considerable number of genetic variants, making its

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[9] Desta Z, Zhao X, Shin JG, Flockhart DA; **Clinical significance of the cytochrome P450 2C19 genetic polymorphism**. *Clin Pharmacokinet* **41** (12): 913–58.

genetic profiling very important due to the high number of polymorphic possibilities. Its variants ultimately divide those carrying the polymorphism into four grades of metabolisers: poor (little to no 2D6 function), intermediate (below average 2D6 function), extensive (normal 2D6 function), and ultrarapid (excess expression of the 2D6 protein and thus much greater metabolic ability than normal 2D6 function).

In addition, like the CYP450 2C19 gene, the CYP2D6 genome also exhibits significant racial heterogeneity. The bulk of the polymorphisms occur in non-Asiatic populations, with approximately 10% in Caucasians whereas only 2% in Asians.[10] In spite of this apparent lack of importance in Asian genetics, it has been found that approximately 50% of Asiatic peoples will exhibit a polymorphism on the CYP450 2D6 gene that gives a slightly lower than normal 2D6 function.[11]

CYP3A4 & 3A5

The CYP3A4 and 3A5 enzymes form the two most frequently used pathways in the human body, accounting for the metabolism of more than 50% of all drugs in existence. While the overall phenotypical variations are similar to that of other CYP enzymes, a unique aspect about these 2 pathways is that they are mutually complementary. It has been shown in research that in metabolic situations where both pathways can be utilized to equal efficiency, the body will prefer to utilize the CYP3A4 pathway. However when the 3A4 pathway is inhibited, the body will automatically defer to using the alternative 3A5 enzyme to continue its metabolic function.[12] It is this unique interplay of 2 pathways in unison that makes it even more important to examine on a genetic level, and better understand the metabolic activities in the body.

DEFINITION OF PHENOTYPES

Normal Metabolizer (NM)

NM phenotypes are characterized as having no known genetic mutations that significantly affect enzyme function in the gene in question. This means that the patient should, according to his/her genetics, be able to metabolize most drugs according to their intended dosages and achieve the expected affects.

Normal/Intermediate Metabolizer (NIM)

NIM phenotypes are characterized as having 1 inactivating and 1 activating genetic mutation in the gene in question. NIMs tend to have very slightly lower enzyme function than normal and thus can be treated as a Normal Metabolizer albeit with added vigilance in monitoring where necessary.

Intermediate Metabolizer (IM)

IM phenotypes are characterized as having only 1 inactivating genetic mutation in the gene in question. IMs tend to have slightly lower levels of enzyme activity than normal but still higher than those who are characterized as Poor Metabolizers. In these situations it can be suggested to continue with standard dosing practices but implement more rigorous monitoring than normal.

Poor Metabolizer (PM)

PM phenotypes are characterized as having 2 inactivating genetic mutations in the gene in question. PMs tend to have lower levels of enzyme activity than normal and thus may not be suitable for drugs which require activation or deactivation by the enzyme. Alternative therapies or dosing strategies are suggested to prevent toxicity and drug interactions.

Ultra Metabolizer (UM)

UM phenotypes are characterized as having 1 or more activating genetic mutations in the gene in question. UMs tend to have higher levels of enzyme activity than normal and thus may not be suitable for drugs which require activation or deactivation by the enzyme. Alternative therapies or dosing strategies are suggested to prevent toxicity and drug interactions.

Additional Notes

Results of DNA genotyping should be interpreted in the full context of the patient's clinical history, including hepatic and renal function, life style, co-administration of other drugs, and other pre-existing conditions. Drug metabolism is known to be affected by non-genetic factors. As thus DNA testing does not replace the necessity for clinical drug monitoring.

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TABLE OF SELECT CYP METABOLIZED DRUGS

Enzyme	Drugs Affected
CYP2C9	***Psychotropics***
	• Fluoxetine
	• Sertraline
	• Valporic Acid
	• Tetrahydro-cannabinol
	NSAIDs
	• Aceclofenac
	• Celecoxib
	• Diclofenac
	• Flurbiprofen
	• Ibuprofen
	• Indomethacin
	• Lornoxicam
	• Meloxicam
	• Naproxen
	• Piroxicam
	• Suprofen
	• Tenoxicam
	Hypoglycemics
	• Chlorpropamide
	• Glipizide
	• Glimepiride
	• Glyburide
	• Nateglinide
	• Rosiglitazone
	• Tolbutamide
	Others
	• Phenobarbital
	• Warfarin

Enzyme	Drugs Affected
CYP2C19	***Psychotropics***
	• Amitriptyline
	• Citalopram
	• Clomipramine
	• Diazepam
	• Escitalopram
	• Flunitrazapam
	• Fluoxetine
	• Imipramine
	• Moclobemide
	• Sertraline
	• Trimipramine
	Anticonvulsants
	• Mephenytoin
	• Phenytoin
	PPIs
	• Esomeprazole
	• Iansoprazole
	• Omeprazole
	• Pantoprazole
	Others
	• Carisoprodol
	• Cilostazol
	• Clopidogrel
	• Isophosphamide
	• Nelfinavir
	• Proguanil
	• Propranolol
	• Tolbutamide
	• Voriconazole

Enzyme	Drugs Affected
CYP2D6	***Psychotropics***
	• Amphetamines
	• Aripiprazole
	• Atomoxetine
	• Benztropine
	• Citalopram
	• Desipramine
	• Doxepine
	• Duloxetine
	• Fluoxetine
	• Haloperidol
	• Imipramine
	• Nortriptyline
	• Paroxetine
	• Risperidone
	• Venlafaxine
	Analgesics
	• Codeine
	• Dihydrocodeine
	• Hydrocodone
	• Loperamide
	• Oxycodone
	• Tramadol
	Beta Blockers
	• Carveodilol
	• Metoprolol
	• Propranolol
	• Timolol
	Others
	• Doxorubicin
	• Estradiol
	• MDMA (ecstasy)
	• Propafenone
	• Ranitidine
	• Tamoxifen
	• Tolerodine

Enzyme	Drugs Affected
CYP3A4	***Psychotropics***
CYP3A5	• Alprazolam
	• Buspirone
	• Clomipramine
	• Estazolam
	• Eszopiclone
	• Midazolam
	• Nefazodone
	• Sertraline
	• Triazolam
	• Zaleplon
	• Zolpidem
	Analgesics
	• Buprenorphine
	• Codeine
	• Fentanyl
	• Hydrocodone
	• Methadone
	• Oxycodone
	• Propoxyphene
	• Sufentanil
	Antibiotics/ Antifungal
	• Itraconazole
	• Ketoconazole
	• Macrolides
	• Telithromycin
	Anticonvulsants
	• Carbamazepine
	• Ethosuximide
	• Tiagabine
	• Zonisamide
	Others
	• Cortisols
	• Fluticasone
	• Progestins
	• Statins

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