

Psycho-, GI, Cancer, Cardiovascular, and Addiction Pharmacogenomics

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Psycho- and GI-pharmacogenomics-

**Polymorphisms of
CYP2D6 and *CYP2C19*-**

A Cross-Ethnic Comparative Study

CYP2D6

- **78 variants**
- **Metabolize >65 commonly used drugs.**

Antipsychotic agents and SSRI-

**Fluoxetine
Haloperidol
Paroxetine
Perphenazine
Venlafaxine**

Beta-blockers-

**Alprenolo
Bufuralol
Carvediol
Metoprolol
Propranolol
Timolol**

Opioids-

**Codeine
Dextromethorphan**

Tricyclic Antidepressants

**Amitriptyline (in part)
Clomipramine (in part)
Desipramine
Imipramine (in part)
Nortriptyline**

Antiarrhythmic agents-

**Flecainide
Mexiletine
Propafenone**

| <i>Allele</i> | <i>Nucleotide changes</i> | <i>Effect</i> | <i>Enzyme activity</i> |
|--|---------------------------|-----------------------|------------------------|
| <i>CYP2D6*1</i> | None | | Normal |
| <i>CYP2D6*2</i> | 2850C>T | R296C | Normal |
| <i>CYP2D6*1 or 2XN</i> (N=2, 3, 4, 5 or 13) | | N normal genes | Increase |
| <i>CYP2D6*3</i> | 2549A>del | Frame shift | None |
| <i>CYP2D6*4</i> | 1846G>A | Splicing defect | None |
| <i>CYP2D6*4X2</i> | | | None |
| <i>CYP2D6*5</i> | <i>CYP2D6</i> deleted | <i>CYP2D6</i> deleted | None |
| <i>CYP2D6*6</i> | 1707T>del | Frame shift | None |
| <i>CYP2D6*7</i> | 2935A>C | H324P | None |
| <i>CYP2D6*8</i> | 1758G>T | Stop codon; | None |
| <i>CYP2D6*9</i> | 2613-2615delAGA | K281del | Decrease |
| <i>CYP2D6*10</i> | 100C>T | P34S | Decrease |
| <i>CYP2D6*10X2</i> | | | Decrease |
| <i>CYP2D6*11</i> | 883G>C | Splicing defect | None |
| <i>CYP2D6*14</i> | 1758G>A | G169R | None |
| <i>CYP2D6*29</i> | 1659G>A; 3183G>A | V136M; V338M | Decrease |
| <i>CYP2D6*41</i> | -1584C; 2850 C>T | R296C | Decrease |
| <i>CYP2D6*45</i> | 1661G>C | E155K | Decrease |
| <i>CYP2D6*46</i> | 843T>G | R26H | Decrease |

CYP2D6 Alleles

CYP2D6 Allele Frequency in Different Ethnic Groups

| Populations (allele number) | *1 | *2 | *3 | *4 | *5 | *10 | *17 | *XN |
|--------------------------------|------------|----|----|----|----|-----|-----|-----|
| | percentage | | | | | | | |
| Amerindians (280) | 61 | 18 | 0 | 13 | 1 | 3 | 0 | 4 |
| Asian (E) (332) | 32 | 13 | 0 | 2 | 5 | 48 | 0 | 1 |
| Asian (SE) (162) | 27 | 11 | 0 | 3 | 3 | 56 | 0 | 1 |
| Jews, Arabs (322) | 37 | 35 | 0 | 9 | 2 | 8 | 4 | 5 |
| African American (474) | 29 | 34 | 0 | 8 | 7 | 6 | 12 | 4 |
| Mexican American (694) | 56 | 26 | 0 | 10 | 2 | 4 | 0 | 1 |
| Caucasian (544) | 40 | 33 | 2 | 16 | 3 | 4 | 0 | 2 |
| Israeli ethnic groups (322) | 37 | 34 | 0 | 9 | 2 | 8 | 4 | 5 |
| Ethiopian Jews (56) | 23 | 34 | 0 | 4 | 4 | 5 | 21 | 9 |
| Sephardic Jews (94) | 31 | 32 | 1 | 19 | 0 | 10 | 1 | 7 |

Predicted Phenotype of CYP2D6

PM-

carry two null alleles (*3, *4, *4xN, *5, *6, *7, *8, *11, *14)

IM-

carry two alleles with decreased enzyme activity (*9, *10, *17, *29, *41[2988A], *45, *46)

or one null allele plus one allele with decreased enzyme activity
or one null allele plus one functional allele (*1, *2, *41[2988G])

EM-

carry two functional alleles

UM-

carry more than two functional alleles

CYP2C19

Others

Citalopram

Imipramine

Propranolol

Pentamidine

Proguanil

Proton-pump (K⁺/H⁺ ATPase) inhibitors

Omeprazole

Lansoprazole

Esomeprazole

Rabeprazole

Pantoprazole

Anticonvulsants

Hexobarbital

Phenbarbital

Diazepam

Diphenylhydantoin

Mephenytoin

CYP2C19 Genotypes in Different Populations

| <i>CYP2C19</i> Genotype | Predicted Phenotype | Mexican-American (n = 346) (%) | Caucasian (n = 273) (%) | African-American (n = 236) (%) | East Asian ^a (n = 161) (%) | Southeast Asian ^b (n = 80) (%) |
|-------------------------|---------------------|-----------------------------------|----------------------------|-----------------------------------|--|--|
| <i>*1/*1</i> | EM | 80.9 | 77.6 | 66.1 | 41.0 | 48.7 |
| <i>*1/*2</i> | EM | 18.2 | 17.2 | 28.8 | 32.3 | 22.5 |
| <i>*1/*3</i> | EM | 0.3 | 0.4 | 0.9 | 8.7 | 6.3 |
| <i>*2/*2</i> | PM | 0.6 | 3.7 | 3.4 | 9.9 | 17.5 |
| <i>*2/*3</i> | PM | 0.0 | 0.7 | 0.8 | 5.6 | 5.0 |
| <i>*3/*3</i> | PM | 0.0 | 0.4 | 0.0 | 2.5 | 0.0 |

^a: East Asian including 86 Chinese, 40 Japanese, and 35 Korean.

^b: Southeast Asian including 2 Vietnamese, 3 Cambodian, and 75 Filipino

n: Number of individuals.

**Use proton-pump inhibitor
Rabeprazole to treat gastroesophageal reflux**

PM - 20 mg once daily

Heterozygous EM - 20 mg twice daily

Homozygous EM - 10 mg 4 times a day

to maintain intragastric pH below 4.0

CYP2C19 polymorphism and H. pylori genotype determine the response to triple therapy for H pylori infection.

139 patients

Lansoprazole 30 mg twice a day

Clarithromycin 200 mg 3 times daily

Amoxicillin 500 mg 3 times daily

Cure Rate:

EM: 58%

IM: 88%

PM: 92%

Cure Rate

HP Mutation + : 48%

HP Mutation - : 87%

Cancer Pharmacogenomics

Colonrectal and Head/Neck Cancer

5-FU

Irinotecan

Platinum

EGFR Inhibitor

Acute Lymphoblastic Leukemia

Methotrexate

Thiopurine

Vincristine

Glucocorticoid

Asparaginase

Anthracyclines

Topoisomerase II Inhibitors

Cytarabine

Cycloheximide

Methotrexate

Thymidylate synthetase

**repeats – higher expression – high dose-
high cytotoxicity – high risk of relapse**

Methylenetetrahydrofate reductase

**C677T and A1298C associated with reduced enzyme activity-
Decreased risk of relapse**

GSTM1, GSTT

**Null genotype – relapse – not conclusive
Other substrate – CHX**

Methionine synthase reductase

Serine hydroxymethyl transferase

Cardiovascular Pharmacogenomics

Beta- Blockers

CYP2D6

CYP2C9 Variants among Different Ethnic Groups

| Ethnic Group | CYP2C9 *1 | CYP2C9 *2 | CYP2C9 *3 | CYP2C9 *4 | CYP2C9 *5 |
|---------------|-----------|-----------|-----------|-----------|-----------|
| Whites | 79-86% | 8-19.1% | 6-10% | ND | ND |
| Indig. Canad. | 91% | 3% | 6% | ND | ND |
| African Amer. | 98.5% | 1-3.6% | 0.5-1.5% | ND | 2.3% |
| Asians | 95-98.3% | 0 | 1.7-5% | 0-1.6% | 0 |

Effect of CYP2C9 Genotype on Warfarin Dosing (mg/day)

Rule -

*2 – reduce dose

*3 – reduce even more

Greater reduction in homozygous than heterozygous

***1/*1 - 5.6**

***1/*2 - 4.9**

***1/*3 - 3.3**

***2/*2 - 4**

***2/*3 - 2.3**

***3/*3 - 1.6**

\$250 to genotype *1, *2, and *3

Alcohol Pharmacogenetics in Mexican Americans

Candidate Genes for Alcoholism

Pharmacokinetics

Alcohol dehydrogenase

Aldehyde dehydrogenase

CYP2E1

Pharmacodynamics

Dopamine receptor and transporter

Serotonin receptor and transporter

GABA receptor

200 alcoholics

250 non-alcoholics

*Alcohol dehydrogenase
dopamine receptor D2,
and serotonin transporter
are associated with alcoholism.*

Alcohol Cessation

Naloxone (Detoxification)
μ-opioid receptor inhibitor

Alcohol Anonymous (Social Treatment)

Disulfiram (Pharmacology Treatment)
ALDH inhibitor

Bupropion - dopamine reuptake inhibitor?

Bupropion associated alcohol cessation (case reports).

Partial dopamine agonist?

Aripiprazole

Grant Support:

NIH, NCI (R01 grant)

Retinoids, Xenobiotic Metabolism, and Tumor Promotion

NIH, NIAAA (R01 grant)

Alcohol Pharmacogenetics in Mexican-Americans

NIH, NIAAA (R01 grant)

SAMe, RXRalpha-Mediated Pathway and ALD

Paul J. Patton Trust

Cancer Pharmacogenomics