



# EXPANDED TEST OFFERING IN PHARMACOGENOMICS: CYP1A2

## THE HUMAN GENOME AND CYTOCHROME P450

The human genome includes 57 cytochrome p450 (CYP) genes, classified into 18 families and 44 subfamilies. This relatively small group is responsible for the observed metabolism of over 90% of all marketed drugs—with CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19 and CYP1A2 performing most of the reactions.<sup>2,3</sup> The variations in these enzymes can increase or decrease an individual's ability to metabolize certain drugs, directly affecting the levels of drug found in the body.<sup>4</sup>

## CYP450 1A2 (CYP1A2)

CYP1A2 accounts for the metabolism of approximately 9% of prescription drugs, and it is estimated that there are over 100 substrates for CYP1A2 isozyme—which composes 13% of the total CYP content.<sup>5</sup> This can be distilled further to approximately 30 medications whose metabolism is primarily reliant on CYP1A2. As with many of the other cytochrome p450 enzymes, *CYP1A2* is highly polymorphic and may exhibit a minimum 10-fold variability within the human body.<sup>6</sup> In fact, there are over 20 variant alleles of *CYP1A2* that have been identified today that can predispose a patient to modified *CYP1A2* activity.<sup>7</sup> Table 1 summarizes the activity level and frequency of commonly genotyped *CYP1A2* alleles (adapted from MRAZEK) in Northern Europeans.<sup>8</sup>

As shown in the Table 1, certain genotypes are referred to as being “inducible,” meaning the activity of these enzymes can be activated by the presence of an “inducer.” *CYP1A2* is inducible by polycyclic aromatic hydrocarbons (PAHs - found in cigarette smoke and charcoal-grilled meat), cruciferous vegetables (broccoli, brussel sprouts, cauliflower, cabbage), caffeine and numerous medications listed on page two.<sup>9</sup> The effects of this “inducible” ultra-rapid metabolizer phenotype has been reported in several studies.

Table 1

| Allele | Activity Level        | Frequency (%) | Allele | Activity Level | Frequency (%) |
|--------|-----------------------|---------------|--------|----------------|---------------|
| *1A    | Normal                | 60            | *4     | Decreased      | 0.5           |
| *1B    | Normal                | 60            | *6     | None           | 0.5           |
| *1C    | Variable Inducibility | 60            | *7     | None           | <0.1          |
| *1D    | Inducible             | 4.8           | *8     | Decreased      | <0.1          |
| *1F    | Inducible             | 30 - 33       | *11    | Decreased      | <0.1          |
| *1K    | Decreased             | 0.4           | *15    | Decreased      | <0.1          |
| *3     | Decreased             | <0.1          | *16    | Decreased      | <0.1          |

## CYP1A2 INDUCERS

### Clozapine (Clozaril®)

Used in patients suffering from treatment-resistant schizophrenia (TRS), this typical antipsychotic is effective approximately 30-60% of the time.<sup>10</sup>

- Balibey and colleagues evaluated clozapine response in relation to specific *CYP1A2* polymorphisms. The study evaluated 55 schizophrenia patients initiated on clozapine 12.5mg/day and titrated to effect for 18 weeks. BPRS (Brief Psychiatric Rating Scale), SANS (Scale for the Assessment of Positive Symptoms), and SAPS (Scale for the Assessment of Negative) scales were performed both at baseline and after treatment, at which point final doses ranged from 200 to 600mg daily. Positive responses included a 20% decline in at least one score between pre- and post- treatment values.
- Results:
  - > Lack of response was found to be 2.4 times higher in carriers of the *CYP1A2*\*1F/\*1F genotype.
  - > Response rate was decreased by 15% in smokers.
- The authors concluded that the *CYP1A2*\*1F/\*1F genotype was a potential risk factor for lack of response to clozapine among psychotic patients, particularly tobacco smokers.

For clozapine, optimum plasma concentrations have been suggested to be between 350 and 400 ng/mL and levels above that range have been associated with risks of adverse effects such as confusion, delirium, and generalized seizures.<sup>11</sup>

- It is estimated that the frequency of clozapine-induced seizures is between 1 and 20% since the medication lowers the threshold for seizures to occur. Dr. Kohlrausch and colleagues studied the association between the -163 C > A polymorphism and clozapine-induced generalized tonic-clonic seizures in schizophrenia patients.<sup>12</sup>
- Kohlrausch et al. evaluated 108 European-descending patients with schizophrenia and no prior history of any type of seizure before treatment with clozapine. The study assessed the occurrence of clozapine-induced new-onset generalized seizures (NOGSs) through data collected from clinical psychiatrists who were unaware of the patient's individual genotype results.
- Results:
  - > Found an overall seizure rate of 22% in the patient population.
  - > Mean clozapine dose was significantly higher in the NOGS group than the non-NOGS group.
  - > Determined that the \*1F/\*1F genotype was significantly associated with NOGS.

### Olanzapine (Zyprexa®)

Atypical antipsychotic olanzapine has been proven effective for the treatment of positive and negative schizophrenia patients; however, its metabolism is highly affected by induction.

Carrillo et al set out to evaluate 17 psychiatric inpatients with schizophrenia and similar DSM-IV diagnoses. Patients had not taken any psychoactive medications within the two months preceding the study and did not ingest alcohol or caffeine. BPRS was used to evaluate patient's response to olanzapine and was measured before dosing, within 72 hours of initial dosing, and on day 15 of medication following constant dosing.<sup>9</sup>

- Results:
  - > The mean BPRS percentage decrease after 15 days of antipsychotic therapy was approximately 22% (+/- 15%).
  - > Smoking had induced a six-fold higher activity in *CYP1A2* for the patients and, as a result, drug efficacy was significantly higher in nonsmokers than in smokers (30.4 +/- 10% compared to 12.5 +/- 14%, respectively)
  - > Poor metabolizers had a higher percentage decrease in total BPRS score than extensive (normal) metabolizers (26.3 +/- 12.8% compared to 20.7 +/- 16.1%, respectively).
  - > The authors noticed that if smokers were excluded from the analysis, no significant correlation could be identified between *CYP1A2* activity and dose-corrected plasma olanzapine concentrations among non-smoking patients, confirming the importance role tobacco smoke plays in enzyme induction.

### Examples of other medications whose metabolism is governed by CYP1A2:

(This list is not all inclusive. Certain medications may fit under more than one category.)

| Cardiovascular            | Musculoskeletal/Pain  | Neurological/Psychiatry   | Oncology                 | Other  |
|---------------------------|---|---|--------------------------|--|
| Mexiletine<br>Triamterene | Chlorzoxazone<br>Duloxetine<br>Riluzole<br>Cyclobenzaprine<br>Lidocaine<br>Tizanidine | Olanzapine<br>Clozapine<br>Frovatriptan<br>Ropinirole<br>Thiothixene<br>Trifluoperazine<br>Zolmitriptan | Dacarbazine<br>Erlotinib | Alosetron<br>Estrogen<br>Caffeine<br>Theophylline<br>Betaxolol |

#### References:

- 1) Samer CF, Lorenzini KI, Rollason V, Daali Y, and Desmeules JA. (2013). Applications of CYP450 Testing in the Clinical Setting. *Mol Diagn Ther*. 17(3): 165-184
- 2) Zaretski J et al. (2011). RS-predictor: a new tool for predicting sites of cytochrome p450-mediated metabolism applied to CYP 3A4. *J Chem Inf Model*. 51(7): 1667-89
- 3) Guengerich FP. (2006). Cytochrome 450s and other enzymes in drug metabolism and toxicity. *AAPS J*. 8(1): E101-E111.
- 4) Kudzma EC, Carey ET. (2009). Pharmacogenomics: personalized drug therapy. *Am J Nurs*. 109(10): 50-7; quiz 58.
- 5) Thorn CF. (2012). PharmGKB summary: very important pharmacogene information for CYP1A2. *Pharmacogenet Genomics*. 22(1): 73-77.
- 6) Basile VS. (2000). A functional polymorphism of the cytochrome p450 1A2 (CYP1A2) gene: association with tardive dyskinesia in schizophrenia. *Molecular Psychiatry*; 5: 410-7
- 7) Sim, SC. The Human Cytochrome P450 (CYP) Allele Nomenclature Database. Available from: <http://www.cypalleles.ki.se/index.htm>
- 8) Mrazek, DA. (2010) *Psychiatric Pharmacogenomics*. New York, New York: Oxford University Press.
- 9) Carrillo JA et al. (2003). Role of the Smoking-Induced Cytochrome P450 (CYP)1A2 and Polymorphic CYP2D6 in Steady-State Concentration of Olanzapine. *J Clin Psychopharmacol*. 23: 119-27.
- 10) Balibey H. (2011). CYP1A2\*1F Polymorphism Decreases Clinical Response to Clozapine in Patients with Schizophrenia. *Bulletin of Clinical Psychopharmacology*; 21(2): 93-9
- 11) Bondolfi G et al. (2005). Increased Clozapine Plasma Concentrations and Side Effects Induced by Smoking Cessation in 2 CYP1A2 Patients. *Ther Drug Monit*; 27: 539-43
- 12) Kohlrausch FB et al. (2013). The CYP1A2 -163 C>A polymorphism is associated with clozapine-induced generalized tonic-clonic seizures in Brazilian schizophrenia patients



CompanionDx Reference Lab, LLC

888.482.5327 | companiondxlab.com