

## Testing for CYP Polymorphisms is Associated with a Reduction in the Frequency of Changes in Psychotropic Prescriptions made by Community Psychiatrists

Yuri Cheung<sup>1</sup>, Robert B. Summerour<sup>1</sup>, Xiaoying Cui<sup>1</sup> and Andrius Baskys<sup>1,2\*</sup>

<sup>1</sup>Riverside Psychiatric Medical Group, Riverside, California

<sup>2</sup>Orange County Healthcare Agency, Santa Ana, California

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### ABSTRACT

Psychotropic medications are typically prescribed based on the assumption that all patients respond to the drug in a similar way; however, inter individual variability exists in drug responses and adverse drug reactions. The aim of this study was to compare the frequency of psychotropic drug changes made by the prescriber before and after patients were tested for cytochrome P450 (CYP) variant alleles in *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4* and *CYP3A5* genes. Those CNS-acting medications (antidepressants, antipsychotics, anticonvulsants, anxiolytics, antihistamines and opiates) that were substrates, inhibitors or inducers of the variant genes were counted and their numbers compared before and after the testing. Of 63 patients, 34.9% had 2, 28.6% had 1, 23.8% had 3, 11.1% had 4 and 1.6% had 5 allele variations. The average number of variant alleles was 2.2 per patient. The average number of drugs that were substrates, inhibitors or inducers of genes with variant alleles and were prescribed to a patient was  $3.8 \pm 2.3$  and  $2.6 \pm 2.0$  before and after genotyping, respectively ( $p = 0.003$ , 2-tailed t-test). We interpret these findings to suggest that there was a significant decrease in the number of patients' prescription changes after pharmacogenomic information became available to the prescriber. These results underscore the clinical utility of pharmacogenomics in a community-based general psychiatric practice.

**Keywords:** CYP2B6, CYP2C9, CYP2D6, CYP2C19, CYP3A4, CYP3A5, Pharmacogenomics

**Abbreviations:** ASW: Americans of African Ancestry in Southwest USA; CEU: Utah residents with Northern and Western European Ancestry; CNS: Central Nervous System; CYP: Cytochrome P450; CYP2B6: Cytochrome P450, Subfamily IIB, Polypeptide 6; CYP2C19: Cytochrome P450, Subfamily IIC, Polypeptide 19; CYP2C9, Cytochrome P450, Subfamily IIC, Polypeptide 9; CYP2D6: Cytochrome P450, Subfamily IID, Polypeptide 6; CYP3A4: Cytochrome P450, Subfamily IIIA, Polypeptide 4; CYP3A5: Cytochrome P450, Subfamily IIIA, Polypeptide 5; dbSNP: Single Nucleotide Polymorphism Database; EHR: Electronic Health Records; IRB: Institutional Review Board; MXL, Mexicans Ancestry from Los Angeles USA; OPMR1: Opioid Receptor mu 1; RPMG: Riverside Psychiatric Medical Group

### INTRODUCTION

Despite the improved side effect profiles of second and third generation psychotropic drugs, many patients experience significant side effects, symptom relapse, lack of treatment response or undesirable drug-drug interactions [1-4]. Psychotropic drugs are often prescribed based on the assumption that all patients respond to a drug in a similar way; however, drug pharmacokinetic properties including absorption, distribution, metabolism and excretion vary markedly between individuals [4]. Numerous genetic variants have now been identified that influence the efficacy, metabolism or other aspects of drug actions.

**Corresponding author:** Andrius Baskys MD, PHD, Riverside Psychiatric Medical Group, Riverside, California, 5887 Brockton Ave, Riverside, CA 92506, USA, Tel: +1 626 239 8378; ; Email: abaskys@gmail.com

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Pharmacogenomic testing to identify genetic mutations that predict patient responses to pharmacotherapy are emerging as a science-based method to select the optimal treatment regimen for individual patients [5,6].

Genetic variations associated with drug effects can be broadly divided into those possessing either pharmacodynamic or pharmacokinetic properties. Gene variants associated with the former are usually directly linked to the drug target. For example, carriers of a mutant G allele in the opioid receptor mu 1 (*OPRM1*) gene have greater sensitivity to pain and require 2-4 times more analgesic drug to achieve a comparable degree of analgesia to non-carriers [7]. Gene variants associated with pharmacokinetic properties of a drug usually involve genes that encode enzymes responsible for drug metabolism such as the Cytochrome P450 system and can either slow or facilitate drug metabolism. For example, *CYP2C19* gene produces an enzyme CYP2C19 that metabolizes several commonly prescribed antidepressants [6, 8, 9]. Mutations of *CYP2C19* could render the enzyme partially or completely ineffective, significantly increasing the likelihood of medication side effects. Alternatively, a gain-of-function mutation in *CYP2C19*, referred to as \*17/\*17 in the *CYP* Allele Nomenclature [10], results in increased transcription that can significantly increase drug metabolism by this enzyme. As a result, homozygous carriers of \*17 allele are at risk for therapeutic failure if treated with drugs that are substrates of CYP2C19 such as escitalopram [9].

Since the adverse drug effect-related mortality ranks 5<sup>th</sup> among the U.S. mortality indicators [11], the attractiveness of pharmacogenomics should be undeniable. Implementation of pharmacogenomic testing in academic and research settings began in 2003-2005 and health, financial and consumer satisfaction benefits of this approach have been well documented [12-14]. Nevertheless, implementation of the pharmacogenomics methods into clinical practice has been slow and its acceptance by prescribers has been wavering [12,13] with anecdotal evidence pointing to a lack of clear clinical utility particularly in a small, non-academic, community practice setting. Here we report the findings of a retrospective data analysis of patients treated in a community psychiatry clinic with the input of patient pharmacogenomic information. Data show that the number of medications prescribed for each patient, and consequently, the number of medication changes made by the prescriber, were significantly higher before testing for *CYP* genetic polymorphisms than after. These results underscore the clinical utility of pharmacogenomics in a community-based general psychiatric practice.

## METHODS

The main goal of this study was to compare the number of medications, and by implication, the frequency of

medication changes made by the prescriber within a fixed interval before and after genotyping the patient for allele variations in *CYP2B6*, *CYP2C9*, *CYP2D6*, *CYP2C19*, *CYP3A4* and *CYP3A5* genes. The study took place in a single general psychiatry community clinic (Riverside Psychiatric Medical Group, RPMG) located near the downtown area of a city of approximately 300,000. The practice has 1 full-time and 3 part-time American Board of Psychiatry and Neurology certified psychiatrists, as well as 2 full-time and 1 part-time non-physician prescribers. RPMG provides general psychiatry services to approximately 5000 patients per year including 200 new patients per month. The study includes a retrospective chart review of consecutive RPMG patients who were subject to pharmacogenomic testing performed by Assurex Health or Millennium Health services between 1/1/2014-6/7/2016. This study was reviewed and deemed exempt from IRB review by Solutions IRB, LLC, Little Rock, Arkansas [15]. Patients' Electronic Health Records (EHR, service by Vālant Medical Solutions, Seattle, Washington [16]) were searched to identify those clinic patients who had pharmacogenomic testing ordered by one of the RPMG prescribers during the above mentioned interval. To minimize data scatter across variables, this study focused on *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4* and *CYP3A5* genes whose reporting format showed a significant concordance between the two service providers (*CYP3A5* data were reported by Millennium Health only). Patients' medication list and prescription start/stop dates were obtained from the electronic prescriber database accessible through the EHR. Patient medications including psychotropics, centrally acting pain medications such as opiates, centrally acting muscle relaxants and antihistamines commonly prescribed in psychiatric practice due to their well-documented central nervous system (CNS) effects were identified. The medications were then entered into the Super CYP database [17] medication interaction search interface and the number of medications that had documented interactions (e.g. inhibitors, substrates or inducers) with any of the genes that had been tested for allele variations, was calculated for each patient. The period for medication selection was from 1/1/2014 to 5/7/2016  $\pm$  1 month. Patients whose genotyping or medication data were not available, those whose genotyping report date was before 6/7/2014 or after 5/7/2016, and those younger than 18 or older than 88, were excluded. All data are presented as mean  $\pm$  s.d. The 2-tailed t-test was used to calculate significance between the means unless indicated otherwise.

## RESULTS

**Patient demographic and diagnostic categories:** Seventy-five pharmacogenomic tests were ordered by RPMG prescribers between 2014 and 2016. Sixty-three patients meeting inclusion/exclusion criteria whose data were selected for analysis included 39 females and 24 males with an average age of 50.9  $\pm$  18.3 years. Patient geographic ancestry (based on 1000 Genomes definition, [18]) was

81.4% CEU (Utah residents with Northern and Western European ancestry), 9.3% MXL (Mexicans Ancestry from Los Angeles USA) and 9.3% ASW (Americans of African ancestry in SW USA). The average interval before the genotyping report date, for which the medication data were

selected, was  $172.4 \pm 70.7$  days and a corresponding time period after the genotyping report date was  $174.3 \pm 124.8$  days (not statistically significant,  $p = 0.918$ , 2-tailed t-test). Patient diagnoses grouped by ICD-10-CM categories [19] are shown in **Table 1**.

**Table 1.** Diagnostic groups present in the RPMG patient sample. Most patients had more than one diagnosis. Medical diagnoses were not routinely available in the EHR and were not included.

ICD-10-CM Disease Codes	Diagnosis	Number of patients with disorder	Percent of patients with disorder
<b>F06.31, F06.33, F32.2, F32.8, F32.9, F33.0, F33.1, F33.2, F33.9</b>	Major depressive disorder, mental disorders due to known physiological conditions	49	77.78
<b>F41.1, F41.9, F40.01, F41.0, F40.10, F43.10, F42</b>	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	28	41.44
<b>E72.12, F02.80, G31.84, F25.1, F90.0, G40.109, F45.22, F51.1, F52.22, F60.9, G27.46, G47.00, G89.29, M79.7, T42.4X5S, T43.215A, T43.221A, T43.404S</b>	Others (Methylenetetrahydrofolate reductase deficiency, cognitive impairment, schizoaffective disorder, ADHD, epilepsy, body dysmorphic disorder, hypersomnia, female sexual arousal disorder, personality disorder, circadian rhythm disorder, insomnia, chronic pain, fibromyalgia, drug adverse effects)	19	30.16
<b>F31.30, F31.81, F31.9, F34.0</b>	Bipolar disorder, cyclothymic disorder	7	11.11
<b>F10.20, F11.20, F12.280, F13.14</b>	Mental and behavioral disorders due to psychoactive substance use	4	6.35

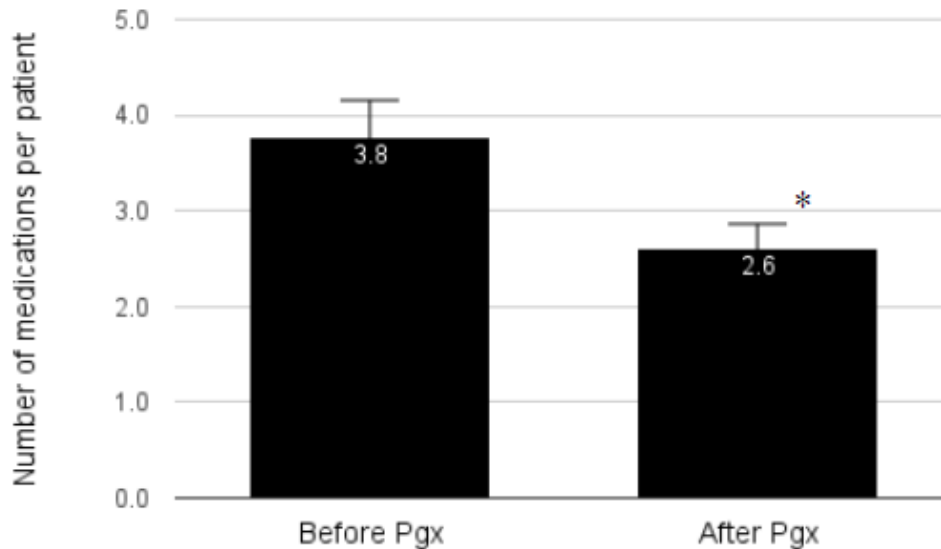
**Allele variations:** The average number of variant alleles was 2.22 per patient and 34.9% of patients had 2, 28.6% had 1, 23.8% had 3, 11.1% had 4 and 1.6% had 5 variant alleles. The most common genetic variations were in the *CYP2D6* gene (33 patients or 52.4%). *CYP2B6* and *CYP2C19* variations were slightly less common (30 patients or 47.6% for each gene). *CYP2C9* variations were present in 23 patients or 36.5%, and *CYP3A4* and *3A5* variations were present in 12 patients each or 19.0% of the sample. Determinations as to whether the particular allele listed in a genotyping report was a gain- or a loss-of-function mutation were made independently by cross-referencing the allele number obtained from the laboratory generated genotyping report against data available in The Human Cytochrome P450 (CYP) Allele Nomenclature Database [20]). Allele variations associated with a loss or reduction of the CYP enzyme activity were found in 84.3% of patients. Variations associated with increased CYP enzyme activity were present

in 14.3% patients. Hardy-Weinberg equilibrium of allele variations for each *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP3A4* and *CYP3A5* genes was calculated using an online calculator [21] and no statistically significant difference between the allele frequency in all of our genotyped samples and the general European population (data from dbSNP, [22]) was found based on Chi-square values calculated using an online calculator [23].

**CNS-active drugs:** The maximum number of CNS-active drugs that were substrates, inhibitors or inducers of any of the genes that had at least one variant allele (homo- or heterozygote) present in a given patient, and were prescribed to that patient at any time during the preset interval before the pharmacogenomics report date, was 10. The maximum number of such medications prescribed after the pharmacogenomics report date was 7. The average number of CNS-active medications that were substrates, inhibitors or inducers of any of the variant genes was  $3.8 \pm 2.3$

medications per patient prescribed before, and  $2.6 \pm 2.0$  medications per patient prescribed after the genotyping

report date. This difference was statistically significant ( $p = 0.003$ , 2-tailed t-test) (**Figure 1**).



**Figure 1.** The average number per patient of CNS-acting drugs that were substrates, inhibitors or inducers of the variant genes prescribed before (left column) and after (right column) the pharmacogenomic test information became available to the prescriber. Vertical bars, s.d., \* indicates statistical significance ( $p = 0.003$ , 2-tailed t-test).

## DISCUSSION

Our data show that the number of CNS-acting drugs that were substrates, inhibitors or inducers of the variant genes and were prescribed after the pharmacogenomic test information became available to the prescriber was lower than the number of such drugs prescribed before the test. This difference was statistically significant lending support to the idea that pharmacogenomic testing has a significant clinical utility. Previously published reports have already shown financial, health and consumer satisfaction benefits associated with pharmacogenomic testing [24-26]. What is noteworthy about our data is that they were obtained not in an academic or research center but in a relatively small, general psychiatry practice setting where the prescribers do not have specialized training in genetics or genomics and where there is no bioinformatics support available. Our findings suggest that pharmacogenomic testing for CYP genotype should be implemented widely without excluding small practice settings. They also support the idea that frequent medication changes by the prescriber could serve as a sign for ordering pharmacogenomic testing.

The information provided in this study is limited, however, because of the small sample size. It remains to be confirmed that prescribing medications based on patient's genetic information related to altered CYP enzyme functions would necessarily translate to symptom improvement. This question could be better addressed in a larger study or studies that use outcome measures that are applicable to the

patient's main diagnosis and patients are stratified by their genotype. A larger study would also help determine if there were significant differences between the contributions of each gene to the medication changes made by a prescriber or whether having multiple variant alleles can influence the likelihood of medication changes that may lead to treatment failure. Only CYP interactions with CNS-acting drugs, including psychotropics, opioid analgesics, centrally acting muscle relaxants, antihistaminic and antiepileptic drugs, were considered in this analysis. It remains unclear whether factoring non-CNS-acting drugs, such as antibiotics or anti hypertensives, would impact the result. Finally, it remains unclear how the prescriber decisions were made given a rather large number of data points that needed to be considered in order to take a full advantage of pharmacogenomic information.

In conclusion, these data support the notion that pharmacogenomic testing has clinical utility in a small, non-academic, general psychiatry practice setting.

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