A Combinatorial Pharmacogenomic Algorithm is Predictive of Sertraline Metabolism in Patients with Major Depressive Disorder

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INTRODUCTION

- Pharmacogenomic (PGx) testing can aid in treatment selection for patients with Major Depressive Disorder (MDD) by identifying gene-drug interactions (GDI) that may impact medication metabolism.
- While multiple genes are known to impact sertraline metabolism, CPIC guidelines for sertraline only include recommendations based on a single gene, CYP2C19.1
- An alternative approach is to apply a weighted combinatorial algorithm which considers the effects of multiple genes in one or more metabolic pathways.
- Here, we compared the ability of a weighted combinatorial PGx (CPGx) algorithm to predict variation in sertraline blood levels relative to single gene approaches involving CYP2C19, CYP2B6, and CYP3A4.7

METHODS

COHORT

- All patients were enrolled in the Genomics Used to Improve Depression Decisions (GUIDED) trial – a large, patient- and rater-blinded, randomized, controlled trial that included patients diagnosed with MDD who had an inadequate response to ≥1 psychotropic medication (N=1,167).3
- All patients received CPGx testing as part of the trial. Medications were categorized according to the predicted level of GDI and change in metabolism (increase, decrease).
- A subset of 124 patients reported taking sertraline within 2 weeks of the screening blood draw and had sertraline blood concentrations quantified using LC-MS/MS.

STATISTICAL ANALYSIS

- A combined phenotype for sertraline pharmacokinetics was generated from a weighted, combinatorial algorithm that included CYP2C19, CYP2B6, and CYP3A4 to predict the level of GDI (no, moderate, or significant) and change in metabolism (increase or decrease).
- The ability to predict variation in sertraline blood levels (log-transformed concentration/dose ratios) was evaluated for:
  - Individual gene phenotypes for CYP2C19 as defined by CPIC and CYP2C19 as defined by the CPGx test
  - Individual gene phenotypes for CYP2B6 and CYP3A4 as defined by the CPGx test
  - CPGx combined phenotype
- All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

RESULTS

- Sertraline blood levels across phenotypes for individual genes and the CPGx test.
- Boxplots of the log-transformed concentration/dose ratios according to (A) individual CYP2C19 phenotypes as defined by CPIC, (B) individual CYP2C19 phenotypes as defined by the CPGx test, (C) individual CYP2B6 phenotypes as defined by the CPGx test, (D) phenotypes as defined by the CPGx algorithm.

Table 1. A multivariate analysis evaluating the ability of individual genes and the CPGx algorithm to predict variation in sertraline blood levels.

The trends in Figure 1 are reflected in this multivariate analysis. After adjusting for all variables in the model, only the CPGx algorithm remained a significant predictor of sertraline blood levels.

Table 1. Multivariate analysis evaluating the ability of individual genes and the CPGx algorithm to predict variation in sertraline blood levels.

<table>
<thead>
<tr>
<th>Variables included in Model</th>
<th>Individual Gene</th>
<th>CPGx Algorithm</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>F Statistic</td>
<td>p-value</td>
</tr>
<tr>
<td>CYP2C19* &amp; CPGx</td>
<td>0.005</td>
<td>0.95</td>
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<tr>
<td>CYP2C19** &amp; CPGx</td>
<td>0.06</td>
<td>0.80</td>
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<tr>
<td>CYP2B6 &amp; CPGx</td>
<td>0.23</td>
<td>0.63</td>
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*Phenotypes as defined by CPIC
**Phenotypes as defined by the CPGx test

DISCUSSION

- Clinically meaningful differences in sertraline blood levels were observed between phenotypes for CYP2C19 defined by CPIC, as well as phenotypes for CYP2C19 and CYP2B6 defined by the CPGx test, suggesting that genetic variation in both enzymes can impact sertraline metabolism.2
- Multivariate analyses revealed that the CPGx algorithm accounted for more variance than individual genes alone, and thus was a superior predictor of medication blood levels. This aligns with previous findings in other psychiatric medications, including olanzapine and escitalopram.4,5
- Collectively, our findings suggest that the CPGx algorithm may provide more clinically relevant information to inform decisions regarding sertraline compared to testing individual genes.2

REFERENCES