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

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INTRODUCTION

• Pharmacogenomic testing can aid in treatment selection for patients with Major Depressive Disorder (MDD) by identifying gene-drug interactions that may impact medication metabolism.
• The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides recommendations for sertraline dosing based on genetic phenotypes for CYP2C19; however, other groups suggest that additional enzymes may be important for sertraline metabolism.1
• Although there have been rapid advancements in this field, there is not a consensus about the approach to pharmacogenomic (PGx) testing or even which genes are relevant for many antidepressants.

• Here, we assessed the ability of pharmacokinetic (PK) genes in a combinatorial PGx test (weighted assessment of multiple genes) to predict meaningful variations in sertraline blood levels.

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).2
• All patients received combinatorial pharmacogenomic testing as part of the trial.
• 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 gene-drug interactions (GDi) 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 as defined by the combinatorial PGx test (CYP2C19, CYP2B6, and CYP3A4)
  - Combinatorial PGx combined phenotype
• All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

REFERENCES:

DISCUSSION

• Clinically meaningful differences in sertraline blood levels were observed between phenotypes for both CYP2C19 and CYP2B6, suggesting that both enzymes are important for sertraline metabolism.
• Multivariate analyses revealed that the combinatorial PGx test accounted for more variance than individual genes alone, and thus was a superior predictor of medication blood levels. This aligns with previous findings across other psychiatric medications.
• Collectively, our findings suggest that the combinatorial PGx test may provide more clinically relevant information to inform decisions regarding sertraline compared to testing individual genes.

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

<table>
<thead>
<tr>
<th>Combinatorial Pharmacogenomic Test Report Category</th>
<th>Individual Gene</th>
<th>Combinatorial PGx Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables included in Model</td>
<td>Individual Gene</td>
<td>Combinatorial PGx Test</td>
</tr>
<tr>
<td>CYP2C19 and Combinatorial PGx</td>
<td>F 0.06 p-value 0.06</td>
<td>F 0.06 p-value 0.06</td>
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<tr>
<td>CYP2B6 and Combinatorial PGx</td>
<td>F 0.03 p-value 0.03</td>
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The trends in Figure 1 are reflected in this multivariate analysis. After adjusting for all variables in the model, only the combinatorial PGx test remained a significant predictor of sertraline blood levels.