A 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 (GDI) that may impact medication metabolism.

The Clinical Pharmacogenomics 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 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) was evaluated for:

- Individual gene phenotypes for CYP2C19 as defined by both CPIC and the combinatorial PGx test
- Individual gene phenotypes for CYP2B6 and CYP3A4 as defined by the combinatorial PGx test
- Combinatorial PGx combined phenotype

All data were analyzed using ANCOVA tests with log-transformed lean body weight as a covariate.

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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.3

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.

REFERENCES:

Fig. 1. Sertraline blood levels across phenotypes for individual genes and the combinatorial PGx test.

Boxplots of the log-transformed concentration/dose ratios according to (A) individual CYP2C19 phenotypes as determined by the combinatorial PGx test, (B) individual CYP2B6 phenotypes as determined by the combinatorial PGx test, or (C) combinatorial PGx test phenotypes. The median (thick horizontal line) interquartile range (box) with plus/minus 1.5x interquartile range (vertical lines) are shown.