A Pharmacogenomics Retrospective Study on cytochrome P450 for the Efficacy of Antidepressant and Antipsychotic Drugs

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ABSTRACT

Purpose: The objective of this retrospective study was to identify genetic variants of gene encoding a major drug-metabolizing enzyme among two different races – African American and Caucasian – based on pharmacogenomics testing and interpretive report (GeneSight). The study might shed lights for the application of precision prescribing in the clinical settings in the near future.

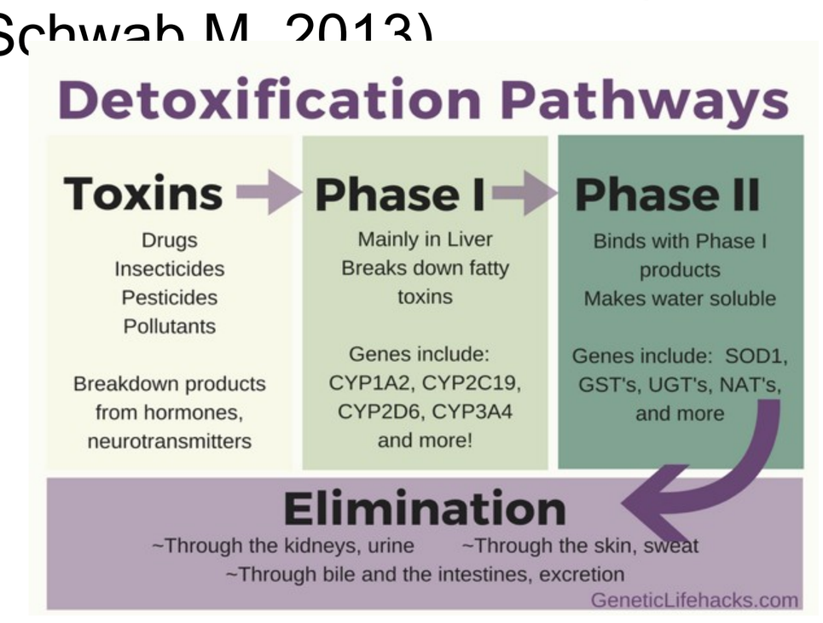
Methods: A retrospective study of de-identified interpretive reports from GeneSight of sixteen individuals (n = 16) at the Mental health Mental Retardation (MHMR) of Tarrant County. There are five reports of male and eleven reports of female in this study, of which six are African American and ten are Caucasians. The study was divided into two groups based to their races. Percentage of different alleles within variants of the CYP gene family were determined. Based on genetic components of patients, drug recommendations were made by AsureRx Healh, Inc.

Hypotheses: CYP2 is known to be highly polymorphic in many scientific literatures. It is hypothesized that genetic variants will be observed in the CYP2 gene.

BACKGROUND

Pharmacogenomics is the study of how genes affect a person's response to drugs. While it is becoming a hot topics in research recently, it is certainly not a new idea. Arno Motulsky, a geneticist at the University of Washington, Seattle, published an article in 1957 discussing that the adverse reactions to the antimalarial drug and the muscle relaxant are "heritable and linked to deficits in the activity of specific enzymes" (Drew, 2016).

Drug metabolism, also known as biotransformation, is a series of chemical reactions, ultimately resulting in modifications of a drug. It is a process in which drugs are broken down, absorb, and excrete with the help of some type of proteins. With an exception of a few drugs, the majority of prescription drugs are metabolized in the liver by "hepatic phase I and II reactions" (Zanger U, Schwab M, 2013).

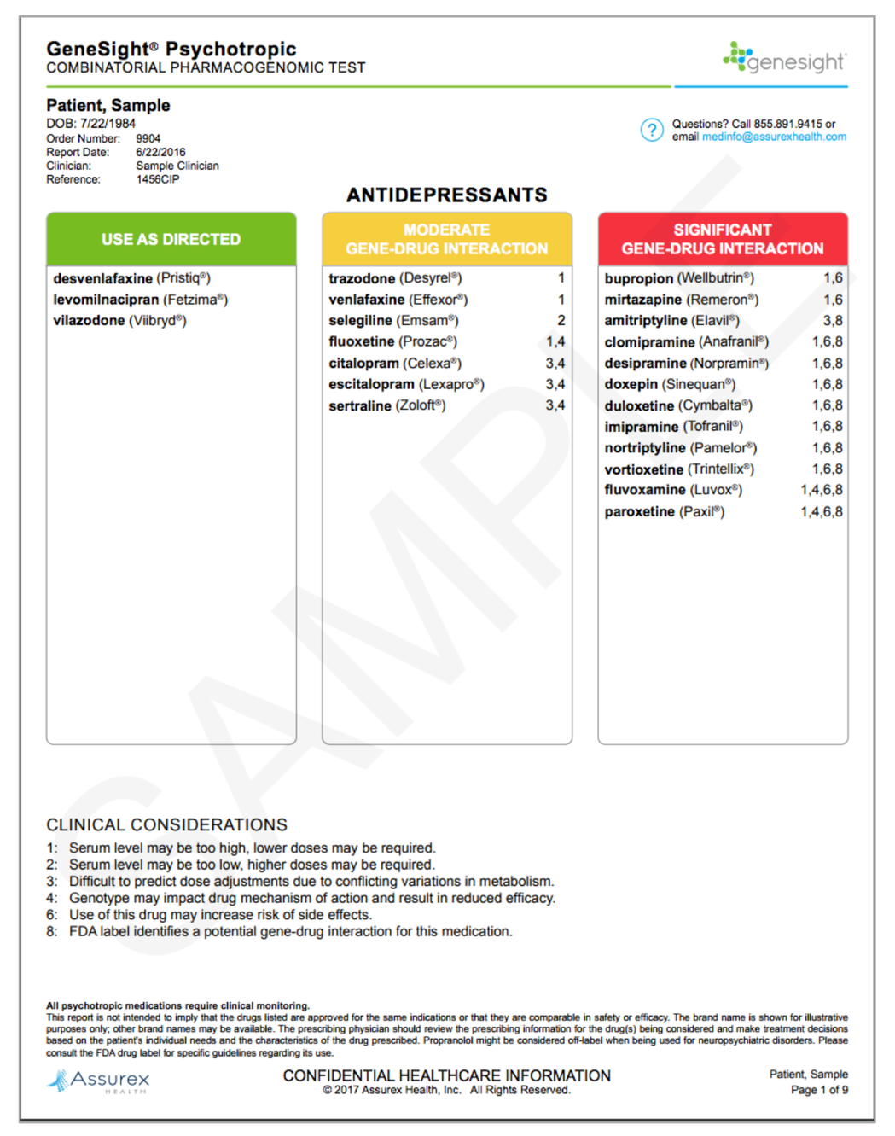


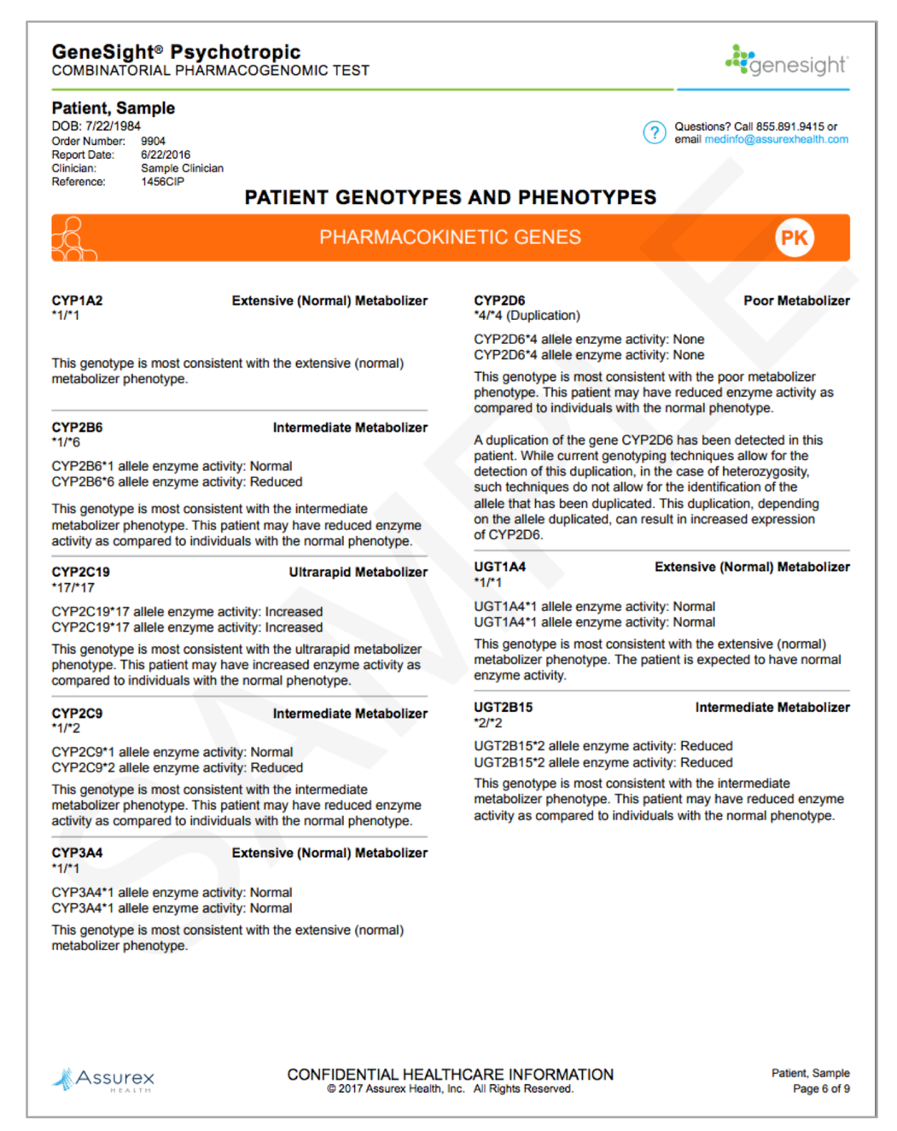
Phase I enzymes, specifically cytochrome P450 (CYP), "modify functional groups (- OH, -SH, -NH2, -OCH3) of endogenous and xenobiotic compounds" and convert them into active metabolites, which travel to target cells in the body and induce their intended purposes (Basic & Clinical Pharmacology 14th Ed.) CYP genes controls the expression of cytochrome P450 proteins. This study focuses mainly on gene encoding for Phase I drug metabolizing enzymes.

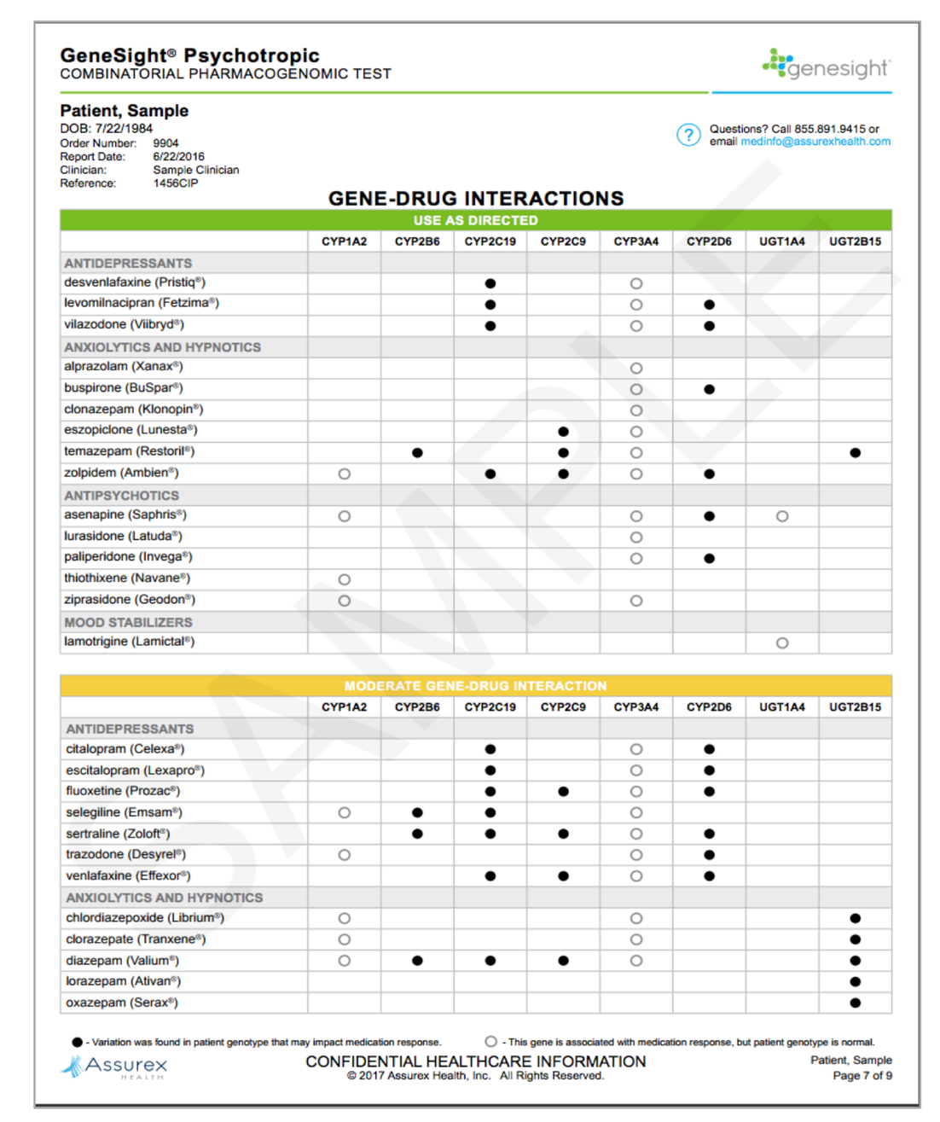
With the use of pharmacogenomics testing, drug recommendations help guide physicians in prescribing medications to patients. Certain adverse side effects associated with various medications can potentially be avoided.

METHOD

The study consists of interpretive reports from GeneSight of sixteen male and female patients, n = 16, (five male and eleven female) between ages of 27-70 across two ethnicities – African American and Caucasian. The genotyping process was performed by AsureRx Health, Inc. from Mason, Ohio, United States. Data was collected by the Mental Health Mental Retardation of Tarrant County (Fort Worth, Texas). Polymorphism were measured among five genes that are known to influence antidepressant and antipsychotic drug metabolism or response: **CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6.**

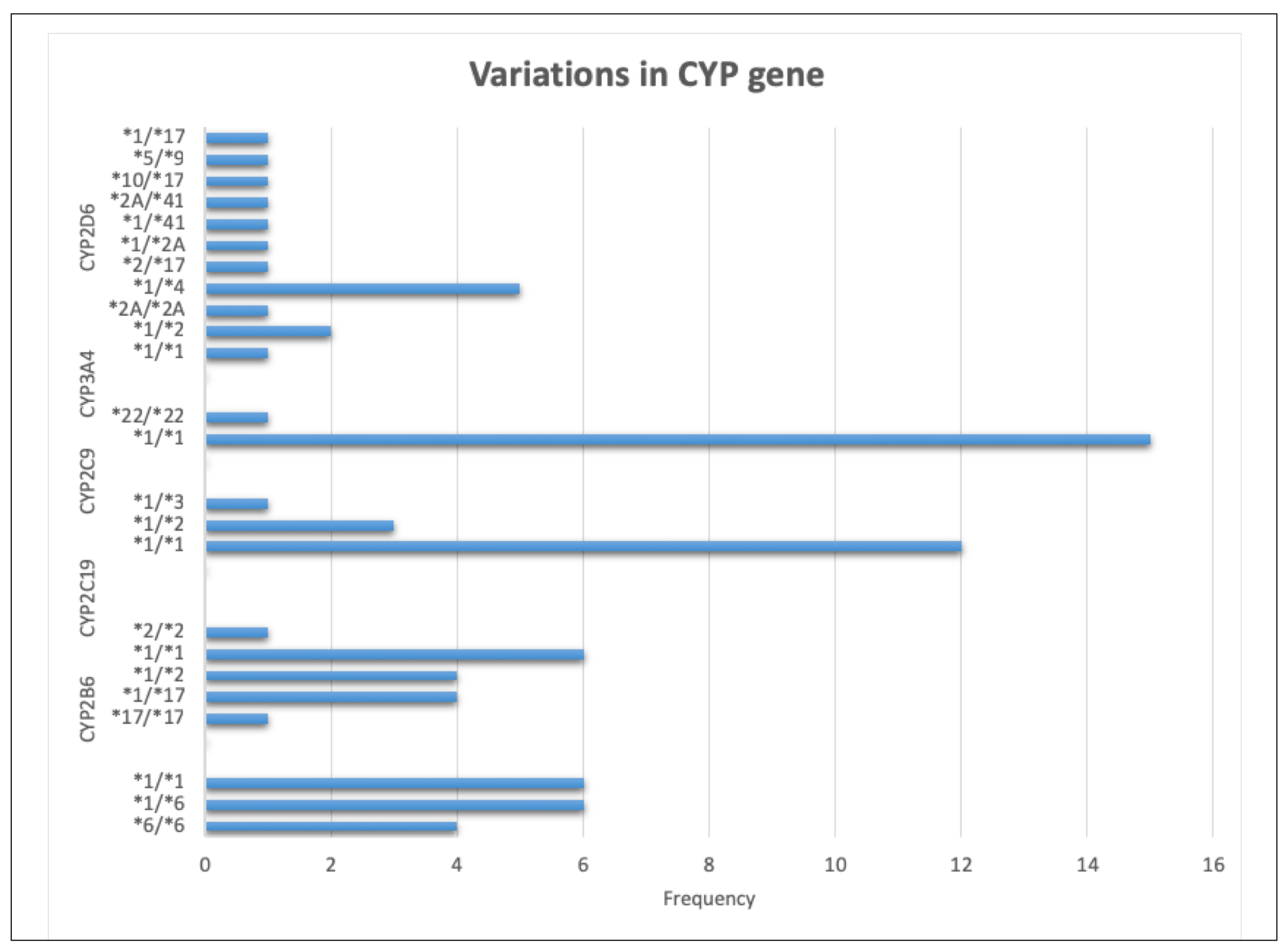


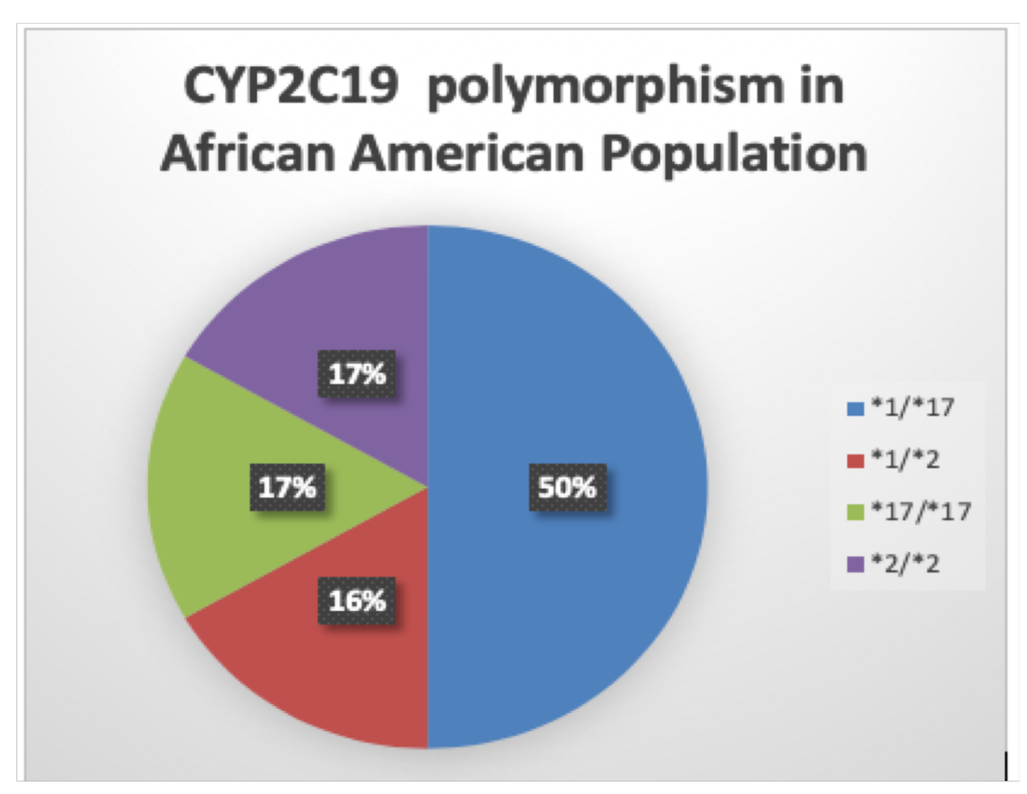


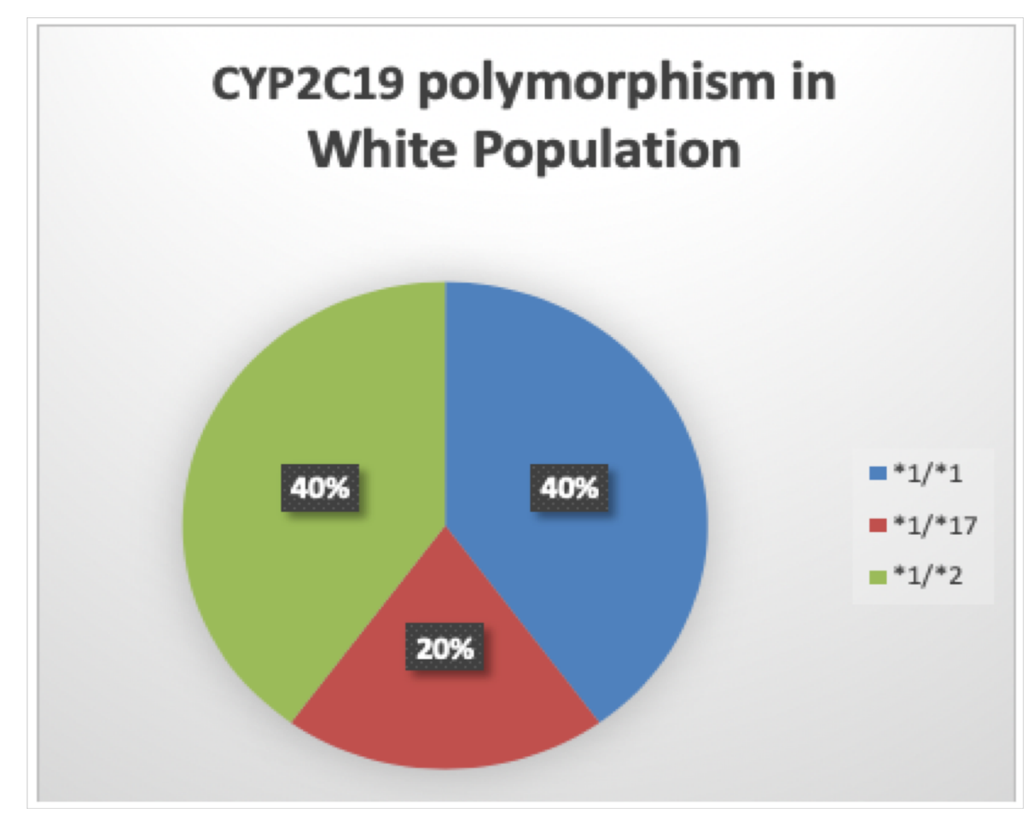


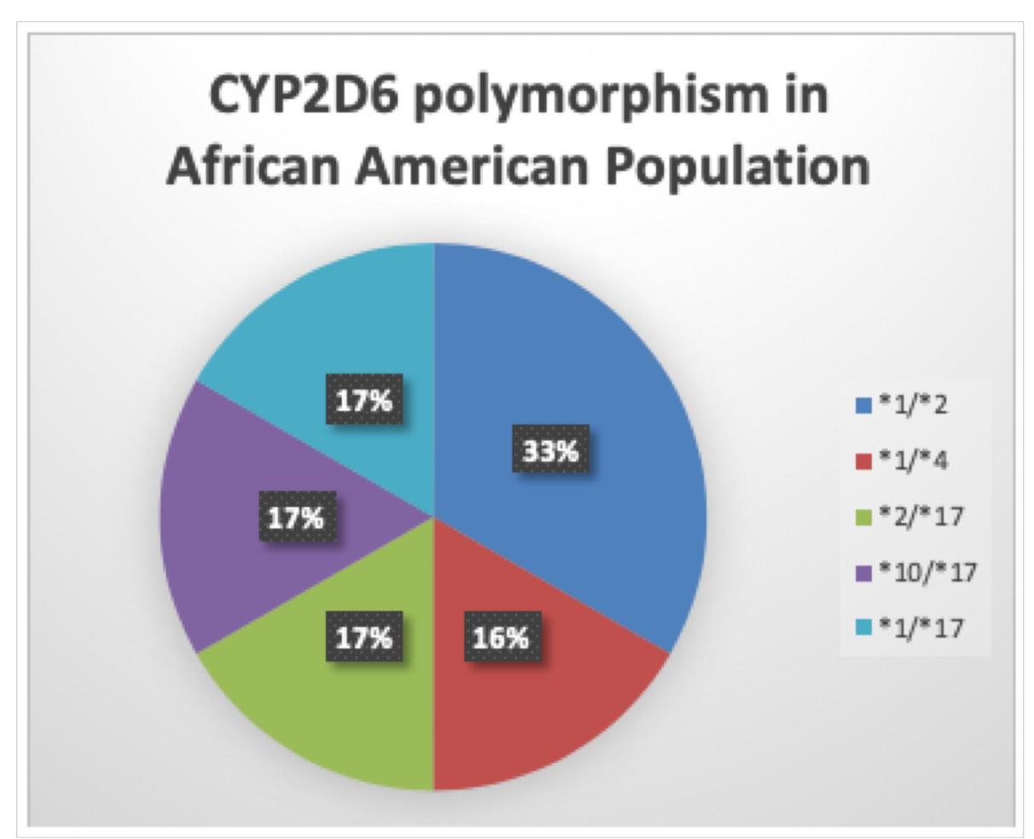
RESULTS

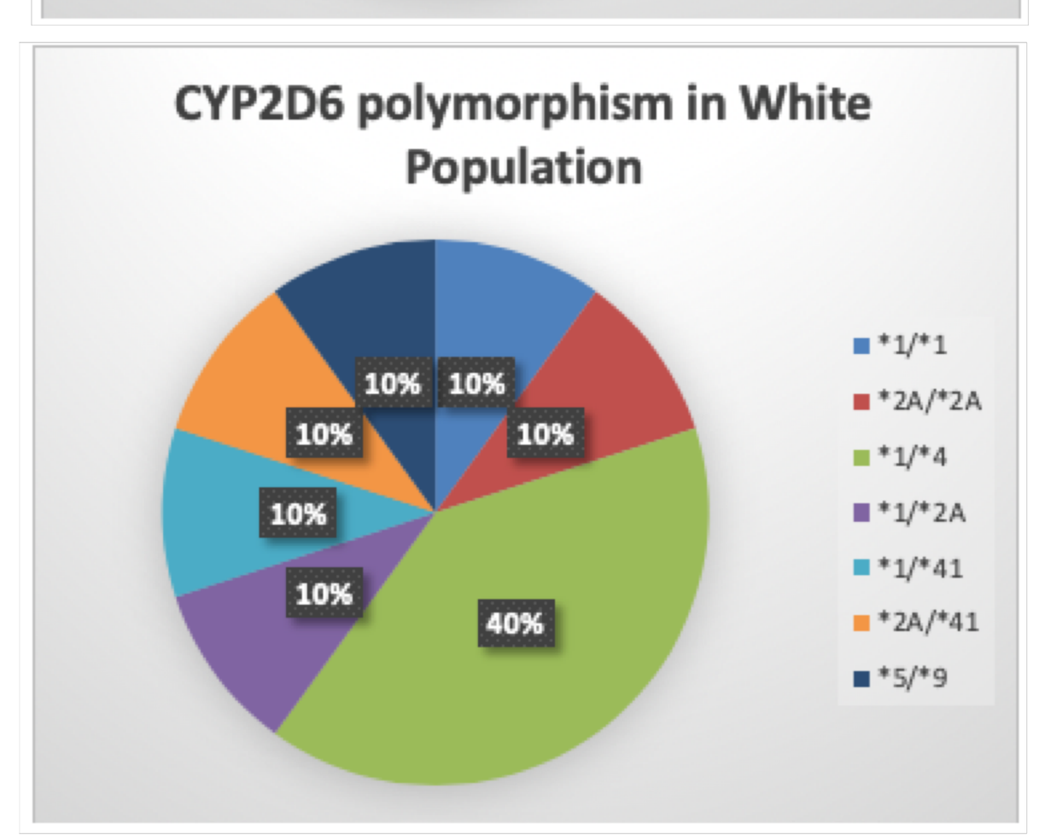
Out of the five variants of the CYP gene family, CYP2D6 is highly polymorphic, with ten different variants besides the wild type allele (*1/*1) – *1/*2, *1/*4, *1/*2A,*1/*41, *1/*17, *2A/*2A, *2/*17, *2A/*41, *5/*9, and *10/*17. Polymorphism is rarely observed in genes CYP2C9 and CYP3A4 within the African American population. Although, there are a few variants within the Caucasian population for genes CYP2C9 and CYP3A4, *1/*2 and *1/*3 (CYP2C9), and *22/*22 (CYP3A4), the wild type allele dominates in both genes with 60% (CYP2C9) and 90% (CYP3A4) of the patients carry allele *1/*1.











DISCUSSION

The main goal of pharmacogenomics is to prospectively predict patients who are more or less likely to have a favorable outcome with specific medications. In order for pharmacogenomic testing to be of value, it must be appropriately integrated into clinical practice. Recently, GeneSight testing was employed for a nationwide randomized control trial (RCT) with patients who failed in respond to their current prescribed antidepressant medications. Rather than executing trial-and-error prescribing, healthcare providers should practice precision medicines using the tool of pharmacogenomics testing. Prescriptions should be personalized to a patient instead of a standardized recommendations from drug manufacturers. In this study, CYP gene is found to be highly polymorphic, suggesting that patients are genetically very different. Therefore, one-size-fits-all approach in prescribing medications is not effective, can be harmful in some cases, and must be changed in the future for better outcome of patients.

CONCLUSION AND FUTURE DIRECTIONS

In conclusion, high polymorphism is observed in cytochrome P450 gene, especially in CYP2D6 and CYP2C19. Variations within genes of drug metabolizing enzymes can impact the efficacy of medications metabolized by the CYP proteins. Depending on the expression level of the CYP gene, patients might experience unintended adverse side effects as a result of overdose or need higher dosage to achieve adequate drug effects.

Future studies can further explore roles of cytochrome enzymes in other categorical drugs sides antidepressant.

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