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Relevance of Pharmacogenomics, CYP450 genes and their genetic variations in drug metabolism and toxicity

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BACKGROUND & INTRODUCTION

Variations in drug responses are related to inherited characteristics of the genome that cause a wide variability in individual drug responses. Pharmacogenetics or pharmacogenomics analyses help us to understand DNA variations that are related to drug action (pharmacodynamics) and drug disposition (pharmacokinetics). Using a pharmacogenomics (PGx) approach, we studied six different CYP450 genes that are associated with drug metabolism, along with their genomic variants, thus strengthening our understanding of personalized medicines. The liver is by far the most important organ for drug metabolism. The clinical response to the same dose of a drug may vary among individuals. Cytochrome P450 (CYP) genes/enzyme metabolizes many psychotropic medications and genetic variations in these genes cause changes in their activity and result in differences in effectiveness and adverse effects.

METHODS

We downloaded the Pharmacogenomics (PGx) database from the FDA website[1] and collated the data utilizing various evolutionary tools and software. We also provided an overview of current progress in computational approaches for the prediction of drug metabolism and toxicity using a combination of knowledge graph- and AI-based approaches. Utilizing ethnicity data from published sources, we also correlated the clinical implications of drug metabolism and toxicity variability in different population cohorts.

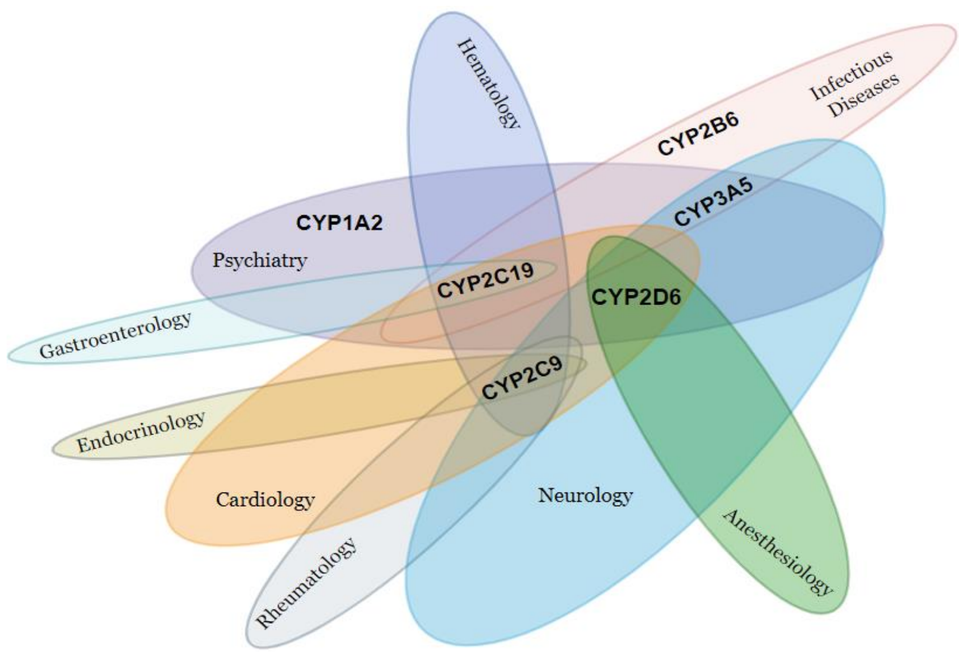

Figure 1: Association of six CYP genes in different therapeutic areas

RESULTS & DISCUSSION

We observed that 42 unique drugs catering to nine different therapeutic areas are associated with six CYP450 (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A5) genes/biomarkers and 32 unique variants/SNPs (Figs 1-3). The allelic frequencies (AFs) of the 32 variants were also studied in different population ethnicity groups (from a published database). We observed unique combinations of drugs, biomarkers and variant associations that highlight how the metabolism of a drug is controlled/regulated/metabolized by the genetic basis of an individual. We observed 32 unique combinations where the same CYP biomarker and its variant are shared by different drugs associated with different therapeutic areas. For sake of brevity, we have taken example of CYP2D6 in figures.

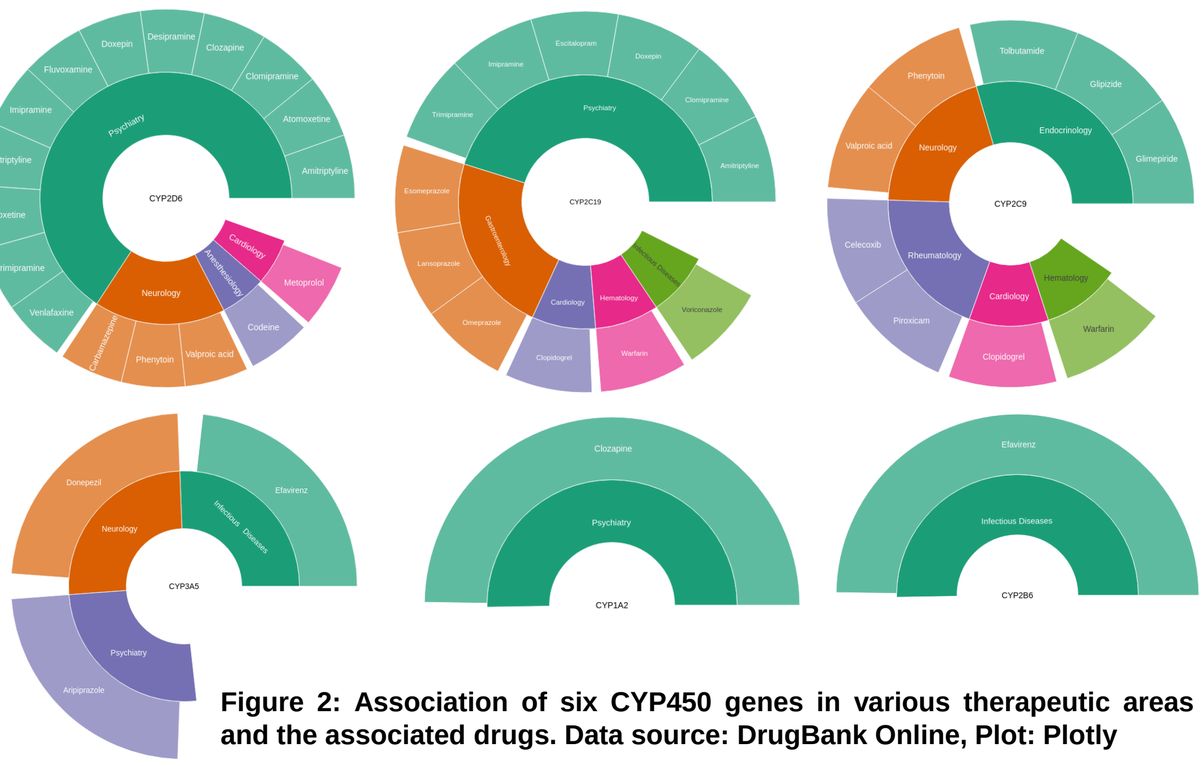

Figure 2: Association of six CYP450 genes in various therapeutic areas and the associated drugs. Data source: DrugBank Online, Plot: Plotly

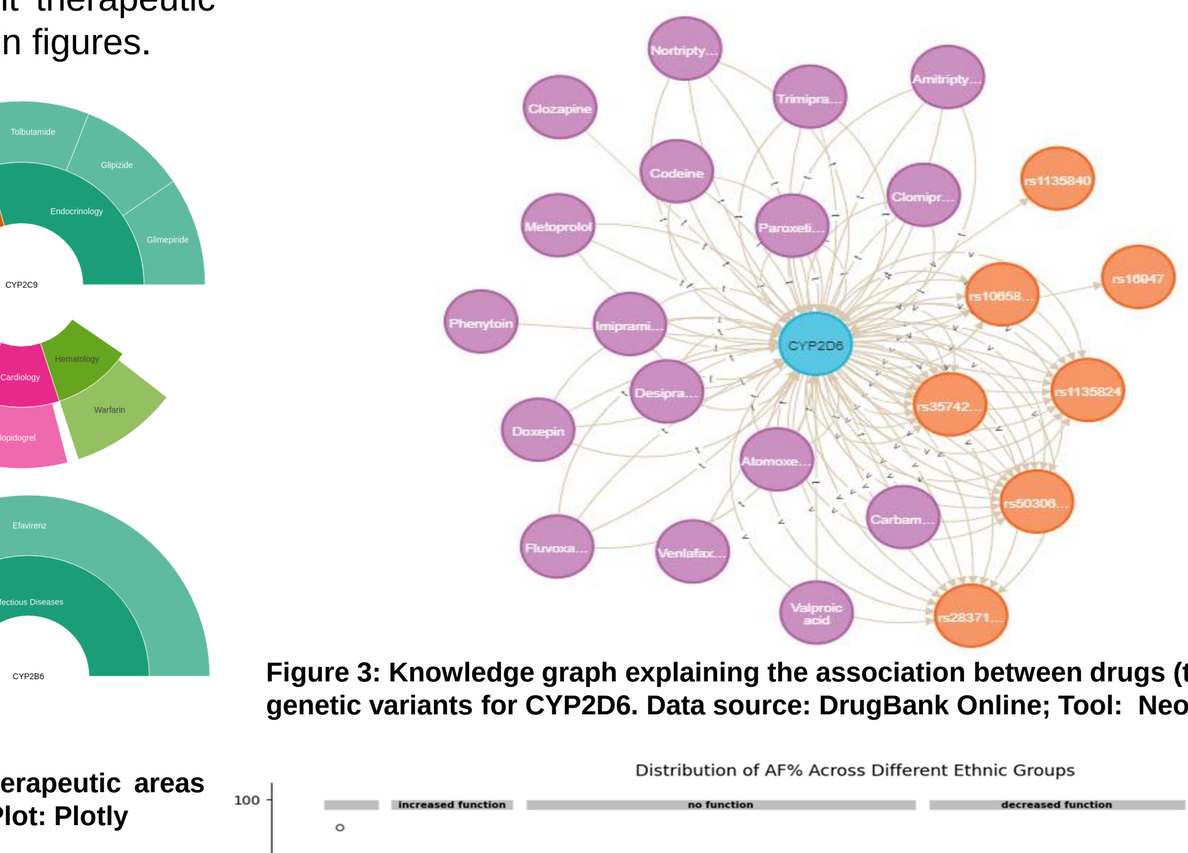

Figure 3: Knowledge graph explaining the association between drugs (targets) and genetic variants for CYP2D6. Data source: DrugBank Online; Tool: Neo4j

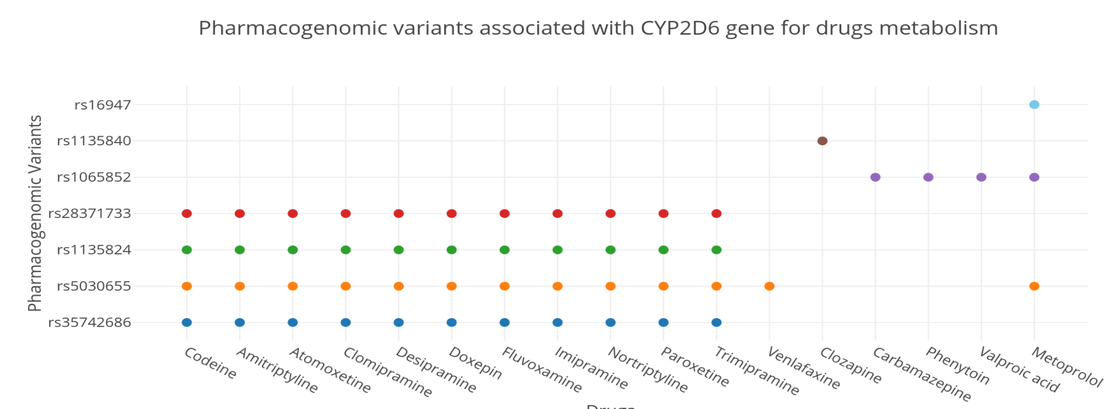

Figure 4: Association of CYP2D6 Pharmacogenomic variants with drugs depicting similar genetic basis and new evolved genetic variants. Data source: DrugBank Online; Plot: Python library, Plotly

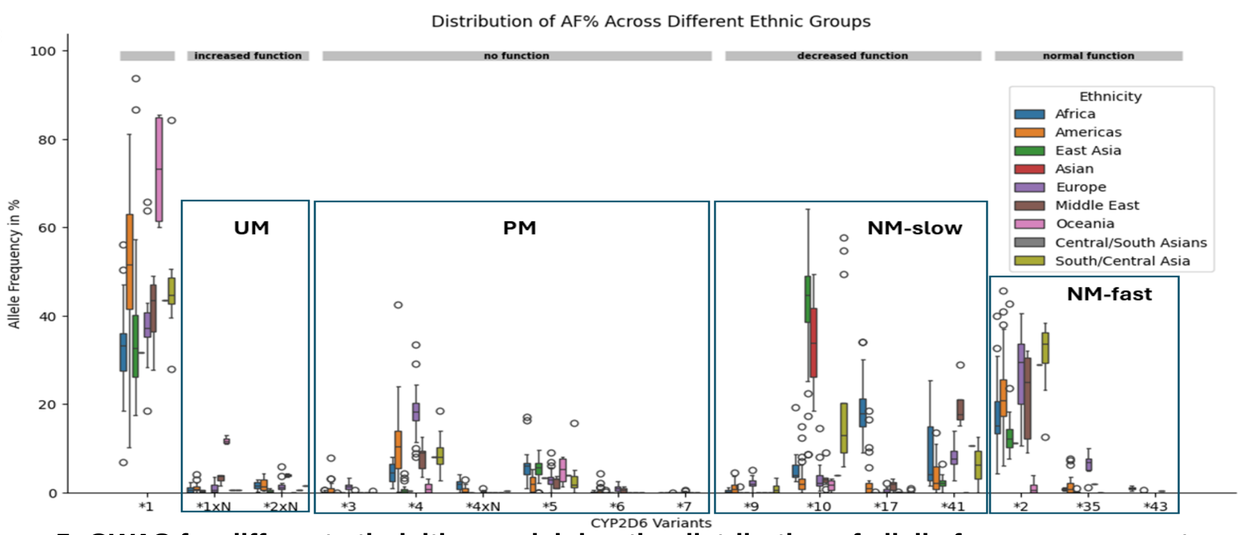

Figure 5: GWAS for different ethnicities explaining the distribution of allelic frequency percentage using Boxplots of CYP2D6 variants and correlating the same with level of allelic function and drug metabolism. PM is Poor Metabolizer, UM is Ultrarapid Metabolizer, NM is Normal Metabolizer. Data extracted from Gaedigk et al., 2017 (https://doi.org/10.1038/gim.2016.80) Plot: Matplotlib, Seaborn

CONCLUSION

PGx studies should be inclusive, and policy makers/drug regulators should include such approaches for better understanding the genetic basis of drug-metabolizing genes for better drug response. The PGx approach also highlights a significant association between Precision Medicine and Pharmacovigilance by understanding drug metabolism and toxicity in accordance with an individual's genetic makeup.