Pharmacogenomics of CYP2C9 and VKOR in a Local Ambulatory Care Clinic

Brooke Heminger, Calynn Murphy, Maria Faber
The University of Findlay

Introduction

Pharmacogenomics research examines DNA to determine if genetics play a role in responses to medication therapy.[1] Differences in genetics can cause medications to not work as well or not at all in certain populations or can cause adverse events such as side effects, toxicity, or even overdose death.[1] Clinical Pharmacogenetics Implementation Consortium (CPIC) and medication package inserts are also including guidelines and recommendations for populations with particular genotypes.[1] Liver enzymes play a key role in activation and breakdown of medications.[1] CYP2C9 and VKORC1 are two key enzymes in the breakdown of the common blood thinning medication warfarin.[2] In addition to the breakdown of warfarin, CYP2C9 breaks down steroid hormones, fatty acids, and other medications such as ibuprofen. The most common alleles for CYP2C9 are *1 (wild-type), *2, and *3.[3] VKORC1 plays a role in the conversion of vitamin K to activate clotting proteins. Individuals can either carry two alleles of wild type, two alleles of the variant, or one of each.[2]

Objectives

To isolate DNA followed by genotyping to determine allele frequencies, and to determine feasibility of pharmacogenomics in an ambulatory care clinic.

Methods

- This study was approved by the IRB at The University of Findlay.
- Participants were 18 years or older and were chosen from a local Ambulatory care center.
- DNA from the participants were collected via a cheek swab.
- A total of 90 samples were collected, and de-identified
- The DNA samples were then isolated and purified
- Samples were isolated using QIAGEN isolation kits
- The DNA was amplified using a BIO-RAD CFX96 real-time PCR machine.
- Genotyping was performed and based upon classification of the metabolic status for the CYP2C9 and VKOR allele.

Results

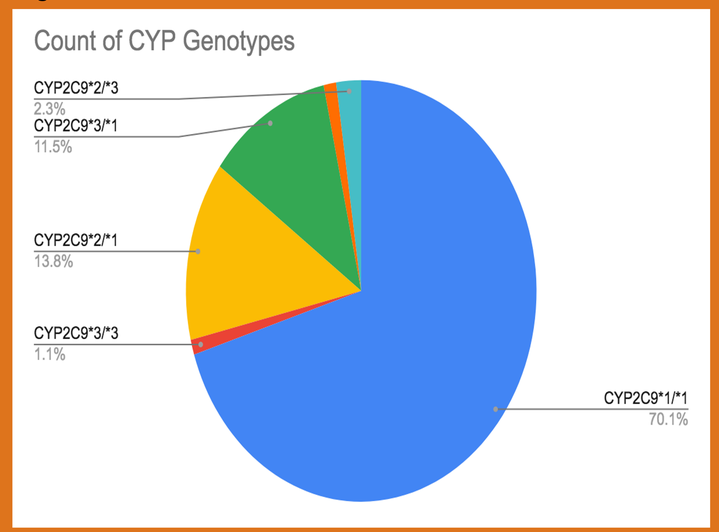
Table 1:

VKOR Alleles	Number of Subjects	Percentage of 90 samples	Phenotype (Metabolism)
Heterozygous (wild/variant)	45	50%	Metabolism Varies
Homozygous Wild	34	38%	Normal Metabolism
Homozygous Variant	7	8%	Poor Metabolism
Indeterminant	4	4%	N/A

Table 2:

CYP2C9 Genotype	Number of Subjects	Percentage of the 90 samples	Phenotype (Metabolism)
CYP2C9 *1*1	61	68%	Normal Metabolizer
CYP2C9 *1*2	12	13%	Intermediate Metabolizer
CYP2C9 *2*2	1	1%	Intermediate Metabolizer
CYP2C9 *2*3	2	2%	Intermediate Metabolizer
CYP2C9 *1*3	10	11%	Intermediate Metabolizer
CYP2C9 *3*3	1	1%	Poor Metabolizer
Indeterminate	0	3%	N/A

Figure 1:



DISCUSSION

Through this study genotypes were able to be ascertained, which then allowed us to determine if the sample was a poor, normal or intermediate metabolizer. A potential future step would be to look at medication profiles to determine which drugs are metabolized by the enzymes CYP2C9 and the VKOR gene. Knowing the type of a metabolism that is occurring allows a physician to make appropriate adjustments to medication therapies. For some individuals, the rate of metabolism may explain why ideal responses were lacking or adverse drug effects were noticed at normal doses of their medications. Pharmacogenetics creates a whole new field of pharmacy that can provide individualized therapy. Based on the percentage of participants with non-wild type genotypes it may be beneficial to determine if personalized medicine could be feasible in a clinic setting.

CONCLUSIONS

In conclusion, over half of the participants in this study were found to be normal metabolizers displaying the wild type CYP2C9 *1*1. The research is still an ongoing study, and the research processes need to be optimized to verify that the methods are accurate. The next steps in this study will be to review the subjects' medication history to determine if the genotype may have contributed to efficacy and side effects.

REFERENCES

1. Pharmacogenomics [Internet]. National Institute of General Medical Sciences. U.S. Department of Health and Human Services; [cited 2021Mar10]. Available from: https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx\
2. Owen RP, Gong L, Sagreiya H, Klein TE, Altman RB. VKORC1 Pharmacogenomics Summary. *Pharmacogenetics and Genomics*. 2010Oct;20(10):642–4.
3. CYP2C9 gene [Internet]. MedlinePlus. U.S. National Library of Medicine; 2020 [cited 2021Mar10]. Available from: https://medlineplus.gov/genetics/gene/cyp2c9/#resources
4. Johnson J, Caudle K, Gong L, Whirl-Carrillo M, Stein C, Scott S, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. *Clinical Pharmacology & Therapeutics*. 2017Sep4;102(3):397–404.
5. Warfarin [package insert]. Princeton, New Jersey: Bristol-Myers Squibb Pharma Company; 2011.

University of Findlay®