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Pharmacogenomics and SSRIs Appropriateness in Older Community Dwelling African Americans

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Introduction

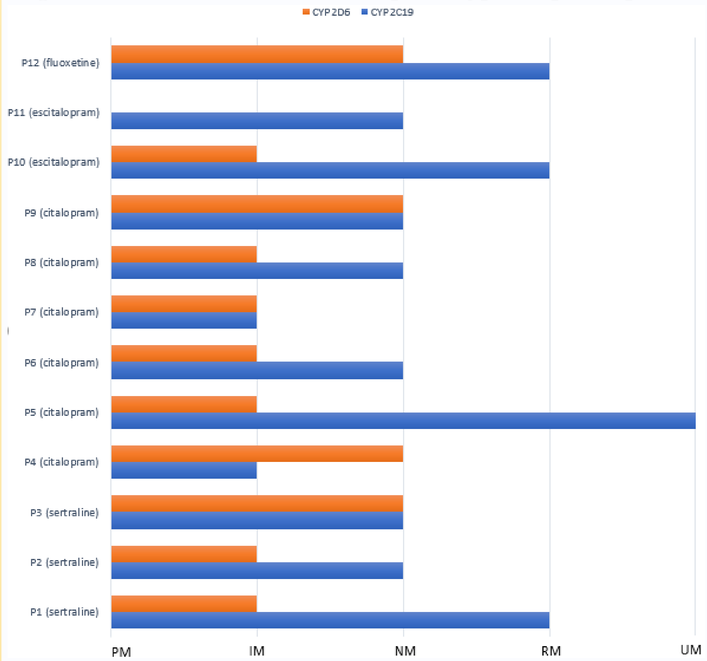
- Depressive and anxiety disorders are among the most common illnesses experienced by older adults (age ≥ 60).[1]
- The selective serotonin reuptake inhibitors (SSRIs) are preferred class of antidepressants for these disorders due to their high efficacy and safety profiles among older adults.[1]
- However, SSRIs are mainly metabolized by cytochrome P450 enzymes, specifically CYP2D6 and CYP2C19, which are known to be polymorphic in populations of African descent.[2] This can lead to variable dose-response outcomes, especially among older African American population.
- Pharmacogenomic data of CYP enzymes can be utilized to predict possible SSRI drug-gene interactions, as part of delivering precision medicine.

Objective

To analyze the frequency of CYP2D6 and CYP2C19 polymorphisms in African American older adults who are taking SSRIs and to identify potential inappropriate use of SSRIs in these older adults using the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SSRIs.

Methods

Figure 1. CYP2D6 and CYP2C19 phenotypes of participants taking SSRIs



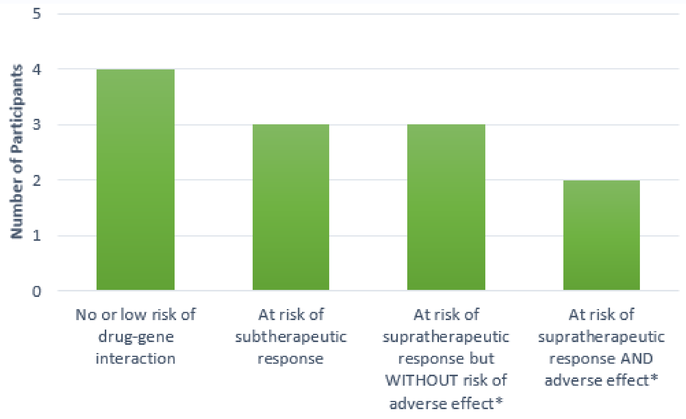
Key: **PM** = poor metabolizer (presence of two null alleles). **IM** = intermediate metabolizer (presence of either two reduced function alleles or one null allele and one reduced function allele). **NM** = normal metabolizer (presence of one normal allele plus another normal or reduced function allele). **RM** = rapid metabolizer (presence of one normal allele and one increased function allele). **UM** = ultrarapid metabolizer (presence of two increased function alleles).

- DNA samples of 64 participants (age ≥ 60), who were enrolled into Translational Approaches to Personalized Health (TAPH) study, were collected via Ora-gene saliva kits and analyzed using the PGx Express Chip on the QuantStudio 12K Flex system.[3]
- Among 64 participants, we focused on the genotypes of only 12 participants, who were taking SSRIs.
- After data collection, phenotypes were assigned to the genotypes of the 12 participants based on the CPIC Guideline for CYP2D6 and CYP2C19 genotypes of SSRIs (Fig. 1).[2]

Results

- Overall, only 2 participants had wild type for both CYP2D6 and CYP2C19. The rest of the participants had at least one variant allele that results in decreased or increased activity level of the CYP2D6 and CYP2C19 enzymes.
- After matching the participants' enzyme activity levels of CYP2D6 and CYP2C19 and the major metabolic pathway of their agent of SSRIs, about ⅔ of the participants are at risk for drug-gene interaction (Fig. 2).

Figure 2: Participants at increased risk of subtherapeutic or supratherapeutic response of SSRIs based on their pharmacogenomic results. *The adverse effect most concerned in the CPIC guideline was citalopram-induced prolonged QT interval.



Conclusion

- Among 8 participants who may experience sub- or supra-therapeutic effects of SSRIs based on their pharmacogenomic results, 2 participants, especially, are at increased risk of serious adverse effect of citalopram-induced prolonged QT interval.
- Pharmacogenomics can improve patients' health and reduce or prevent these kinds of adverse drug effects by predicting the drug-gene interactions.[4]

Limitations

- TAPH is still enrolling participants. However, we were still able to observe high prevalence of CYP2D6 and CYP2C19 variant alleles and identify potential drug-gene interactions in this study. After reaching our enrollment goal of 250 African Americans older adults (age ≥ 60) into the TAPH study, we will perform statistical analyses of their genotypes of CYP2D6 and CYP2C19 polymorphisms.
- Participants' SSRI dosing, measures of depressive and anxiety disorders, and self-reported drug side-effects will be collected to compare with the CPIC guidelines and further identify inappropriate use of SSRIs in these older adults.

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