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PhD Dissertation Defense

Entitled

PHARMACOGENOMICS IN THE EMIRATI POPULATION: APPLICATIONS IN CARDIOVASCULAR DISEASES AND ONCOLOGY

by

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Date & Venue

3:00 PM

Wednesday, 11 November 2020

Venue: Online on MS Teams

https://teams.microsoft.com/l/meetup-join/19%3ameeting_MWEyZDY5MDgtYWFkNi00NWE1LThkZmYtZDVjYTMyMWYyMThh%40thread.v2/0?context=%7b%22Tid%22%3a%2297a92b04-4c87-4341-9b08-d8051ef8dce2%22%2c%22Oid%22%3a%225950c224-2cb6-4b34-8000-228506f96458%22%7d

Abstract

Pharmacogenetic variations contribute to interindividual differences in drug response. Advances in molecular techniques provided insights into interpopulation pharmacogenomic variations. A new population pharmacogenomics field has emerged, exploring the population-specific variants to be exploited in precision medicine.

A few studies covering a limited number of pharmacogenes were conducted in the UAE. There is a need to assess the spectrum of variation in important pharmacogenes and examine the importance of pharmacogenomic implementation.

In the current study, variants, haplotypes, star alleles, and diplotypes in 100 important pharmacogenes were defined in 100 healthy Emiratis. Out of 1234 detected variants, 63% were rare, 30% were novel, and 141 variants were novel and damaging, as predicted by in silico tools. Filtering the detected variants on their clinical annotations resulted in 99 clinically actionable variants, from which 20 variants and 24 diplotypes had highly evident clinical annotations. Revising the results against the clinical pharmacogenetics implementation consortium (CPIC) guidelines demonstrated that 93% of participants were carrying at least one actionable variant that would lead to a dosing recommendation. Most of these recommendations were related to cardiovascular drugs.

The effect of *VKORC1* variants on warfarin dose was explored in a group of 90 patients. A model built from two *VKORC1* variants; rs9923231and rs61742245, with age, was a strong predictor of warfarin dose. A haplotype composed of the population-specific variants performed better than the common star-alleles haplotypes.

High incidence rates of adverse chemotherapy effects were reported from 66 pediatric acute lymphoblastic leukemia patients. The variability in oral chemotherapy doses were demonstrated and compared to other populations. Adverse effects-related hospitalizations and febrile neutropenia events exemplified the burden of chemotherapy adjustments. Although few cases had pharmacogenetic testing of *TPMT* and *NUDT15*, this approach's benefits were noticeable.

Finally, exploring the adverse drug effects and pharmacogenomic implementation in a group of 77 breast cancer patients was faced by deficiencies in adverse effects reporting and the absence of pharmacogenomic testing.

This research highlighted significant candidate pharmacogenes, population-specific variants, gene-drug associations, unexplored adverse drug effects, and possible pharmacogenomics implications in the UAE population. Various future research opportunities were underscored and made available for the scientific community.

Keywords: Pharmacogenomics, United Arab Emirates population, Cardiovascular diseases, Warfarin, Cancer pharmacogenomics, Drug adverse effects.