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Genetics of Pharmacokinetic Drug-Drug Interactions of Most Commonly Used Drug Combinations in the UK: Uncovering Unrecognised Associations

Authors : Mustafa Malki, Ewan R. Pearson

Abstract : Tools utilized by health care practitioners to flag potential adverse drug reactions secondary to drug-drug interactions ignore individual genetic variation, which has the potential to markedly alter the severity of these interactions. To our best knowledge, there have been limited published studies on the impact of genetic variation on drug-drug interactions. Therefore, our aim in this project is the discovery of previously unrecognized, clinically important drug-drug-gene interactions (DDGIs) within the list of most commonly used drug combinations in the UK. The UKBB database was utilized to identify the top most frequently prescribed drug combinations in the UK with at least one route of interaction (over than 200 combinations were identified). We have recognised 37 common and unique interacting genes considering all of our drug combinations. Out of around 600 potential genetic variants found in these 37 genes, 100 variants have met the selection criteria (common variant with minor allele frequency ≥ 5%, independence, and has passed HWE test). The association between these variants and the use of each of our top drug combinations has been tested with a case-control analysis under the log-additive model. As the data is cross-sectional, drug intolerance has been identified from the genotype distribution as presented by the lower percentage of patients carrying the risky allele and on the drug combination compared to those free of these risk factors and vice versa with drug tolerance. In GoDARTs database, the same list of common drug combinations identified by the UKBB was utilized here with the same list of candidate genetic variants but with the addition of 14 new SNPs so that we have a total of 114 variants which have met the selection criteria in GoDARTs. From the list of the top 200 drug combinations, we have selected 28 combinations where the two drugs in each combination are known to be used chronically. For each of our 28 combinations, three drug response phenotypes have been identified (drug stop/switch, dose decrease, or dose increase of any of the two drugs during their interaction). The association between each of the three phenotypes belonging to each of our 28 drug combinations has been tested against our 114 candidate genetic variants. The results show replication of four findings between both databases : (1) Omeprazole +Amitriptyline +rs2246709 (A > G) variant in CYP3A4 gene (p-values and ORs with the UKBB and GoDARTs respectively = 0.048,0.037,0.92,and 0.52 (dose increase phenotype)) (2) Simvastatin + Ranitidine + rs9332197 (T > C) variant in CYP2C9 gene (0.024,0.032,0.81, and 5.75 (drug stop/switch phenotype)) (3) Atorvastatin + Doxazosin + rs9282564 (T > C) variant in ABCB1 gene (0.0015,0.0095,1.58,and 3.14 (drug stop/switch phenotype)) (4) Simvastatin + Nifedipine + rs2257401 (C > G) variant in CYP3A7 gene (0.025,0.019,0.77,and 0.30 (drug stop/switch phenotype)). In addition, some other non-replicated, but interesting, significant findings were detected. Our work also provides a great source of information for researchers interested in DD, DG, or DDG interactions studies as it has highlighted the top common drug combinations in the UK with recognizing 114 significant genetic variants related to drugs' pharmacokinetic.

Keywords : adverse drug reactions, common drug combinations, drug-drug-gene interactions, pharmacogenomics
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