Publication

ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir

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An ADME (absorption, distribution, metabolism and excretion)-pharmacogenetics association study may identify functional variants relevant to the pharmacokinetics of lopinavir co-formulated with ritonavir (LPV/r), a first-line anti-HIV agent.; An extensive search of literature and web resources helped select ADME genes and single nucleotide polymorphisms (SNPs, functional and HapMap tagging SNPs) with a proven or potentially relevant role in LPV/r pharmacokinetics. The study followed a two-stage design. Stage 1 (discovery) considered a Caucasian population (n=638) receiving LPV/r, where we selected 117 individuals with low LPV clearance (cases) and 90 individuals with high clearance (controls). Genotyping was performed by a 1536-SNP customized GoldenGate Illumina BeadArray. Stage 2 (confirmation) represented a replication study of candidate SNPs from the stage 1 in 148 individuals receiving LPV/r. The analysis led to formal population pharmacokinetic-pharmacogenetic modeling of demographic, environmental and candidate SNP effects.; One thousand three hundred and eighty SNPs were successfully genotyped. Nine SNPs prioritized by the stage 1 analysis were brought to replication. Stage 2 confirmed the contribution of two functional SNPs in SLCO1B1, one functional SNP in ABCC2 and a tag SNP of the CYP3A locus in addition to body weight effect and ritonavir coadministration. According to the population pharmacokinetic-pharmacogenetic model, genetic variants explained 5% of LPV variability. Individuals homozygous rs11045819 (SLCO1B1*4) had a clearance of 12.6 l/h, compared with 5.4 l/h in the reference group, and 3.9 l/h in individuals with two or more variant alleles of rs4149056 (SLCO1B1*5), rs717620 (ABCC2) or rs6945984 (CYP3A). A subanalysis confirmed that although a significant part of the variance in LPV clearance was attributed to fluctuation in ritonavir levels, genetic variants had an additional effect on LPV clearance.; The two-stage strategy successfully identified genetic variants affecting LPV/r pharmacokinetics. Such a general approach of ADME pharmacogenetics should be generalized to other drugs.

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