

IDENTIFICATION OF EXPRESSION QUANTITATIVE TRAIT LOCI (eQTLs) AND THEIR FUNCTIONAL IMPACT ON ADME GENES

ABSTRACT

Polymorphisms in absorption, distribution, metabolism and excretion (ADME) genes result in inter-individual variation in drug response, drug efficacy and adverse drug effects caused by drug toxicity. Expression quantitative trait loci (eQTLs) are genetic variants that are involved in gene expression regulation that may result in phenotype variation. In the context of this study, the phenotype being studied is variation in drug response. ADME gene-associated eQTLs can help predict the clinical outcome of treatment as they affect the expression of ADME genes that modulate drug metabolism and transport. eQTLs play an important role in pharmacogenomics as it is easier and less costly to determine an individual's genotype as a proxy for gene expression than to isolate RNA or protein to guide drug choice and dose best suited to an individual's genetic makeup. A robust bioinformatic pipeline was developed that identifies tissue-specific eQTLs (<https://github.com/phelelani/nf-eqtl>). We focussed on identifying eQTLs that affect ADME gene expression in the liver. The pipeline identified cis-eQTLs for six core ADME genes (*CYP2C19*, *CYP3A5*, *DPYD*, *SULT1A1*, *UGT1A1* and *UGT2B17*). Though the pipeline identified cis-eQTLs for 63 extended ADME genes, only *UGT1A6*, *UGT2B15*, *ABCC3*, *ABCC4*, *XDH* and *CES1* were involved in the metabolism of drugs commonly prescribed in South Africa (SA) for human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), tuberculosis, diabetes, hypertension, pain, and cardiovascular diseases. The cis-eQTLs identified in this study were found to be present at very different frequencies in African populations compared to other populations. This highlights the importance of doing more eQTL studies with data from individuals of African origin to understand differences pertaining to pharmacogenetics. eQTLs identified in this study are hypothesized to predict the level of protein produced and therefore potential clinical outcomes of drug treatment. If validated, treatment response predictions/algorithms can be enhanced by adding these eQTLs in combination with existing knowledge of genetic variations and other clinical factors. Developing pharmacogenetic tests that include eQTLs in addition to existing well-known genetic variants can be a novel strategy to optimise treatment and identify individuals who may be at risk for adverse drug events as well as those who are more likely to achieve a therapeutic response or require alternative treatment.