

Title: Gene Regulatory Region Variations Potentially Modulating the Drug Metabolism Response

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Abstract

Background: Adverse Drug Reaction (ADR) is amongst the most common causes of hospitalization in paediatric patients. The abundance of drug metabolism enzymes is one of the many key factors that affect drug metabolism, which may result in dose-dependent ADRs. We hypothesize that variations in the transcription factor binding sites (TFBS) located at the DNA regulatory regions can also impact individual drug metabolism responses by altering the abundance of detoxification enzymes.

Methods: We focus our research on 3 transcription factors (TF) that are well known for regulating drug metabolism enzymes transcriptions. The TFBS for each TF was predicted with motif finding software, using sequences from ChIP-Seq or ChIP-ChIP datasets. A list of drug metabolizing genes was compiled based on an existing list contributed by the CFRI pharmacological lab and key term search, using gene ontology terms and Medical Subject Headings. We matched the TFBS profile to the regulatory regions of all the genes proposed in the gene list. Among all the predicted TFBS, we looked for the ones with Single Nucleotide Polymorphisms (SNPs). We calculated the absolute scores for the reference sequence (data from UCSC) and the SNP sequences (data from dbSNP) to derive the differential scores.

Results and Future Directions: We have proposed a prioritized list of regulatory region variations that may be responsible for individual drug metabolism differences based on the differential scores. In future research, we hope to propose more accurate TFBS profiles for the TFs by searching for ChIP experimental sequences.