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Systems Pharmacology Approach for the Prediction of Adverse Drug Reactions

Abstract. In drug development ensuring patient safety is crucial, and new ways to predict adverse drug reactions are needed. An adverse drug reaction is a harmful and unintended reaction to a drug that may be considered as 'on-target' or 'off-target.' A systems pharmacology approach to collating information about proteins in a pathway beyond a known drug target, along with clinical information about adverse effects of drugs known to interact with different proteins in the same pathway, could potentially predict a new drug's adverse reactions. The article "Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010," describes novel therapeutics with significant safety findings identified after drugs were approved, including adalimumab, golimumab, sunitinib, and pregabalin. These drugs all act within the MAPK pathway, which has sub-pathways linked by the MEK1 gene. This gene was therefore selected as a proof-of-concept evaluation to test the systems pharmacology pathway approach. Using R, a statistical analysis programming language, and Metabase, an R interface to Metacore, a manually-curated database of molecular interactions, an algorithm was developed to find genes within a parameterized distance of MEK1 and drugs that target those genes. Additionally FAERS, the FDA's adverse event reporting system will provide adverse reactions of drugs of interest. Using visual-analytic descriptive techniques, the adverse effects mapped to the MAPK pathway by will be compared with the adverse effects of the four drugs named above to evaluate this systems pharmacology approach to help predict what adverse reactions may be related to a new drug.

Keywords: Adverse Event, R, Metabase, FAERS, Tableau, pharmacology