Identification of Liver Toxicity Biomarkers for Predicting Patient-Specific Hepatotoxic Drugs

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Drug-induced liver injury (DILI) is the primary adverse event that results in withdrawal of drugs from the market and a frequent reason for the failure of drug candidates in the pre-clinical or clinical phases of drug development. This paper presents an approach for identifying potential liver toxicity genomic biomarkers from a Liver Toxicity Biomarker Study (LTBS). In the LTBS, a pair of compounds, entacapone ("non-liver toxic drug") and tolcapone ("liver toxic drug"), was studied in rats in order to investigate differences in biochemical responses elicited by the two compounds. Molecular analysis of the rat liver and plasma samples, combined with statistical analyses, revealed many similarities and differences between the in vivo biochemical effects of the two drugs. The genomic markers were classified into four ideal categories based on the statistical testing and biological considerations: Tolcapone-Specific (T), Entacapone-Specific (E), Common-Behavior (C), and Divergent Behavior (D). The stringent criteria for inclusion in these ideal categories were loosened to create four expanded categories of markers, t, e, c, and d, respectively. Six hundred and ninety-five (695) genes were identified, of which 238 genes were ideal markers, T, E, C, or D. A Self-Organizing Map (SOM) clustering, with a 5 x 5 grid structure, was applied to the 695 genes. Among the 238 genes, 138 were classified consistently into T, E, C, or D. Sixty-one pathways were identified from the 695 categorized genes, which 5 were associated with a "tolcapone-specific pathway". Two animals in the tolcapone high dose group were found to have high ALT, AST, or TBIL levels. Six tolcapone-specific genes were identified for one animal and three tolcapone-specific genes were identified for another animal. The Vars2 (valyl-tRNA synthetase 2) gene was in common in both animals; this gene is in one of the top 3 most significant tolcapone-specific pathways, the aminoacyl-tRNA biosynthesis pathway. The Vars2 gene may be a potential biomarker of DILI.