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Using the ToxMiner™ Database for Identifying Disease-Gene Associations in the ToxCast™ Dataset

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The US EPA ToxCast™ program is using *in vitro*, high-throughput screening (HTS) to profile and model the bioactivity of environmental chemicals. The main goal of the ToxCast program is to generate predictive signatures of toxicity that ultimately provide rapid and cost-effective methods to prioritize chemicals for targeted *in vivo* testing, thus improving efficiency of the use of animals in those bioassays. The chemicals selected for Phase I are composed largely of a diverse set of pesticide active ingredients, which had sufficient supporting *in vivo* data included as part of their registration process with the EPA. These were supplemented with a number of non-pesticide, high-production volume chemicals of environmental concern. Application of HTS to environmental toxicants is a novel approach to predictive toxicology, and differs from what is required for drug efficacy screening in several ways. Biochemical interaction of environmental chemicals are generally weaker than that seen with drugs and their intended targets. Additionally, the chemical diversity space covered by environmental chemicals is much broader compared to that of pharmaceuticals.

The ToxMiner™ database was created in order to link biological, metabolic, and cellular pathway data to genes and *in vitro* assay data for the chemicals screened in the ToxCast Phase I HTS assays. Also included in ToxMiner was human disease information, which correlated with ToxCast assays that target specific genetic loci. We have implemented initial pathway inference and network analyses, which allow linkage of the types of adverse health outcomes with exposure to chemicals screened in Phase I. This approach permits exploration of disease at a higher level of cellular and organismal organization, focusing on multiple, related disorders, and may aid in the understanding of common disease outcomes (*e.g.* cancer or immune disorders) that are characterized by locus heterogeneity. Through the use of the ToxMiner database and the analysis framework presented here, we hope to gain insight in to relationships between potential disease states in humans and environmental chemicals, as well as contribute to the larger goals of toxicogenomics by clarifying the role of gene-environment interactions in pathobiology.