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Quantitative high-throughput screening for chemical toxicity in a population-based in vitro model

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Abstract: A shift in toxicity testing from in vivo to in vitro may efficiently prioritize compounds , reveal new mechanisms, and enable predictive modeling. Quantitative high-throughput screening (qHTS) is a major source of data for computational toxicology, and our goal in this study was to aid in the development of predictive in vitro models of chemical-induced toxicity, anchored on interindividual genetic variability. Eighty-one human lymphoblast cell lines from 27 Centre d'Etude du Polymorphisme Humain trios were exposed to 240 chemical substances (12 concentrations, 0.26nM-46.0?M) and evaluated for cytotoxicity and apoptosis. qHTS screening in the genetically defined population produced robust and reproducible results, which allowed for cross-compound, cross-assay, and cross-individual comparisons. Some compounds were cytotoxic to all cell types at similar concentrations, whereas others exhibited interindividual differences in cytotoxicity . Specifically, the qHTS in a population-based human in vitro model system has several unique aspects that are of utility for toxicity testing, chemical prioritization, and high-throughput risk assessment. First, standardized and high-quality concentration-response profiling, with reproducibility confirmed by comparison with previous experiments, enables prioritization of chemicals for variability in interindividual range in cytotoxicity. Second, genome-wide association analysis of cytotoxicity phenotypes allows exploration of the potential genetic determinants of interindividual variability in toxicity. Furthermore, highly significant associations identified through the analysis of population-level correlations between basal gene expression variability and chemical-induced toxicity suggest plausible mode of action hypotheses for follow-up analyses. We conclude that as the improved resolution of genetic profiling can now be matched with high-quality in vitro screening data, the evaluation of the toxicity pathways and the effects of genet