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Population-based in vitro hazard and concentration-response assessment of chemicals: the 1000 genomes high-throughput screening study

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Abstract: BACKGROUND: Understanding of human variation in toxicity to environmental chemicals remains limited, so human health risk assessments still largely rely on a generic 10-fold factor (10? each for toxicokinetics and toxicodynamics) to account for sensitive individuals or subpopulations. OBJECTIVES: We tested a hypothesis that population-wide in vitro cytotoxicity screening can rapidly inform both the magnitude of and molecular causes for interindividual toxicodynamic variability. METHODS: We used 1,086 lymphoblastoid cell lines from the 1000 Genomes Project, representing nine populations from five continents, to assess variation in cytotoxic response to 179 chemicals. Analysis included assessments of population variation and heritability, and genome-wide association mapping, with attention to phenotypic relevance to human exposures. RESULTS: For about half the tested compounds, cytotoxic response in the 1% most "sensitive" individual occurred at concentrations within a factor of 10? (i.e., approximately 3) of that in the median individual; however, for some compounds, this factor was > 10. Genetic mapping suggested important roles for variation in membrane and transmembrane genes, with a number of chemicals showing association with SNP rs13120371 in the solute carrier SLC7A11, previously implicated in chemoresistance. CONCLUSIONS: This experimental approach fills critical gaps unaddressed by recent large-scale toxicity testing programs, providing quantitative, experimentally based estimates of human toxicodynamic variability, and also testable hypotheses about mechanisms contributing to interindividual variation.