GWAS and Benzene Induced Hematotoxicity in the Mouse John E. French, Ph.D., Host Susceptibility Group, Biomolecular Screening Branch, DNTP, NIEHS, RTP, NC 27709

Individual response to exposure-related disease may be based upon differences in exposure and/or genetic-epigenetic variations. For example, many, but not all, smokers develop chronic lung disease, including cancer. Acute exposures to benzene, a component of tobacco smoke and a ubiquitous environmental carcinogen, may result in hematotoxicity and genotoxicity, while chronic exposure may result in cancer of the lymphohematopoietic systems of humans and rodents. To link environmental exposure to benzene and susceptibility or resistance to toxicity we performed a genome-wide association study (GWAS) using a new population based mouse resource – the Diversity Outbred mice created from the Collaborative Cross (CC), a population of advanced intercross recombinant inbred lines (AIRILs)[1-4]. Selected generations of breeders from the CC AIRILS were used to create the diversity outbred (DO) mice using a randomized breeding protocol[5]. Each DO mouse is genetically different from every other DO mouse from generation to generation and represent a significant degree of genetic diversity in the mouse genome that is equal or greater than that of human populations[6,7]. To test for genome-wide association in DO mice based upon individual responses to benzene-induced toxicity, we exposed the mice to 0 (air control), 1, 10, or 100 ppm benzene by inhalation in 2 independent experiments. The results of this mouse GWAS describe a link between environmental exposure and susceptibility-resistance to benzene induced hematotoxicity and genotoxicity through quantitative-trait analysis in a new experimental population-based mouse model. The CC AIRILs, from which the DO have been created, are a critical tool for validating candidate genes identified in the QTLs using molecular biology and reverse genetics approaches[5,8-13]. Also, determination of a variable range of response and the genetic basis can aid in improving the extrapolation of results from rodent models to human hazard identification and risk assessment[14]. These observations will be placed into context of the new NIEHS Strategic Plan 2012-2017 – Goals 1 and 2.

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