Diversity Outbred mice better predict potential human responses to chemical exposures

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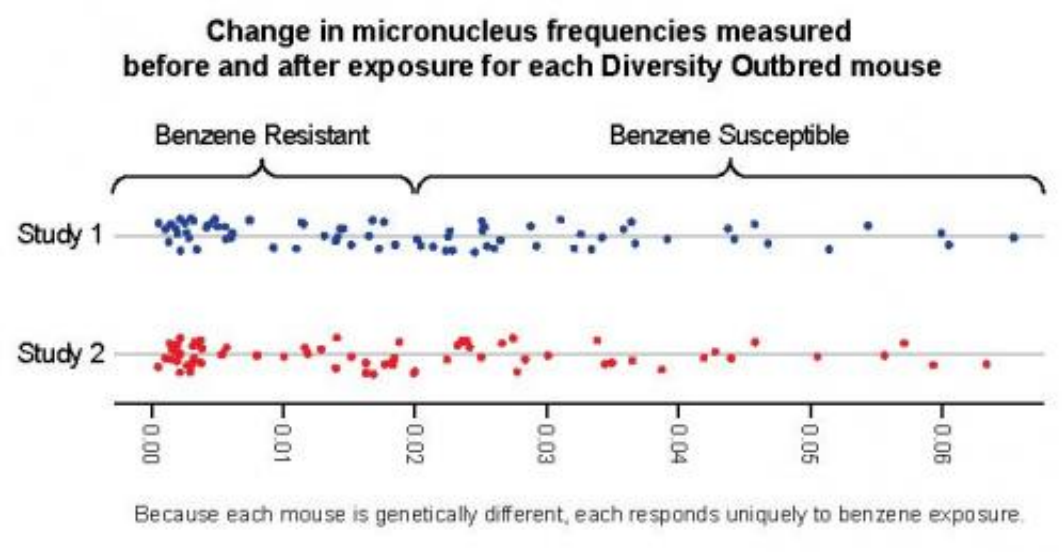

This graph shows the change in micronucleus frequencies measured before and after exposure for each Diversity Outbred mouse. Credit: NIEHS

A genetically diverse mouse model is able to predict the range of response to chemical exposures that might be observed in human populations, researchers from the National Institutes of Health have found. Like humans, each Diversity Outbred mouse is genetically unique, and the extent of genetic variability among these mice is similar to the genetic variation seen among humans.

Using these mice, researchers from the National Toxicology Program (NTP), an interagency program headquartered at the National Institute of Environmental Health Sciences (NIEHS), were able to identify specific genes or chromosomal regions that make some mice more susceptible, and others more resistant, to the toxic effects of benzene. Benzene is a common air pollutant and human carcinogen found in crude oil, gasoline, and cigarette smoke, and naturally produced by wildfires and volcanoes.

The scientists found that, like humans, each Diversity Outbred mouse developed at The Jackson Laboratory, Bar Harbor, Maine, responded to the effects of the chemical exposure differently. Exposure responses were assessed by measuring the frequency of micronucleated red blood cells, a biological marker of chromosomal damage, which is a hallmark of benzene exposure. The researchers measured the levels of this biomarker in each mouse before and after exposure.

Some mice demonstrated extraordinary sensitivity to the exposure, while others showed no response. The range of response from lowest to highest was approximately 5-fold. Since the researchers knew the genetic makeup of each mouse, they could pinpoint the regions involved in susceptibility or resistance to the chemical exposure, and then look for related genetic regions in human chromosomes.

"This paper points out the significant genetic differences that are found throughout every population that must to be taken into account when extrapolating data from animals to humans," said Linda Birnbaum, Ph.D., director of NTP and NIEHS. "The Diversity Outbred mouse is a useful model for predicting the range of response that might be observed in humans following exposure to a chemical."

Benzene was selected by NTP as a case study for testing the mouse model, because there is an abundance of animal and human toxicity data

for comparison. Benzene can affect people differently, depending on the level and duration of exposure, making it important to accurately estimate the levels at which it may cause harm to the most susceptible individuals.

"These genetically diverse mice provided a reproducible response to benzene exposure across two independently exposed groups, suggesting that each group of genetically unique mice demonstrated the same range of differential susceptibility, much like what you would find in human epidemiology studies," said Jef French, Ph.D., lead author on the paper. "It's important to be able to accurately measure the impact of exposure and to develop appropriate permissible safety levels for toxic compounds. This model can help us do that with greater accuracy."

These results may lead to further research to better understand genetically regulated responses to toxicity in humans, as well as mechanisms of susceptibility and resistance to environmental exposures as they relate to disease. "In addition to informing the design of human epidemiology studies evaluating associations between chemical exposures and biological effects in diverse populations, the Diversity Outbred mouse model may also provide valuable data for use by regulators and manufacturers conducting chemical risk assessments," said co-author Kristine Witt of NTP.

More information: French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA. 2014. Diversity Outbred mice identify population based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ Health Perspect*; DOI: 10.1289/ehp.1408202