Unique pattern of gene expression can indicate acetaminophen overdose

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In a new study, researchers found they could detect toxic levels of acetaminophen in laboratory animals by analyzing gene expression in the blood.

This study by the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health, could be a first step in developing accurate new tools to detect acetaminophen overdose in humans. Overdose of acetaminophen, the active ingredient in many over-the-counter pain relievers, is a leading cause of liver failure in the United States and is often difficult to diagnose. An estimated 50,000 people seek emergency room treatment for acetaminophen overdose each year.

The research published online this week in the *Proceedings of the National Academy of Sciences* shows that gene expression data from blood cells can provide valuable information about acetaminophen levels well before liver damage can be detected by other methods, including serum markers and liver biopsies.

“In time, this approach could give physicians a powerful new genomics tool to help patients who cannot estimate how much acetaminophen they consumed. Early detection of acetaminophen overdoes can be helpful in preventing or treating resulting liver damage,” said Richard S. Paules, Ph.D., principal investigator and director, Microarray Core Facility at NIEHS and senior author on the new paper.

The researchers would like to build on this body of research to develop a

simple procedure that clinicians could use in the emergency room to estimate the level of acetaminophen exposure and the potential damage to the liver. This would be especially beneficial for patients such as the elderly, suicidal, semi-comatose who are unable to provide an accurate estimate.

To carry out their study, the researchers developed and then analyzed gene expression signatures — patterns of gene activity —in rats exposed to various doses of acetaminophen. Using microarrays, or tools that allow scientists to see how differences in gene expression are linked to specific diseases, the researchers were able to determine which genes were turned on or turned off in response to the different levels of acetaminophen. Once they selected the gene sets, they tested them for accuracy, and found the signature gene lists were able to predict exposure to toxic versus nontoxic doses with very high accuracy (88.9-95.8 percent), while the more traditional predictors, of clinical chemistry, hematology and pathology were approximately 65 to 80 percent accurate.

“Although it was not the main focus of our study, we wanted to see how applicable this gene expression profiling of blood cells was to humans,” said Raymond W. Tennant, Ph.D., in the NIEHS Laboratory of Molecular Toxicology, and a co-author on the study.

The NIEHS researchers compared the animal data with data from RNA from blood drawn from individuals who had been admitted to the University of North Carolina emergency room for acetaminophen overdose intoxication. When they compared the toxic blood samples to the samples from normal healthy volunteers they saw a striking difference.

“Although there are already some good tools available to emergency room physicians to detect liver injury, additional information concerning

the level of exposures and/or the degree of liver injury could significantly help us in treating acetaminophen overdose patients," said Paul Watkins, M.D., Director, General Clinical Research Center at the University of North Carolina, Chapel Hill and co-author on the paper.

Source: National Institute of Environmental Health Sciences