New approach promises greater success for predicting drug safety

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Adverse reactions to drugs represent one of the leading causes of death in the United States. But there may be a way to predict who is most likely to suffer a toxic side effect to a drug before they have even taken it.

A study published online in the journal *Genome Research* describes a new, more effective and less costly method for testing drugs for potential toxicity and one that could also result in more people benefiting from existing drugs, said senior author David Threadgill, Ph.D., professor of genetics in the University of North Carolina at Chapel Hill School of Medicine. He also heads the genetics department at North Carolina State University.

Drug safety has become the major bottleneck in getting new drugs to patients, said Paul Watkins, M.D., distinguished professor of medicine at UNC and study co-author. Over the last several years, the pharmaceutical industry has made progress in developing drugs that are likely to work, but sometimes potentially deadly effects still do not emerge until they are on the market. In the case of Vioxx, millions of people had already used the pain-killer and arthritis medication before researchers found it could increase the risk of having a heart attack or stroke.

"The reality is that there is no safe drug," Watkins said. "Good drugs are bad for some people. Because different people respond differently to drugs, where you draw the line is not exactly black and white."

But Watkins also argues that while drugs currently on the market are not entirely safe, they are harmless in 99.9 percent of people . Therefore, if it were possible to identify in advance the one person in 1000 that will react poorly, scientists could make drugs that are safe for everybody.

With that purpose in mind, Threadgill, Watkins and a team of researchers created a new testing method that exploit the genetic similarities between mice and humans. The researchers took a group of mice that were genetically distinct from each other and looked to see if variations in their genetic makeup could predict their response to treatment with acetaminophen (the chemical component of Tylenol and which is extensively used in liver toxicity studies). The mice were bred at the Jackson Laboratory in Bar Harbor, Maine.

After identifying many genes that were associated with side effects to acetaminophen in their mouse models, Threadgill and his colleagues then went back to humans to see which of these gene variants were also associated with response to the drug.

The researchers found that a subset of people taking the maximum daily recommended dose of the drug exhibited an elevation in specific enzymes that can indicate damage to the liver, Threadgill said. Variations in one gene in particular - called CD44 - were responsible for almost half of the differences in toxic side effects experienced from one person to another.

"One of the fascinating things that came out of this study was that the genetic variation in acetaminophen toxicity is not what all of the toxicologists would have predicted in the first place," said study co-author Ken Paigen, Ph.D., Jackson Laboratory executive research fellow. "CD44 doesn't have anything to do with the rate of metabolism of the drug, but it does have something to do with the immune response."

In effect, the study has created a system that enables researchers to gather interesting clues about what makes some people susceptible to drug toxicity and then explore them in mouse models. But the team believes perhaps the greatest impact this research could have is to improve the drug development process - to begin to understand what properties of a drug can make it toxic, and to identify the people most vulnerable to those toxicities.

"Just look at the drug industry's own numbers on how much it costs to develop a drug," said Threadgill. "To get a drug to the market takes close to $1 billion, whereas a study like this can be done for $100,000. This approach could be used to determine early on if the drug is not going to be viable because of a high level of toxicity, or it could give important insights into whether the drug is likely to be beneficial."

Source: University of North Carolina School of Medicine (news : web)