MedicalXpress

Tiny mutation might help indicate proper dosage for half of all drugs

May 10 2010

A tiny gene mutation in human liver cells could one day influence how high or low a dose patients need of about half of the clinically used drugs on the market, new research suggests.

Scientists at Ohio State University and their colleagues have identified this mutation, and have shown that it alters the level of a protein in the liver responsible for processing between 45 percent and 60 percent of medications used to treat a wide range of conditions.

Each gene contains two alternative forms - called alleles - that are identical in most people. However, in this case, the researchers found that the activity level, or expression, of one allele differs from its partner allele in a single gene. That small difference is called a single nucleotide polymorphism, or SNP (pronounced snip).

This SNP affects the gene's protein-producing process, in turn lowering the level of an enzyme known as CYP3A4.

The faster a drug is processed, or metabolized, by this enzyme in the liver, the more quickly it is eliminated from that tissue and the body as a whole. When this enzyme level is lowered by the presence of this SNP, people are likely to require smaller doses of medicines that the enzyme metabolizes. But this also means that higher doses of these same drugs can be dangerous to people with the mutation if those levels become toxic.

The study further showed that people with the mutation who take a certain class of cholesterol-lowering drugs do indeed require lower doses of these medications to achieve the same effect that higher doses produce in people without the SNP.

The researchers suggest that this mutation could serve as a molecular biomarker to aid doctors in clinical practice, affecting dosing requirements, patients' response to medications and toxicity levels of numerous drugs, especially anti-cancer medications.

"With some cancer drugs, there is a very narrow therapeutic index, meaning that if doctors give patients a slightly higher dose, it will cause toxicity. We believe this same biomarker could be used to predict that toxicity threshold in cancer patients," said Danxin Wang, a research scientist and adjunct assistant professor of pharmacology at Ohio State and lead author of the study.

The research appears online in *The Pharmacogenomics Journal*.

Previous research already had determined that the levels of the CYP3A4 enzyme in humans could vary widely and that those varying levels influence people's drug response and toxicity. But studies to date on why that is have been inconclusive.

Wang and colleagues obtained human liver samples from the Cooperative Human Tissue Network Midwestern Division. The scientists sought to identify mutations in the gene that makes the target enzyme in the liver.

Wang noted that most sequence variations are meaningless because they don't alter the activity of the encoded protein. Mutations can affect the proteins' function directly by altering the protein sequence, or they can work by changing the messenger RNA (mRNA), the intermediate step in

producing the protein. The latter is the case for the SNP discovered by Wang and colleagues.

The researchers used a technique that measures for what is known as allelic mRNA expression imbalance, which was developed in the Pharmacogenomics Core Lab, Program in Pharmacogenomics directed by Wolfgang Sadee, a co-author of this paper and a professor and chair of pharmacology at Ohio State.

The functional SNP that the scientists found was located on what is known as intron 6, a reference to a specific location within the gene that is typically overlooked when searching for a functionally relevant mutation. Further tests showed that the presence of this mutation in liver samples was associated with lower levels of the target enzyme.

The scientists then sought to test their findings in a clinical setting.

Among the drugs metabolized by the CYP3A4 enzyme are three specific types of statins, or cholesterol-lowering drugs. Wang collaborated with cardiologist and co-author Glen Cooke, formerly of Ohio State's Medical Center, to test for the presence of this intron 6 mutation as a biomarker in patients taking statins to control their cholesterol.

Of 273 patients in the group, 235 were taking one of the three statins metabolized by the target enzyme: atorvastatin (brand name Lipitor), lovastatin (brand name Mevacor) and simvastatin (brand name Zocor). The patients taking these three relevant statins were consuming doses ranging from 5 milligrams to 80 milligrams per day.

Patients were assessed for the presence of the intron 6 SNP as well as a number of other mutations related to liver enzymes.

Among those taking the three relevant statins, 22 were carriers of the

intron 6 mutation. The doses that these patients took were significantly lower than the doses taken by patients without the mutations. Cholesterol levels among all the patients were similar.

To further test the relationship, the researchers divided the doses into three levels - below 10 milligrams, 20 milligrams and more than 40 milligrams - and adjusted for the difference in potency among the drugs. They then determined that carriers of the intron 6 mutation were less likely to be taking a higher statin dose based on lower levels of the CYP3A4 enzyme present in their livers.

The findings applied only to Caucasians because the number of African-American patients in the study was too small to have statistical merit, Wang said. The presence of the mutation in the white patients represented the expected frequency of this mutation in the overall population: about 10 percent.

Wang noted that using this SNP as a biomarker could reduce the guesswork associated with prescribing drugs.

"Right now, because there are no biomarkers available to predict CYP3A4 activity, trial and error determines whether cholesterol goes down with the prescribed dose," Wang said. "You never know who has what enzyme level, so you never really know what dose to give an individual if you don't have a biomarker."

The biomarker also could be applied to early clinical trials of new drugs, Wang said, by identifying research participants ahead of time who will not respond well to new formulations.

Using a genetic biomarker to determine patient response to drugs is simplified by the fact that once a biomarker is found in a blood sample, it is good for a lifetime of information. The same can't be said for tests

for liver enzymes or levels of drugs in the blood, which change all the time, Wang noted.

Though a test for this biomarker is not yet available, and similar tests currently cost several hundred dollars, Wang predicted that in the future, technology advances will make the test easy to conduct in clinical settings and affordable for patients.

Provided by The Ohio State University