New genetic discovery could reduce the guesswork in drug dosing

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The discovery of genetic differences affecting up to a third of the population could take the guesswork out of prescribing the correct dose of 25 percent of drugs currently on the market, researchers say.

The scientists found two genetic variants that alter the activity level of an enzyme responsible for processing, or metabolizing, drugs ranging from the painkiller codeine to the breast cancer drug tamoxifen.

The Ohio State University researchers who found these differences say that pending additional research, the variants are good candidates for inclusion in an existing biomarker test that guides drug dosing.

The current test is designed to determine the enzyme's activity level, or expression, to predict whether a patient will fall into one of four categories: poor, intermediate, extensive or ultra-rapid metabolizer. Metabolism speed affects how much medicine a patient needs.

But there are limits to the existing test: The current biomarker panel is based on variants that have been associated with how patients respond to different doses of drugs.

The researchers who found these previously unidentified variants, however, have determined the specific effects that the variants have on drug metabolism. One reduces the enzyme's activity twofold by turning off a function of its gene, and the other is located in an enhancer region of the gene, meaning it increases the enzyme's expression between two-

and fourfold.

"If you don't consider these two variants, the current biomarker panel can cause incorrect dosing," said senior author Wolfgang Sadee, professor and chair of pharmacology and director of the Center for Pharmacogenomics at Ohio State. "The better the test, the more value it has. Adding these variants to the panel would make the test more predictive and robust with respect to application in the clinic."

Ohio State has applied for a patent on the addition of these variants to a clinical biomarker test.

The research is published online in the journal *Human Molecular Genetics*.

The study included a clinical trial of 164 children, about one-third of whom were African American. The results show that these two variants are common in both Caucasians and African Americans, and confirmed that the variants influence how patients metabolize the cough suppressant dextromethorphan.

Being able to apply this testing to more than one ethnic group is significant, Sadee said, because most current dosing decisions are made based on genetic findings in only whites.

The findings suggested that about one-third of people would be expected to have lower enzyme activity, and therefore slower, or intermediate, drug metabolism – not so low that they are poor metabolizers. Another 6 percent would have higher enzyme activity and be categorized as ultra-rapid metabolizers. Only by testing for these variants would clinicians know for sure.

The variants were found by lead author Danxin Wang, a research

scientist and adjunct associate professor in pharmacology at Ohio State. They are called single-nucleotide polymorphisms, or SNPs (pronounced "snips").

Each gene contains two alternative forms – called alleles – that are functionally identical in most people. However, in some cases, the activity level, or expression, of an allele can differ from its partner allele in a single gene. That difference – the genetic variant, or SNP – affects the function of the protein or enzyme produced by that gene.

Wang used liver tissue samples from Caucasians to conduct the analyses that identified where these two functional variants are located on the CYP2D6 gene. The clinical trial testing these variants' effects against dextromethorphan is just the beginning – the researchers hope to expand these trials with multiple drugs and eventually enter clinical biomarker tests.

"The current panel can determine whether an individual is a poor or ultra-rapid metabolizer. The SNPs we found will more precisely predict whether an individual is in the ultra-rapid or intermediate metabolic range," Wang said. "The poor metabolizers are well-defined by the current panel with variants with no enzyme activity at all."

A poor metabolizer is likely to experience high toxicity from medications processed by this enzyme, or get minimal or no benefit at all if a drug such as codeine needs to be activated by it. Ultra-rapid metabolizers, on the other hand, may not benefit from drugs processed by the enzyme or suffer adverse reactions from drugs that need it for activation. Metabolizer status has pronounced effects on treatment outcomes and cost of therapy.

"If you could give a drug and get an immediate response, then that in itself would be a marker for the drug's effect. But there is no immediate

response for many drugs," Sadee said. "Having a pharmacogenomics marker test that's viable and useful could predict when caution is needed in prescribing drugs."

In the case of antidepressants or antipsychotics, for example, with delayed clinical effect, an ultra-rapid metabolizer would have to take the drug for weeks before finding out that a drug isn't having any effect, while a poor metabolizer is likely to have toxic side effects. And with codeine, which is converted into morphine in the body, an ultra-rapid metabolizer could inadvertently overdose on morphine by taking too much codeine.

The Ohio State pharmacogenomics group is among the few in the world pursuing hard-to-find genetic variants that significantly alter biological functions. For the past 30 years, scientists studying genetic variants have focused on genetic variants that change enzyme function by altering the encoded amino acid sequence.

Sadee's lab, however, focuses on variants that are harder to detect and analyze because they have no direct role in determining the protein sequence; they exist in deeper and often overlooked regions of genes. Sadee has designed a technique to determine variant functions based on measurements of how much messenger RNA (mRNA), a carrier of genetic information, each specific allele expresses – an activity that occurs before amino acids are assembled.

"We're finding now that in 90 percent of cases, it would appear that the SNP working at the protein level is not the one that affects function – instead it's the SNP that affects mRNA expression," Sadee said. "It turns out SNPs in the middle of nowhere – in regions formerly called junk DNA – are actually in the middle of something."