The genetics of drug tolerance

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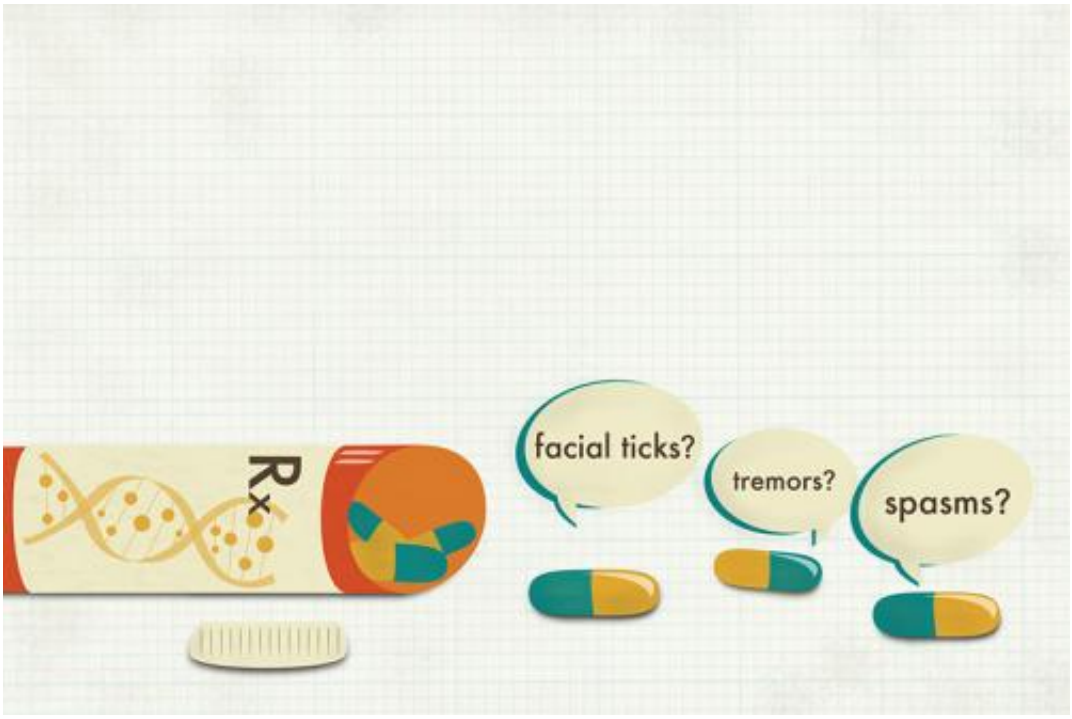

(Medical Xpress)—Put yourself in the shoes of a psychiatrist. You just diagnosed a person with schizophrenia, and you can prescribe any number of antipsychotic drugs, all of which can cause serious side effects. You know that older drugs, such as haloperidol, work well, but a third of all schizophrenia patients who take it suffer from Parkinsonian-like symptoms, such as tremors, involuntary spasms, and uncontrollable facial movements. You also know that those side effects are permanent in about half the people who experience them. In other words, you could

be prescribed a drug that causes permanent brain damage.

So you consider prescribing a newer drug, such as clozapine, which also helps a large portion of patients. But clozapine causes severe weight gain and diabetes in many people. You check your patient's history. He smokes, as do 90 percent of people diagnosed with schizophrenia. He weighs a lot for his height. Taking clozapine will substantially increase his risk of heart disease, and the drug costs much more than haloperidol. Your patient can't afford it.

Choosing the right drug is difficult, but you have to choose one. Letting the patient go without medication is not an option; untreated schizophrenia is much worse than even the most serious side effects.

What do you do?

You know what you'd like to do: run a blood test to figure out your patient's genetic susceptibility to the permanent side effects of haloperidol. But that genetic screen doesn't exist. In fact, the genetic underpinnings of drug side effects, in general, are not well understood.

Researchers at the UNC School of Medicine are trying to change that.

Two labs headed by statistical geneticist William Valdar, PhD, and psychiatric geneticist Patrick Sullivan, MD, have developed a new statistical model that scientists can use to parse the complex genetics of side effect susceptibility.

In a paper featured in the journal *Genetics*, their teams describe how they've begun to strip away the mystery behind haloperidol. Their findings represent the first quantitative description of the genetic architecture of haloperidol response.

Genetic smoke screen

There are few examples of doctors screening patients to make sure they're not susceptible to the worst side effects of a drug. The blood-thinner warfarin is the best example. Two genes dictate how people respond to it.

"Those genes provide so much information for doctors that screening for them is now done in hospitals," says Jim Crowley, PhD, a research assistant professor in Sullivan's lab and first author of the Genetics paper. "That's the goal for haloperidol – to be able to screen for genes. Unfortunately, it will be more like hundreds, if not thousands of genes that play roles in different side effects. That's one of our findings—the effects of haloperidol are extremely complicated."

Crowley and Valdar, an assistant professor in the department of genetics, aren't yet able to pinpoint which specific genes play roles. That's still difficult for schizophrenia itself, let alone side effects of schizophrenia drugs. Instead, Crowley and Valdar's team has created a statistical model that will allow them and other researchers to conduct the best kinds of genetics experiments that are needed to find those genes.

For instance, using eight inbred mouse lines and their new statistical model, Valdar and Crowley's teams found that mice reacted to haloperidol in specific ways because they inherited certain genes from their mother or father. This is called parent-of-origin effect. In other words, some mice experienced a particular side effect because of genes they got from their mother.

Crowley and Valdar's team also discovered that other side effects were due to the fact that some mouse breeds had genes that are genetically dominant. That is, when two kinds of mice were bred, the genes of one breed were expressed more in the offspring.

Such general findings won't translate to the clinics where people with schizophrenia seek treatment. Rather, the findings give researchers new clues about how to conduct experiments.

"If you told someone that it matters whether they inherited genes from their mother or father, then that would change the way you conducted an experiment," Valdar says, "because now you know what to look for."

The unfortunate complexity

Think of it like this: if you want to study the effect of a drug, then you could theoretically give the drug to a random person and a placebo to another random person. But the genes of those two people are very different. It would be tough to figure out the roles of genes in two different people.

But if you knew that the effect of a drug had a lot to do with whether you inherited specific genes from your mother or father, then you could design an experiment that would include parents.

Researchers can do this with inbred mouse models because the offspring are genetically identical to their parents. Researchers can find out if genes come from a specific parent or a specific breed of mouse.

"This sort of knowledge matters a lot," Valdar says. "In any kind of experimental design you have to make tradeoffs because you have a certain amount of money and subjects. You have to pick your battles. So any information that helps focus your experiment is very valuable."

This is the genius of the statistical methodology developed by Valdar and his postdoctoral fellow Alan Lenarcic, PhD. Their model can tease apart the genetics of a complex response to a drug.

In the case of haloperidol, they found that one side effect—such as muscle rigidity—involved one set of genes while another side effect – such as spasms – involved a different set of genes.

So, think of the complexity. One person takes a drug and has a set of side effects, all of which could involve different genes. A second person takes the same drug and has different side effects. And those side effects involve completely different genes.

Still, this finding will allow Valdar, Crowley, Sullivan, and other scientists to design experiments that home in on those sets of genes. Building on each subsequent experiment, researchers using Valdar and Lenarcic's methodology could eventually pinpoint which genetic variations play roles in the side effects of a given drug.

Down the road, such findings could help doctors who desperately want to help patients without rolling the dice on something as serious haloperidol-induced permanent brain damage.

"That's part of the promise of our statistical methodology," Valdar says. "We want to make that decision for doctors a lot easier."

More information: "Genetics of Adverse Reactions to Haloperidol in a Mouse Diallel: A Drug–Placebo Experiment and Bayesian Causal Analysis." James J. Crowley, Yunjung Kim, Alan B. Lenarcic, Corey R. Quackenbush, Cordelia J. Barrick, Daniel E. Adkins, Ginger S. Shaw, Darla R. Miller, Fernando Pardo-Manuel de Villena, Patrick F. Sullivan, and William Valdar. *Genetics* January 2014 196:321-347; Early online November 15, 2013, DOI: 10.1534/genetics.113.156901

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