New Genetic Targets Being Explored for Diabetes

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WASHINGTON — Technology has driven down the cost of genetic research, allowing for greater progress in finding gene targets associated with chronic diseases, including diabetes, according to Dr. Francis S. Collins, director of the National Human Genome Research Institute.

To search across the entire human genome for genes involved in a particular disease would have cost about $10 billion 5 years ago; thanks to the Human Genome Project, the same work now can be done for $500,000, said Dr. Collins at a diabetes meeting sponsored by Avalere Health.

Currently, there are more than a dozen genetic variants thought to predispose people to type 1 diabetes, "many of which were previously not suspected," said Dr. Collins.

Three genes—TCF7L2, KCNJ11, and PPAR gamma—have previously been identified as having variants associated with type 2 diabetes risk. Now, with advances in methods for detecting gene variants, the list has grown to 10, with "5 more in press from additional studies," he said.

Genetic information could be useful in predicting which patients will suffer from particular complications.

DR. COLLINS

One interesting new variant is SLC30A8, "which I never heard of or thought about until it popped out of [an] analysis," said Dr. Collins. SLC30A8 codes for a protein that is expressed only in β cells.

"What it does is serve as a zinc transporter; it apparently is the pump that moves the zinc into the granules where it complexes with insulin getting ready for secretion," he said. "Insulin is complexed with zinc in a crystal, and if you don't have the right amount of zinc, that's probably not going to help your ability to secrete insulin when you need to."

A variation like that might serve as a worthy target for therapeutic intervention, according to Dr. Collins.

"There is some interesting data in animal models [showing] that zinc itself may actually be effective in preventing diabetes," he said, adding that there is very little human data in this area. "We might discover that it could be useful for people who have this particular zinc transporter [variant] that causes it not to work as well as we'd like—maybe simply by zinc supplementation, we could accommodate that. We don't know that; that's speculation, but we're thinking about ways to test that hypothesis."

Discoveries of particular variants related to diabetes also might help more people than just those who have the variant, Dr. Collins said. For example, one already-discovered variant, KCNJ11, "codes for the protein that is the product of a sulfonylurea class of drugs. And what is PPAR gamma? That is the gene that codes for the protein that is the target of thiazolidinediones. So here you have proof that this strategy is capable of identifying drug targets, and we know those drugs work [on people other than] those who have one spelling or the other of these particular genes."

In terms of the increased risk posed by the gene variants, "most of these are pretty modest"—for instance, if you have the variant of PCF7L2, your likelihood of getting diabetes would go up 37%, he explained. "But of course that doesn't mean you're definitely going to get the disease."

However, some people have argued that this information could be used to predict whether certain healthy individuals are likely to get diabetes, "and in fact, if you have a fair number of these risk factors, you can already use this to predict that some people have about twice the average baseline risk of diabetes and others may have as little as half that baseline risk, and that's starting to get into the zone where that might be useful information," Dr. Collins said.

Another area where genetic information could be useful is in predicting which diabetes patients will wind up with particular complications. "It may also be that some of these [variants] predispose some people to complications more than others, and we need to know that information as soon as we can," Dr. Collins said. "We have a study going on right now with diabetic nephropathy, with results expected later this year." ■