

Study points to a novel culprit type 2 diabetes gene at well-established genomic location

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Gene researchers have used sophisticated scientific tools to reveal a new gene for type 2 diabetes at a well-established genomic location. Because this gene, *ACSL5*, codes for a protein that regulates how the body recognizes insulin, that protein may represent an important target for future treatments for the disease.

"Type 2 diabetes is increasingly common, with an impact on millions of people," said study leader Struan F.A. Grant, PhD, a genomics researcher at The Children's Hospital of Philadelphia (CHOP). "But it has complex causes, involving multiple [genes](#) and environmental influences, and we are still learning the details of its complicated biology. Our goal in investigating these biological functions is to develop more effective therapies."

Grant and colleagues at CHOP and the Perelman School of Medicine at the University of Pennsylvania co-authored the study that appeared online Aug. 18 in *Diabetologia*.

The new research sheds light on some of the twists and turns of applying [gene discovery](#) to help unravel a complex disease. Grant led a research team that discovered in 2006 that variation within the gene *TCF7L2* raised the risk of type 2 diabetes (T2D). Subsequent research has shown that a variant in this gene region has one of the strongest effects on T2D susceptibility of any of the roughly 100 variants linked to T2D to date, but this is only one piece of the puzzle.

"In genome-wide association studies, which have been instrumental in finding signals like those within *TCF7L2*, it's often assumed that the gene nearest to the genetic signal is the most likely cause for a disease, but in fact an actual culprit gene may be a number of genes away and is being regulated from a distance," said Grant. "Our task becomes that of converting an association signal to the correct disease-causing gene or genes at each of these locations."

In addition, the strongest genetic signals associated with a disease very often arise in a portion of DNA that does not code for a protein. Instead, the DNA may have a regulatory function, interacting with other DNA elements called enhancers or promoters, to increase a gene's expression. Those regulatory elements may be separated from each other by intervening sections of the DNA sequence.

In the current study, Grant and colleagues used a gene editing tool called CRISPR and a three-dimensional structural biology technique called circularized chromosome conformation capture, or 4C, to better understand what was occurring at the molecular level.

Using cells derived from the colon, the study team used CRISPR to edit out precisely defined sequences immediately around the type 2 diabetes-associated variant harbored within the *TCF7L2* gene to examine how this deletion changed global gene expression. The team also used 4C technology in the same cell lines to study interactions between the *TCF7L2* variant and other gene locations, because 4C can show which interactions involve direct physical contact between looping sections of DNA.

In addition to showing a degree of impact on the *TCF7L2* gene itself, the experiments revealed that the variant within *TCF7L2* was strongly regulating another gene, identified as *ACSL5*. Because the *ACSL5* gene codes for the enzyme acyl CoA synthetase 5 that plays a role in lipid

metabolism, say the authors, developing drugs to act on this enzyme might help patients with T2D by increasing their sensitivity to insulin—an underlying issue in the disease.

However, cautioned Grant, much remains to be learned about the action of *ACSL5*. "This well-known genomic location harbors an especially strong signal, and may control multiple other genes, yet to be identified. In addition, we still don't know which specific tissue or tissues that these T2D-related signals operate in to affect patients—whether they act primarily in the gut, in the liver, in adipose tissue or on beta cells in the pancreas. As we continue to better understand the biological mechanisms functioning in type 2 diabetes, we expect to find better strategies for treatment."

The Pennsylvania Department of Health, the Spatial and Functional Genomics Initiative at The Children's Hospital of Philadelphia, and the Daniel B. Burke Endowed Chair for Diabetes Research supported this research. In addition, Grant recently received NIH grant funding to follow up other T2D genetic signals in a similar manner.

More information: Qianghua Xia et al, The type 2 diabetes presumed causal variant within *TCF7L2* resides in an element that controls the expression of *ACSL5*, *Diabetologia* (2016). [DOI: 10.1007/s00125-016-4077-2](https://doi.org/10.1007/s00125-016-4077-2)

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