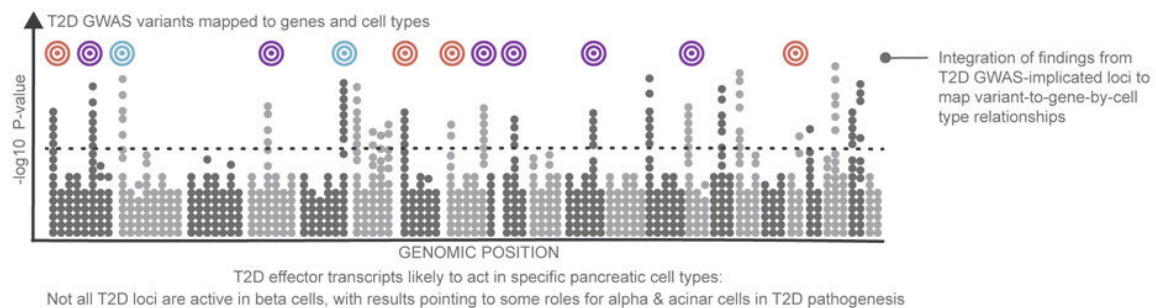
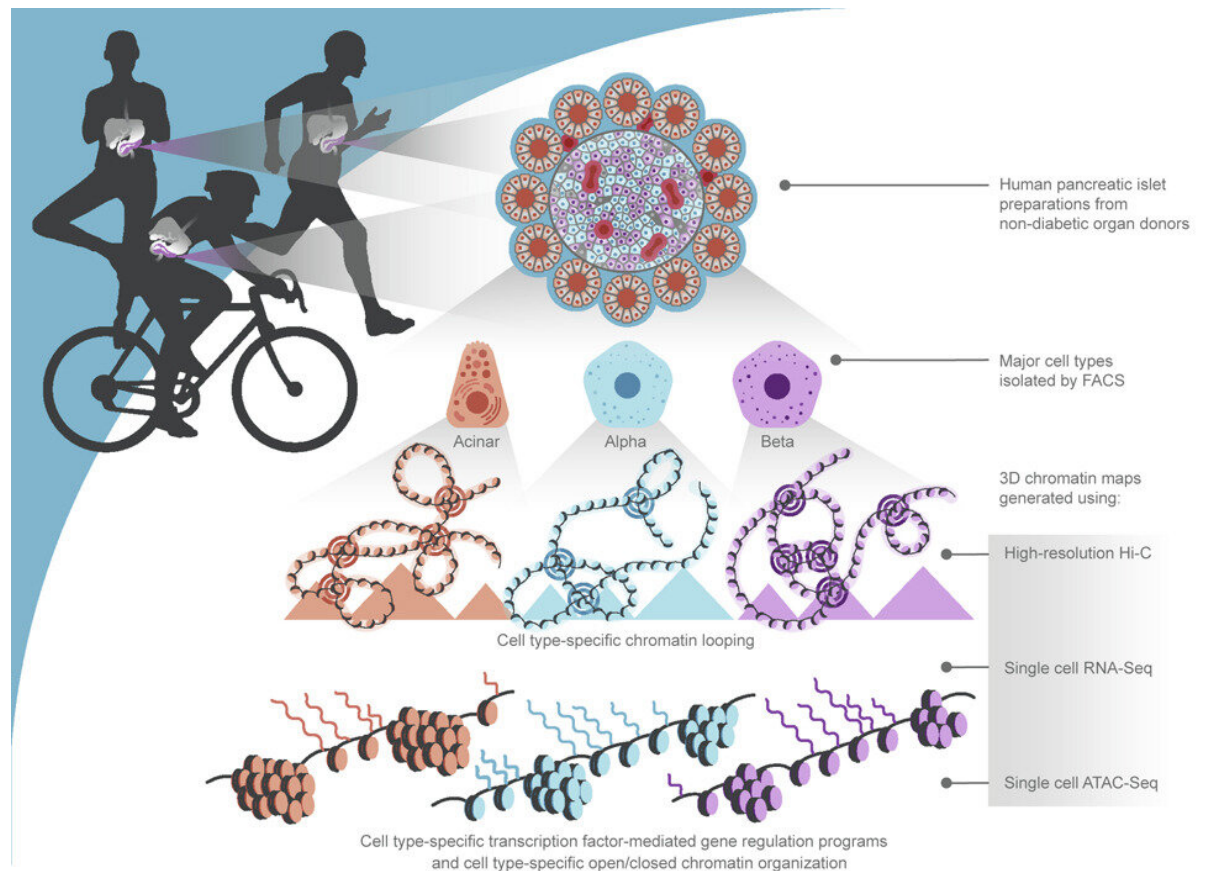


Researchers identify multiple causal genes that drive type 2 diabetes risk

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Credit: Su et al, *Cell Metabolism* (2022). DOI: 10.1016/j.cmet.2022.08.014

Researchers from Children's Hospital of Philadelphia (CHOP) have used advanced three-dimensional mapping techniques at a microscopic level to identify a multitude of genetic variants and corresponding target gene pairings in the pancreas that are implicated in type 2 diabetes. In addition to these discoveries, the resulting datasets will serve as a key resource for researchers all over the world to delve deeper into the genetic origins of type 2 diabetes and further explore the roles of different types of cells in the development of the disease.

The findings were published today in the journal *Cell Metabolism*.

Type 2 [diabetes](#) cases are on the rise and being diagnosed in patients earlier in life than what has been historically observed. However, while many cases can be attributed to a rise in obesity and [sedentary lifestyle](#), increasing evidence suggests a strong role that genetic risk factors play in this relatively common disease. Prior genome-wide association studies (GWAS) have identified hundreds of genetic variants associated with an increased risk of developing type 2 diabetes.

One of the challenges for researching genetic variants is to envision chromosomes functioning while packed densely within microscopic cells. If the DNA from one cell was stretched out end-to-end, it would measure more than six feet long. Protein complexes called chromatin act to fold chromosomes and compact them into each cell. Therefore, genes and variants that appear distant and unrelated in a one-dimensional map of the genome sequence can be closely associated in 3D in a cell, helping to explain the root of how genetic diseases are caused.

"If you do not have an accurate map of how genes are folded together in

a cell, you're essentially guessing the role that these genetic variants play," said one of the study's senior authors Andrew D. Wells, Ph.D., an Associate Professor of Pathology and Laboratory Medicine and Director of the Spatial and Functional Genomics Collaborative at CHOP. "In this study, we applied three-dimensional mapping techniques to chromosomes of highly relevant cell types, which allowed us to identify a series of genes that have never been implicated before in type 2 diabetes."

In this study, researchers created three-dimensional epigenomic profiles of purified acinar, alpha, and beta cells in the human pancreas, using a variety of techniques that examined each of them at the single-cell level. When comparing these profiles, the researchers found differences in how chromatin was compartmentalized, how the chromatin was looped, and how genes were being regulated and transcribed. As a result, the study team identified a series of causal variants and target gene pairs at 194 different type 2 diabetes signals using the three-dimensional [chromatin](#) maps. Additionally, the study revealed that alpha and [acinar](#) cells likely play a greater role in the development of type 2 diabetes than previously thought.

One of the limitations of the paper is that these newly implicated gene variant pairings were not fully validated in functional follow up studies. However, the goal of this paper was to provide critical information so that different labs could further explore and validate these discoveries.

"Prior studies appear to support many of the findings we made in the process of this work, and with additional validation and imaging tools, more aggressive drivers of type 2 diabetes pathogenesis at a genetic level can be isolated," said one of the study's senior authors, Struan F.A. Grant, Ph.D., the other Director of the Center for Spatial and Functional Genomics and the Daniel B. Burke Endowed Chair for Diabetes Research at CHOP. "We believe the findings of this study will serve as a

crucial resource for the diabetes research community."

The other senior author was Klaus Kaestner from the Department of Genetics at the University of Pennsylvania.

More information: Chun Su et al, 3D chromatin maps of the human pancreas reveal lineage-specific regulatory architecture of T2D risk, *Cell Metabolism* (2022). [DOI: 10.1016/j.cmet.2022.08.014](https://doi.org/10.1016/j.cmet.2022.08.014)

Provided by Children's Hospital of Philadelphia

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