Newly discovered genetic markers help pinpoint diabetes risks, complications

February 19 2024

Credit: CC0 Public Domain

In the largest genome-wide association study to date on type 2 diabetes, a team of international researchers, co-led by a University of

Massachusetts Amherst genetic epidemiologist, has located 1,289 genetic markers associated with type 2 diabetes (145 of which are newly identified) and generated risk scores for diabetes complications.

In research published Monday, Feb. 19 in the journal *Nature* that advances understanding into the inheritability of type 2 diabetes, the scientists used cutting-edge computational approaches to identify eight distinct mechanistic clusters of genetic variants linked to the disease. They also discovered associations between individual clusters and diabetes complications.

"We tried to figure out some of the mechanisms for how these genetic variants are working—and we did," says co-senior author Cassandra Spracklen, assistant professor of biostatistics and epidemiology in the School of Public Health and Health Sciences.

Ultimately, the goal is to identify potential genetic targets to treat or even cure the chronic metabolic disease that affects and sometimes debilitates more than 400 million adults worldwide, according to the International Diabetes Federation.

The study—emerging from the newly formed Type 2 Diabetes Global Genomics Initiative—included data from a highly diverse group of more than 2.5 million individuals, 428,452 of whom have type 2 diabetes.

"We found eight clusters of type 2 diabetes-associated variants that have also been associated with other diabetes risk factors—such as obesity and liver-lipid metabolism—suggesting the mechanisms for how the variants may be acting to cause diabetes," Spracklen says. "Then we asked if these clusters were also associated with type 2 diabetes complications. And we found that several of them to also associated with vascular complications, such as coronary artery disease and end-stage diabetic nephropathy."

Even though effective treatments are available for type 2 diabetes, the option for precision medicine tailored to the individual is still limited. For many people with the disease, treatment strategies still rely on trial and error. Being better able to understand the disease mechanisms will help predict individuals' risk of type 2 diabetes and allow for earlier intervention.

"We're trying to understand how diabetes develops," says Spracklen, adding that the new research includes data from cohorts not available in an earlier genome-wide association 2022 study published in *Nature Genetics*, for which Spracklen was co-first author. "And we're trying to better understand how these genetic variants are actually working within a biological tissue or at the cellular level, which can ultimately lead to new drug targets and treatments."

Senior corresponding author Eleftheria Zeggini, director of the Institute of Translational Genomics at Helmholtz Munich and a professor at the Technical University of Munich, notes that collaboration among scientists is essential for evaluating vast patient data and achieving a comprehensive understanding of genomic risk variants.

"The genetic information in our cells harbors secrets about the risks, progression and complications of many diseases," she says. "Our work leads to an improved understanding of disease-causing biological mechanisms. Better knowledge of progression risk for type 2 diabetes complications can help put in place early interventions to delay or even prevent these debilitating medical conditions."

The paper concludes, "Our findings … may offer a route to optimize global access to genetically informed diabetes care."

More information: Genetic drivers of heterogeneity in type 2 diabetes pathophysiology, *Nature* (2024). DOI: 10.1038/s41586-024-07019-6.

www.nature.com/articles/s41586-024-07019-6

Provided by University of Massachusetts Amherst