# Researchers identify novel genetic variants linked to type-2 diabetes

June 23 2020


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After examining the genes of more than 200,000 people all over the world who have type-2 diabetes, researchers from the Perelman School of Medicine at the University of Pennsylvania and the Veterans Health

Administration's (VHA) Corporal Michael J. Crescenz Veterans Affairs Medical Center (CMCVAMC) found hundreds of genetic variants never before linked to the disease.

The study also identified gene variants that vary by ethnicity, as well as variants tied to conditions related to type-2 diabetes like coronary heart disease and chronic kidney disease. This expansive genetic investigation, the largest of its kind, has the potential to dramatically impact care for millions of people worldwide who suffer from this disease. The study is published in the latest edition of the journal *Nature Genetics*.

Using data from the world's biggest biobank—the Million Veteran Program (MVP) in the VHA—plus the DIAGRAM Consortium, the UK Biobank, the Penn Medicine Biobank, and Biobank Japan, the researchers analyzed a study population of 1.4 million people around the world, of which almost 230,000 people had type-2 diabetes.

From there, they broke down the genetic makeup of those hundreds of thousands of people and found 558 independent genetic variants that are differentially distributed between people with and without type-2 diabetes, 21 being European-ancestry-specific and seven African American-ancestry specific. Of the 588 variants found, 286 had never before been discovered. Researchers then set out to see if certain genetic variants among this group of people could be tied to specific type-2-diabetes-related diseases.

"Ultimately, three were linked to coronary heart disease, two to acute ischemic stroke, four to retinopathy, two to chronic kidney disease, and one to neuropathy," said Marijana Vujkovic, Ph.D., a biostatistician at both the Perelman School of Medicine at the University of Pennsylvania, VHA's CMCVAMC and a co-leader for the VHA's national MVP Cardiometabolic Working Group. "Building on this research, the scientific community can assess which of the surrounding genes nearby

the identified genetic variants is likely to be the causal gene that alters the risk of type-2 diabetes, and that could lead to early interventions to limit controllable risks of developing the condition."

While so many genetic variants were found in people with type-2 diabetes, no one variant was implicated as the "worst" or "most dangerous," said co-senior author Benjamin F. Voight, Ph.D., an associate professor of Systems Pharmacology and Translational Therapeutics at Penn, and a co-leader for the VHA's national MVP Cardiometabolic Working Group. "However, just like heart disease, schizophrenia, or obesity, it is the accumulation of a large number of these variants that can add up to a considerable increase in risk. We hope this study can not only help find that subset of patients with substantial risk, but also to motivate new, future studies for treatments based on these findings."

These Penn and VHA researchers say more knowledge about genetic variants related to type-2 diabetes may help identify potential therapeutic targets for type-2 diabetes. They also say it can help guide treatment plans for people with the condition who may also be predisposed to specific diabetes complications.

"Knowing the genetic susceptibility for diabetes complications in a patient already diagnosed with type-2 diabetes, for example through a cumulative genetic risk score, could help guide that patient's care," said co-senior-author Kyong-Mi Chang, MD, a professor of Medicine at Penn, Associate Chief of Staff for Research at VHA's CMCVAMC and the Co-PI for the VHA's MVP Merit Award that supported this work. "As clinicians, we hope that these findings can ultimately be applied to improve the health outcomes for our patients including veterans."

Following the patients from this analysis over the long term will help illuminate the risk associated with these genetic variants, the study

authors say. Accordingly, they are planning to do a long-term examination of how genetics influence disease progression among patients with type-2 diabetes and associated metabolic disorders. The summary statistics from this work also have been released via dbGaP repository for public use to facilitate further discoveries. In addition, the researchers are currently using the list of newly-discovered genes to investigate medication interactions.

**More information:** Vujkovic, M. et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet* (2020). doi.org/10.1038/s41588-020-0637-y

Provided by Perelman School of Medicine at the University of Pennsylvania