Genetic variants may affect treatment response to commonly prescribed type 2 diabetes medication

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Various medications can be prescribed to lower blood sugar levels in individuals at high risk for developing type 2 diabetes, but it's often

unclear which patients will benefit most from which drugs.

In a study published in *Diabetologia,* investigators at Massachusetts General Hospital (MGH), founding member of Mass General Brigham (MGB), identified genetic variants associated with response to two such drugs: metformin and glipizide. The findings may help personalize care to prevent and treat type 2 diabetes.

Current available treatments for type 2 diabetes do not consider an individual's underlying genetics or disease pathophysiology, making it a burden to develop tailored interventions.

The team of investigators, co-led by Josephine Li, MD, endocrinologist in the Diabetes Unit at MGH and an Instructor in Medicine at Harvard Medical School, studied whether a genome-wide approach could unravel new pharmacogenetic associations and develop insight to understand the relevance of known genetic risk factors for type 2 diabetes.

In the Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH), researchers collected genetic data on 1,000 individuals at risk of developing type 2 diabetes who received a short course of metformin and glipizide. The team also documented patients' blood sugar and insulin levels after receiving these drugs.

"We performed a genome-wide association study to comprehensively identify genetic variants associated with drug response. We also tested the influence of previously reported genetic variants for type 2 diabetes and glycemic traits on SUGAR-MGH outcomes," says Dr. Li. "Our study was unique in that over a third of SUGAR-MGH participants were of non-European descent, in contrast to existing pharmacogenetic genome-wide association studies."

Five genetic variants were significantly associated with acute response to metformin or glipizide. Three were more common in participants of African ancestry. One of these African ancestry–specific variants (called rs111770298) was confirmed in the Diabetes Prevention Program, where individuals with this variant experienced a weaker response to metformin treatment than participants without.

"Understanding the impact of ancestry-specific variants can help guide and tailor treatment selection for population subgroups in the future," notes Li.

In a separate analysis, another variant (called rs703972), previously known to help protect against type 2 diabetes, was associated with higher levels of active glucagon-like peptide 1, a hormone that stimulates insulin secretion and reduces appetite.

"Next steps include functional experiments to confirm the implications of the novel genetic variants we've identified that are associated with the body's response to these glucose-lowering therapies," says Li.

"SUGAR-MGH is designed to allow investigators to use two commonly-used drugs with different mechanisms of action to probe the role of specific genes on glucose regulation," says co–senior author Jose C. Florez, MD, Ph.D., chief of the Endocrine Division and the Diabetes Unit at MGH and a professor of Medicine at Harvard Medical School.

The scientists made their findings available as a public resource to enable other researchers to complement their work.

Additional authors include co–lead authors Laura N. Brenner and Varinderpal Kaur; co–senior author Josep M. Mercader; and Katherine Figueroa, Philip Schroeder, Alicia Huerta-Chagoya, Miriam S. Udler, and Aaron Leong.

More information: Josephine H. Li et al, Genome-wide association analysis identifies ancestry-specific genetic variation associated with acute response to metformin and glipizide in SUGAR-MGH, *Diabetologia* (2023). DOI: 10.1007/s00125-023-05922-7