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Study reveals new genetic risk factor for type 2 diabetes

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An international team of researchers in Mexico and the United States has uncovered a new genetic clue that contributes to an increased risk of developing type 2 diabetes, particularly the elevated risk among Mexican and other Latin American populations.

The team, known as the SIGMA (Slim Initiative in Genomic Medicine for the Americas) Type 2 Diabetes Consortium, performed the largest genetic study to date in Mexican and Mexican American populations, discovering a risk gene for type 2 diabetes that had gone undetected in previous efforts. People who carry the higher risk version of the gene are 25 percent more likely to have diabetes than those who do not, and people who inherited copies from both parents are 50 percent more likely to have diabetes. The higher risk form of the gene has been found in up to half of people who have recent Native American ancestry, including Latin Americans. The variant is found in about 20 percent of East Asians and is rare in populations from Europe and Africa.

The elevated frequency of this risk gene in Latin Americans could account for as much as 20 percent of the populations' increased prevalence of type 2 diabetes—the origins of which are not well understood.

"To date, genetic studies have largely used samples from people of European or Asian ancestry, which makes it possible to miss culprit genes that are altered at different frequencies in other populations," said co-corresponding author José Florez, a Broad associate member, an

associate professor of medicine at Harvard Medical School and an Assistant Physician in the Diabetes Unit and the Center for Human Genetic Research at the Massachusetts General Hospital. "By expanding our search to include samples from Mexico and Latin America, we've found one of the strongest genetic risk factors discovered to date, which could illuminate new pathways to target with drugs and a deeper understanding of the disease."

A description of the discovery of the newly implicated gene – named SLC16A11 – and the consortium's efforts to characterize it, appear online in *Nature* December 25.

"We conducted the largest and most comprehensive genomic study of type 2 diabetes in Mexican populations to date. In addition to validating the relevance to Mexico of already known genetic risk factors, we discovered a major new risk factor that is much more common in Latin American populations than in other populations around the world. We are already using this information to design new studies that aim to understand how this variant influences metabolism and disease, with the hope of eventually developing improved risk assessment and possibly therapy," said Teresa Tusie-Luna, project leader at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and principal investigator at the Biomedical Research Institute, National University of Mexico.

This work was conducted as part of the Slim Initiative for Genomic Medicine for the Americas (SIGMA), a joint U.S.-Mexico project funded by the Carlos Slim Foundation through the Carlos Slim Health Institute. SIGMA focuses on several key diseases with particular relevance to public health in Mexico and Latin America, including type 2 diabetes and cancer. The current paper is the team's first report on type 2 diabetes.

"For the Carlos Slim Foundation, the SIGMA project has been a story of total success. Our extraordinary partners, both in Mexico and the U.S., have made it possible to make historic advances in the understanding of the basic causes of type 2 diabetes mellitus. We hope that through our contributions we will be able to improve the ways in which the disease is detected, prevented and treated," said Roberto Tapia-Conyer, CEO of the Carlos Slim Foundation.

The frequency pattern for this variant of SLC16A11 is somewhat unusual. Humans as a species first arose in Africa, so nearly all common human genetic variants are present in African populations. However, the SLC16A11 variant—despite being common in Native American populations—is largely absent in African populations, and rare in Europeans.

In order to understand this unusual pattern, the team conducted additional genomic analyses, in collaboration with Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology, and discovered that the SLC16A11 sequence associated with risk of type 2 diabetes is found in a newly sequenced Neanderthal genome. Analyses indicate that the higher risk version of SLC16A11 was introduced into modern humans through mixing with Neanderthal.

Inheriting a gene from Neanderthal ancestors is actually not uncommon: approximately 1 to 2 percent of the sequences present in all modern day humans outside of Africa were inherited from Neanderthals. Importantly, neither people with diabetes nor populations of Native American or Latin American ancestry have an excess of Neanderthal DNA relative to other populations.

Since this is the first time SLC16A11 has been highlighted as playing a role in human disease, little information was previously available about its function. The Nature paper reveals some initial clues about its

possible connection to type 2 diabetes. SLC16A11 is part of a family of genes that code for proteins that transport metabolites—molecules involved in the body's various chemical reactions. The SIGMA Type 2 Diabetes Consortium paper reports that SLC16A11 is expressed in the liver, in a cellular structure called the endoplasmic reticulum.

The researchers went on to show that altering the levels of the SLC16A11 protein can change the amount of a type of fat that has previously been implicated in the risk of diabetes. These findings have led the team to hypothesize that SLC16A11 may be involved in the transport of an unknown metabolite that affects fat levels in cells and thereby increases risk of type 2 diabetes.

"One of the most exciting aspects of this work is that we've uncovered a new clue about the biology of diabetes," said co-senior author David Altshuler, deputy director and chief academic officer at the Broad Institute and a Harvard Medical School professor at Massachusetts General Hospital (MGH). "We are now hard at work trying to figure out what is being transported, how this influences triglyceride metabolism, and what steps lead to the development of type 2 diabetes."

The team's ultimate goal is to leverage a deeper understanding of this pathway to find new drug targets for treating diabetes. The Broad Institute recently announced that the Carlos Slim Foundation has made an additional contribution of $74M to launch the second phase (SIGMA 2) of the biomedical partnership that made the discovery of SLC16A11 – and many other discoveries – possible. SIGMA 2 will, among other things, help fund studies of this gene in cells and in mice, allow researchers to study the variant in more samples from people in Mexico City and Boston, and gain insights into the progression of the disease.

More information: The SIGMA Type 2 Diabetes Consortium. "Sequence variants in SLC16A11 are a common risk factor for type 2

diabetes in Mexico." *Nature*, DOI: 10.1038/nature12828

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