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Diabetes' genetic underpinnings can vary based on ethnic background, studies say

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Ethnic background plays a surprisingly large role in how diabetes develops on a cellular level, according to two new studies led by researchers at the Stanford University School of Medicine.

The researchers reanalyzed disease data to demonstrate that the physiological pathways to diabetes vary between Africa and East Asia and that those differences are reflected in part by genetic differences. The studies will be published online simultaneously May 23 in the journals *PLoS Genetics* and *Diabetes Care*.

"We have new insights into the differences in diabetes across the world, just by this new perspective applied to older studies," said Atul Butte, MD, PhD, senior author of the studies and chief of the Division of Systems Medicine and associate professor of pediatrics and of genetics. "There's more still to learn about diabetes than we knew."

The early stages of type-2 diabetes, or adult-onset diabetes, can develop when the pancreas has problems creating sufficient insulin, a hormone critical for regulating blood sugar, or when the body's cells have trouble responding to insulin, a condition called "insulin resistance." Both problems will lead to the same result: too much sugar in a person's blood stream, which is the main criterion for diagnosing diabetes. Diabetics develop both low insulin secretion and insulin resistance as the disease progresses.

In the study to be published in *PLoS Genetics*, the researchers started by

studying genome information of more than 1,000 people in 51 populations from around the world. These individuals were from indigenous populations, representing the earliest groups of humans at various locations. Lead author and former graduate student in Butte's lab, Erik Corona, PhD, studied more than 100 diseases searching for genetic differences in risk across these native populations, and found a clear geographic pattern in the genetics behind type-2 diabetes. The genetic risk is highest for Africans and drops along the trajectory the first humans took when migrating out of Africa toward East Asia (primarily Japan, China and Korea), where diabetes-linked genes appear to be more protective. Based solely on what is currently known about type-2 diabetes genetics, native Africans would appear to be at higher risk for diabetes, while East Asians would appear to be protected. But East Asians are not necessarily at lower risk of diabetes than Africans. Butte pointed out that "East Asians definitely get diabetes. What we would argue is that diabetes may be a different disease" in East Asian populations. An interactive tool that displays the results can be found at http://geneworld.stanford.edu/hgdp.html.

The genetics study's findings led Butte's team to wonder if there was clinical evidence of these differences in African and East Asian populations. For the second paper, lead author and staff engineering research associate Keiichi Kodama, MD, PhD, pulled data from more than 70 papers looking at simultaneously measured insulin secretion and insulin resistance in individuals across three different ethnic groups: Africans, Caucasians and East Asians. They found that at baseline, Africans had higher insulin resistance but were able to compensate with higher insulin secretion. East Asians were more likely to have less insulin-secretion ability, but this was compensated by having normal insulin resistance. Caucasians fell between these two groups, though they were more likely to develop problems with insulin secretion.

The researchers showed that because individuals from each ethnic group

start at a different baseline position, they each reach diabetes in a different way: Africans through increased insulin resistance, and East Asians through lower insulin-secretion ability. "Africans are already pretty insulin resistant," Butte said. "They need their beta cells to work really hard. If their cells fail, that's how they head toward diabetes." East Asians, in contrast, "don't have a lot of spare capacity to secrete more insulin." The findings will be published in *Diabetes Care*.

Butte notes that a shift in how clinicians think about diabetes could lead to more targeted therapies, much as how thinking about cancer has evolved over the past 10 years, leading to new treatments. "Other fields of medicine have undergone a radical rethinking in disease taxonomy, but this has not happened yet for diabetes, one of the world's public health menaces," he said. "If these are separate diseases at a molecular level, we need to try to understand that."

Provided by Stanford University Medical Center