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Newly discovered protein has link to gestational diabetes

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For at least 40 years, scientists who study how the body metabolizes sugar have accepted one point: there are four enzymes that kick-start the body's process of getting energy from food.

The discovery of these four catalysts for energy production, called hexokinases, generated more research into how the body metabolizes carbohydrates, and how interfering with those enzymes through medications could help manage metabolic disorders such as diabetes.

But this biochemical foursome may not deserve all of the credit. According to research by scientists at Duke and Northwestern universities, the hexokinase team actually has a fifth player. The findings appear in the online journal *Nature Communications*.

"This swims against the past 40 years of research and what we thought we knew," said Tim Reddy, Ph.D., a senior author of the study and assistant professor of biostatistics and bioinformatics at Duke. "Hexokinases are critical to basically all of our energy production. Finding a fifth one opens the door to more study into how we metabolize sugar, as well as genetic links to metabolic disorders."

The new protein is called HKDC1, and the researchers report that this enzyme may be a genetic predictor for whether an expectant mother develops hyperglycemia, or excess blood sugar, during pregnancy. Hyperglycemia is a potentially harmful environment for a growing fetus and can contribute to obesity and diabetes later in the child's life.

While at least 4 percent of pregnant women develop diabetes during pregnancy, as many as 400,000 women each year in the U.S. have gestational hyperglycemia, which equals about 10 percent of expectant mothers. Hyperglycemia during pregnancy may have many of the same harmful long-term health effects as full-blown gestational diabetes, according to a landmark study published in the New England Journal of Medicine in 2008.

"We know that these children may be more likely to be born large and be subject to health impacts down the road, such as obesity and diabetes," Reddy said.

Doctors have counseled expectant mothers on the risks of high blood sugar and the benefits of proper diet and exercise to lessen the risk. But there currently isn't a method to screen women for their risk of developing high blood sugar while pregnant. Often, mothers are diagnosed too late, after they have developed diabetes.

While all humans have this fifth hexokinase, it appears during pregnancy, women with less of this gene are not able to metabolize glucose as well, the study showed. Researchers hope the new findings could lead to a test for pregnant women that indicates their potential for developing hyperglycemia.

"The discovery of this gene creates a path forward to better predicting a woman's risk," Reddy said. "Knowing that there is this new hexokinase at play could also give us more information on how to inhibit or activate it, and anything we can to do disrupt the cycle would be an important advance to stem the epidemic of diabetes we see today."

Further investigation into the enzyme could create potential targets for new therapies for metabolic conditions, said William Lowe, M.D., a senior author of the study and professor of medicine at Northwestern

University Feinberg School of Medicine.

"This study shows the benefit of large-scale genetic studies as they begin to shed light on new molecules that are important for metabolism," Lowe said.

The idea that this enzyme has been hidden in the human genome all these years is somewhat shocking, said Christopher Newgard, Ph.D., an author of the paper and director of the Duke Molecular Physiology Institute.

"It's ancient history in the field of carbohydrate biochemistry that there were four members of the family," Newgard said. "Something like 40 years goes by, and then here comes this cowboy, showing up late to the party."

Provided by Duke University Medical Center