

Gene That Controls Fat Identified

Finding the lipin gene may offer a new target for treating obesity and diabetes.

REVIEWED BY KAREN REUE, PHD

Scientists at the University of California-Los Angeles Veterans' Affairs have identified a new gene that controls how the body produces and uses fat.¹ The gene, lipin, may offer a target for therapies to treat obesity, diabetes and other weight-related disorders. The findings are published in the first issue of the journal *Cell Metabolism*.

"Lipin regulates how the body stores and burns fat. By varying the levels of lipin expression in fat and muscle, it is possible to modulate body fat content from one extreme to the other," said principal investigator Karen Reue, PhD, in a news release. Dr. Reue is a professor of medicine and human genetics at the David Geffen School of Medicine at UCLA and a researcher at the Veterans Affairs Greater Los Angeles Healthcare System.

IMPAIRED ADIPOCYTE DIFFERENTIATION

Previously, Dr. Reue and colleagues demonstrated that lipin deficiency impaired adipocyte differentiation in mice and caused lipodystrophy.² Paradoxically, the lack of normal adipose tissue in lipodystrophy causes metabolic complications similar to those found in obesity. In the current study, Dr. Reue, and coauthor Jack Phan, PhD, investigated the effect of elevated lipin expression on the development of obesity.¹ They used two different tissue-specific lipin transgenic mouse strains to show that enhanced lipin expression, in either adipose tissue or skeletal muscle, promotes obesity.

After a high-fat diet for 6 weeks, the transgenic mice with enhanced lipin expression in adipose tissue or muscle gained weight at double or triple the rate of normal mice, respectively. This occurred despite no increase in food intake, indicating that lipin in adipose tissue and skeletal muscle influences the efficiency by which food energy is converted into stored energy.

INFLUENCED FAT STORAGE

The researchers also found that lipin affected adipose tissue and skeletal muscle differently. In adipose tissue,

lipin levels influenced the fat storage capacity of the adipocyte, while lipin levels in skeletal muscle deterred whole-body energy expenditure. Muscle lipin content also influenced the type of fuel used for energy production.

"When we increased lipin in the muscle, the cells preferentially use carbohydrates before fat. When lipin is absent, however, the cells preferentially burn fat before carbohydrates," Dr. Reue explained. "We saw a different effect when lipin acted in fat tissue. High levels of lipin increased fat storage capacity in adipose tissue. This was in contrast to lipin deficiency, which prevented the cells from forming and storing fat."

USED MORE ENERGY

The study showed that lipin-deficient mice expended more energy to perform daily activities. Because lipin moderates calorie use in muscle, its absence caused the mice to expend more calories to fulfill the same tasks as normal mice. "Our study suggests that variations in lipin levels could determine a person's tendency to gain weight by influencing how their body stores and burns fat," Dr. Reue said.

Enhanced lipin expression in adipose tissue and skeletal muscle had distinct effects on glucose homeostasis and insulin sensitivity, Drs. Reue and Phan also found. They wrote that while lipin overexpression in muscle produced obesity-associated insulin resistance, enhanced lipin expression in mature adipocytes improved insulin sensitivity over that in nontransgenic mice despite increased adiposity.

KEEP FAT IN THE RIGHT PLACE

It is suggested that preferential fatty acid uptake and triglyceride storage specifically in adipose tissue may prevent unwanted lipid deposition in muscle or pancreatic beta-cells, leading to improved insulin sensitivity. This enhanced ability to keep fat in the "right" place could explain why mice overexpressing lipin in adipose tissue showed improved insulin sensitivity despite becoming obese.

“Because obesity and lipodystrophy are both associated with insulin resistance, we hope that our results may point to a new therapeutic target for conditions such as diabetes,” Dr. Reue said. ■

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Karen Reue, PhD, and Jack Phan, PhD, are in the departments of human genetics and medicine, and the

1. Phan J, Reue K. Lipin, a lipodystrophy and obesity gene. *Cell Metabolism*. 2005;1:73-83.
2. Peterfy M, Phan J, Xu P, Reue K. Lipodystrophy in the fld mouse results from mutation of a new gene encoding a nuclear protein, lipin. *Nat Genet*. 2001;27:121-124.

GENE VARIANT MAY PREDICT TYPE 2 DIABETES

ENPP1 K121 Q could be an important genetic marker for identifying diabetes risk.

Reviewed by Nicola Abate, MD

Nicola Abate, MD, and researchers from the University of Texas Southwestern Medical Center have identified a gene variant that may predict type 2 diabetes.

The findings indicate that the ENPP1 K121 Q polymorphism was as much as 13% more common in people with type 2 diabetes and those at greater risk for the disease. While further studies are needed, researchers said these results suggest that the variant may serve as an important genetic marker in identifying people at risk for type 2 diabetes.

“This important study uncovers one of the genes that appears to predispose to type 2 diabetes,” said Scott Grundy, MD, senior author and director of UT Southwestern’s Center for Human Nutrition, in a news release from UT Southwestern’s Medical Center.

THREE STUDY GROUPS

The study, published in *Diabetes*, evaluated a specific gene in three study groups – South Asians; South Asians living in Dallas; and Caucasians living in Dallas. Some patients had type 2 diabetes, others had risk factors for the disease, and others had no signs of diabetes or any apparent risk factors.

“The implication from our study is that if a person has this gene variation, then – without waiting for the development of insulin resistance – he or she should be encouraged to follow lifestyle changes that could help prevent the onset of diabetes,” said Dr. Abate, coauthor and associate professor of internal medicine in the Center for Human Nutrition. She was quoted in the news release.

Certain ethnic populations appear to have a higher risk of developing type 2 diabetes, whether overweight or not, particularly South Asians.

The study focused on 679 South Asians living in Chennai, India (of which 223 had type 2 diabetes); 1,083 South Asians living in Dallas who were new immigrants or first-generation immigrants from India, Pakistan or Bangladesh (of which 121 had type 2 diabetes); and 858 nonimmigrant Caucasians living in Dallas (of which 141 were type 2 diabetic). All patients were evaluated for diabetes and family history of diabetes, as well as overall general health, and they had blood tests conducted for genetic sampling. All study participants with type 2 diabetes had diabetes onset before age 60 years, according to the research.

BLOCKS ACTION OF INSULIN

Results showed the presence of the ENPP1 K121Q allele in 25% of the nondiabetic group and in 34% of the diabetic group of South Asians living in India; in 33% and 45%, respectively, in the nondiabetic and diabetic South Asians in Dallas; and 26% and 39%, respectively, in the nondiabetic and diabetic Caucasians. The gene ENPP1 encodes a protein that blocks the action of insulin. The genetic variation increases the action of this protein and blocks insulin action even more.

“Earlier studies we conducted showed a propensity toward insulin resistance and type 2 diabetes in South Asians, even when they were thin,” Dr. Abate said. “This study expanded that to include diabetic patients and Caucasians of European descent. It also took into account the possible influence of environmental factors by comparing South Asians in both Dallas and in Chennai. “Consistently, we found that this gene variant in all three groups predicted diabetes.” ■

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Abate N, Chandalia M, Satija P. ENPP1/PC-1 K121Q polymorphism and genetic susceptibility to type 2 diabetes. *Diabetes*. 2005;54:1207-1213.