UT SOUTHWESTERN MEDICAL CENTER NEWS

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'Skinny gene' does exist, UT Southwestern researchers find

DALLAS – Sept. 4, 2007 – Researchers at UT Southwestern Medical Center have found that a single gene might control whether or not individuals tend to pile on fat, a discovery that may point to new ways to fight obesity and diabetes.

"From worms to mammals, this gene controls fat formation," said Dr. Jonathan Graff, associate professor of developmental biology and internal medicine at UT Southwestern and senior author of a study appearing in the Sept. 5 issue of *Cell Metabolism*. "It could explain why so many people struggle to lose weight and suggests an entirely new direction for developing medical treatments that address the current epidemic of diabetes and obesity.

"People who want to fit in their jeans might someday be able to overcome their genes."

The gene, called *adipose,* was discovered in fat fruit flies more than 50 years ago by a graduate student at Yale University, but few people knew about it. Its mechanism was unknown, and whether it's important in other genes was a mystery.

In the current study, the UT Southwestern researchers examined how *adipose* works by analyzing fruit flies, tiny worms called *C. elegans,* cultured cells, and genetically engineered mice, as well as by exploiting sophisticated molecular techniques. Using several methods, they manipulated *adipose* in the various animals, turning the gene on and off at different stages in the animals' lives and in various parts of their bodies.

It was discovered that the gene, which is also present in humans, is likely to be a high-level master switch that tells the body whether to accumulate or burn fat.

In the mice, the researchers found that increasing *adipose* activity improved the animals' health in many ways. Mice with experimentally increased *adipose* activity ate as much or more than normal mice; however, they were leaner, had diabetes-resistant fat cells, and were better able to control insulin and blood-sugar metabolism.

In contrast, animals with reduced *adipose* activity were fatter, less healthy and had diabetes.

The researchers' work on flies showed that the gene is "dose-sensitive" – that is, the various combinations of the gene's variants lead to a range of body types from slim to medium to obese.

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"This is good news for potential obesity treatments, because it's like a volume control instead of a light switch; it can be turned up or down, not just on or off," Dr. Graff said. "Eventually, of course, the idea is to develop drugs to target this system, but that's in the years to come."

This genetic mechanism makes survival sense, he said, because if a population has many versions of the gene scattered among many different individuals, at least some will survive in different conditions. For instance, a fat fruit fly may be able to survive famine, but a sleeker model might be better at evading predators.

Dr. Graff said the next step is to understand better the exact mechanisms by which *adipose* exerts its control.

Although the current study finally identifies the *adipose* gene's function, the gene was discovered more than 50 years ago when Winifred Doane, now a professor emeritus at Arizona State University, was studying fruit flies and noticed that some contained more fat than others. She linked this trait to a gene she named *adipose* and hypothesized that this natural variation gave the chubbier flies an evolutionary advantage; they could hoard more fat on the same amount of food as their skinnier counterparts, allowing them to survive times of famine.

But for people in developed countries, this trait has backfired. It's all feast and no famine, so the fat builds and builds.

"Even a pound a year adds up over a lifetime," Dr. Graff said.

Other UT Southwestern researchers involved in the study were Dr. Jae Myoung Suh, postdoctoral researcher in developmental biology; Daniel Zeve, Robert Li and Michael Wang, students in the Medical Scientist Training Program; Dr. Renee McKay, instructor of developmental biology; Dr. Jin Seo, postdoctoral researcher in developmental biology; and Zack Salo, undergraduate at UT Arlington.

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