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Researchers identify fat-storage gene mutation that may increase diabetes risk

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Researchers at the University of Maryland School of Medicine have identified a mutation in a fat-storage gene that appears to increase the risk for type 2 diabetes and other metabolic disorders, according to a study published online today in the *New England Journal of Medicine*.

The researchers discovered the mutation in the hormone-sensitive lipase (HSL) gene by studying the DNA of more than 2,700 people in the Old Order Amish community in Lancaster County, Pa. HSL is a key enzyme involved in breaking down stored fat (triglycerides) into fatty acids, thereby releasing energy for use by other cells.

"We found that Amish people with this mutation have defects in fat storage, increased fat in the liver, high triglycerides, low "good" (HDL) cholesterol, insulin resistance and increased risk of developing type 2 diabetes," says the study's senior author, Coleen M. Damcott, Ph.D., an assistant professor of medicine in the Division of Endocrinology, Diabetes and Nutrition and member of the Program for Personalized and Genomic Medicine at the University of Maryland School of Medicine.

In this study, 5.1 percent of the Old Order Amish study participants had at least one copy of the mutation. Four people had two copies of the mutation and consequently produced no HSL enzyme, Dr. Damcott says. The mutation is less common in non-Amish Caucasians of European descent (0.2%), thus the higher prevalence of the mutation in the Amish makes it possible to characterize its full range of effects.

"Future studies of this gene will allow us to look more closely at the effects of its deficiency on human metabolism to better understand the function of the HSL protein and its impact on fat and glucose metabolism," Dr. Damcott says. "These studies will also examine the potential of using HSL as a drug target for treating type 2 diabetes and related complications."

She notes that type 2 diabetes is a complex disease whose susceptibility is often determined by interactions between genetics and lifestyle factors, such as overeating and physical inactivity. Susceptibility genes for diabetes may be involved in several different metabolic pathways in the body, including storage and release of fat for energy. "Discovery of this mutation adds to the growing list of insights gained from genomic studies that can be used to develop new treatments and customize existing treatments for type 2 diabetes and related metabolic disorders," Dr. Damcott says.

Co-author Alan R. Shuldiner, M.D., the John L. Whitehurst Endowed Professor of Medicine, associate dean for personalized medicine and director of the Program for Personalized and Genomic Medicine, and his colleagues at the University of Maryland School of Medicine have previously identified a number of susceptibility genes for diabetes as well as for obesity, high blood pressure and other complex diseases. In 2008, they discovered a novel gene mutation among the Old Order Amish population that significantly reduces the level of triglycerides in the blood and appears to help prevent cardiovascular disease. Dr. Shuldiner's team has been conducting genetic research with the Old Order Amish in Pennsylvania since the early 1990s.

The Old Order Amish are ideal for genetic studies because they are a genetically homogenous population who trace their ancestry back 14 generations to a small group who came to Pennsylvania from Europe in the mid-1700s.

Provided by University of Maryland