MedicalXpress

Type 2 diabetes linked to single gene mutation in 1 in 10 patients

March 2 2011

A multinational study has identified a key gene mutation responsible for type 2 diabetes in nearly 10 percent of patients of white European ancestry.

The study, which originated in Italy and was validated at UCSF, found that defects in the HMGA1 gene led to a major drop in the body's ability to make insulin receptors – the cell's sensor through which insulin tells the cell to absorb sugar. This drop in insulin receptors leads to insulin resistance and type 2 diabetes, according to the paper.

Findings appear in the March 2 issue of the *Journal of the American Medical Association* and online at www.jama.org.

The results provide the unique opportunity for a test to predict potential for the disease in patients, as well as the possibility of identifying which of the current diabetes medications work best for people with this gene mutation, the authors said. Ultimately, it also could help drive research to find new and improved drugs for those patients.

While the study focused on Caucasians, it also lays the groundwork for similar analyses in patients of Asian, African and Native American descent, who suffer from higher rates of the disease, according to diabetes researcher Ira Goldfine, MD, a UCSF professor of medicine and of physiology who led the U.S. arm of these studies.

"This is a major breakthrough in type 2 diabetes," said Goldfine, noting

that 26 million Americans have diabetes and an estimated 79 million have pre-diabetes. "Many of our current diabetes drugs are very effective in some patients and not in others. This finding could not only explain why that is, but also could help us target the right drug for the right person, so diabetics can manage their disease better and lead healthier lives."

Type 2 diabetes, which was previously referred to as "adult-onset" diabetes, is a growing global concern and is estimated to affect more than 250 million people worldwide. The disease has long been known to have both hereditary and lifestyle components, but until now, no single gene mutation has been pinpointed as playing a significant role in causing it.

The advance originated in 1993, when Antonio Brunetti, MD, PhD – at the time a postdoctoral fellow in Goldfine's laboratory – discovered that insulin receptors were turned on in cells by a certain protein, which is now understood to be produced by the HMGA1 gene. Brunetti, the senior author on this paper, continued his research at the University of Catanzaro, in Italy, and ultimately identified this gene mutation in a population of 3,278 Italians with diabetes, matched against a similar number of their compatriots who had neither diabetes nor pre-diabetes.

Brunetti's current study found at least one mutation on that gene in 9.8 percent of the diabetics in the Italian population, versus only 0.6 percent of the control group.

The UCSF team then ran a genetic analysis on 1,928 similar patients from the Genomic Resource in Arteriosclerosis, a DNA bank in the UCSF Cardiovascular Research Institute, a repository for 30,000 patient samples dating back to 1994. That data, mined in the UCSF laboratories of Clive Pullinger, PhD, and John Kane, MD, PhD, generated the same percentages as the Italian population, as did a subsequent study of 404

patients at the University of Reims, in France, by Vincent Durlach, MD.

"This is an excellent example of how international collaborations can find significant patterns in diseases," Brunetti said. "Diabetes is one of the most complex chronic diseases and it affects millions of people throughout the world. We hope to extend this research to see whether the same percentages hold true throughout the world population."

Brunetti said future research will include further study of variants within the HMGA1 gene, including studies in people with other racial heritages.

Provided by University of California, San Francisco