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Contact: Krista Conger

kristac@stanford.edu

650-725-5371

Stanford University Medical Center

New associations between diabetes, environmental factors found by novel Stanford analytic technique

STANFORD, Calif. — Got diabetes? If so, you probably know that the adult-onset form of the disease can be triggered by, among other things, obesity and a fatty diet. You're also more likely to develop diabetes if other family members have it. But a new study by researchers at the Stanford University School of Medicine suggests that you should also begin looking suspiciously at other aspects of your life — like your past exposure to certain pesticides or chemicals and even one form of vitamin E.

In fact, the association of some of these so-called "environmental" cues with diabetes surpasses that of the best genetic markers scientists have identified for the disease.

Identifying relationships between a person's environment (such as tobacco exposure) and specific health repercussions (such as cancer) is nothing new. Epidemiological studies of large groups of people have been doing just that for decades. But they are limited in their ability to assess the hundreds or even thousands of variables that comprise the intricate fabric of our everyday lives. (What's your risk of heart disease if you smoke sparingly and eat fatty foods, but are also a marathoner?) They're also not open-ended: The researcher has to begin with presuppositions about possible relationships. (Does folic acid prevent birth defects?)

In this new study, the scientists relied instead on an unconventional approach that treats environmental variables as "genes." That conceptual shift allowed them to use some of the same techniques initially developed to identify the many sections of DNA throughout the genome that might contribute to disease development. Bioinformatics expert Atul Butte, MD, PhD, assistant professor of pediatric cancer biology, compared the data generated by the new approach to the amount and types of information gleaned from a DNA microarray.

"This approach catapults us from being forced to ask very simple, directed questions about environment and disease into a new realm in which we can look at many, many variables simultaneously and without bias," said Butte, who is also director of the Center for Pediatric Bioinformatics at Lucile Packard Children's Hospital. "In the future, we'll be able to analyze the effect of genes and environment together, to find, perhaps, that a specific gene increases the risk of a disease only if the person is also drinking polluted well water."

Specifically, in this study, Butte and his coworkers used the technique to identify a previously known association between people with type-2 diabetes and a class of organic compounds called polychlorinated biphenyls, or PCBs, commonly used for many applications until the late 1970s. They also uncovered a strong, but unexpected, relationship between diabetes and high levels of a form of vitamin E called gamma-tocopherol, which is prevalent in fruits, vegetables, nuts and milk.

The scientists are careful to caution, however, that an association doesn't necessarily mean that vitamin E or pollutants cause type-2 diabetes, and that more research is needed to fully understand these complex relationships.

Butte is a senior author of the research, which will be published May 20 in the online journal *PLoS ONE*. The genetic studies on which the research is based are called "genome wide association studies" or GWAS. In a nod to its origin, the scientists coined the term "environment wide association studies," or EWAS, for the new technique. They expect that EWAS will be useful in the analysis of many complex diseases.

"We've known for decades that environmental factors play a major role in diseases like diabetes, cancer and heart disease," said Jeremy Berg, PhD, director of the National Institute of General Medical Sciences, which partially supported the work. "By enabling us to measure the impact of these factors, this new approach will shed light on how genes and the environment influence our health and could provide insights into new ways to control some of our nation's most serious health problems."

Graduate student Chirag Patel conceived of, designed and executed the computer software for the EWAS. He, Butte and associate professor of medicine Jayanta Bhattacharya, MD, PhD, used existing population studies conducted from 1999 to 2006 by the U.S. Centers for Disease Control and Prevention as part of the National Health and Nutrition Examination Survey. The researchers realized that the databases contained a goldmine of information, including the levels of pollutants and vitamins in subjects' blood and urine as well as clinical measurements such as fasting blood sugar levels.

In all, the scientists analyzed the relationship of 266 unique environmental variables to the likelihood that a person's fasting blood sugar level was 126 milligrams or higher per deciliter (between 70 and 110 mg/dL is considered normal). Higher-than-normal blood sugar levels after an overnight fast are a telltale

sign of diabetes. They adjusted for the subjects' age, gender, body mass index, socioeconomic status and ethnicity. Finally, they grouped related variables into 21 classes — such as dioxins, polychlorinated biphenyls, phthalates, etc. — similar to how individual genes are assigned to chromosomal units in GWAS.

Butte and his colleagues found that people with relatively higher levels of the pesticide-derivative heptachlor epoxide (a chemical whose use stopped in the '80s but is still prevalent in food, soil and water) in their blood were more likely than those with lower levels to also have high fasting blood sugar levels (odds ratio = 1.7). The same was true for those with high levels of PCBs (OR = 2.2) and the gamma-tocopherol form of vitamin E (OR = 1.5). In contrast, high beta-carotene levels were slightly protective (OR = 0.6).

Scientists have recently made large strides in measuring genetic associations to complex disease, but are still far from using genes to predict risk for complex chronic diseases or even plan preventive measures. On the other hand, our environmental profile is potentially more modifiable and also may provide a more complete model of disease risk when combined with genetic information.

"Studying relationships between a person's environment and their disease burden in this manner is going to be far more impactful," said Butte. "We can now imagine what it might be to look at everything in the environment, in the same way that we've been doing with the genome for the past decade. Imagine one day wearing a chip on your clothing that assesses your exposure to hundreds or thousands of environmental toxins. You could bring that in to your annual physical and you and your doctor could incorporate the information into discussions about disease risk and prevention."

The researchers are planning to conduct similar EWAS studies focused on other diseases, including cancers. They'll also try to reproduce the data from the National Health and Nutrition Examination Survey studies on specific populations in California.

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