The gene-environment enigma

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This is a DNA molecule. Credit: Washington University in St. Louis

Personalized medicine centers on being able to predict the risk of disease or response to a drug based on a person's genetic makeup. But a study by scientists at Washington University School of Medicine in St. Louis suggests that, for most common diseases, genes alone only tell part of the story.

That's because the environment interacts with DNA in ways that are difficult to predict, even in simple organisms like single-celled yeast, their research shows.

"The effects of a person's genes – and, therefore, their risk of disease – are greatly influenced by their environment," says senior author Barak Cohen, PhD, a geneticist at Washington University School of Medicine. "So, if personalized medicine is going to work, we need to find a way to measure a human's environment."

The research is available online in *PLoS Genetics*.

To understand gene-environment interactions at the most basic level – at the individual DNA letters that make up the genetic code – the researchers turned to a model organism, the yeast Saccharomyces cerevisiae, culled from North American oak trees and vineyards, where it grows naturally. They asked whether growing the yeast in different environments would influence the rate at which the yeast produce spores, a form of sexual reproduction.

This complex trait is heavily influenced by genetics, Cohen's earlier research has shown. In a study published in 2009 in Science, he determined that just four DNA variants, called single nucleotide polymorphisms (SNPs), account for 90 percent of the efficiency with which yeast produce spores.

In that study, the researchers noted that yeast from oak trees produced spores with 99 percent efficiency; the vineyard strains were far less efficient, at 7 percent. Then, they put each combination of the four SNPs in both the oak and vineyard strains, to determine how the genetic variants interacted with one another.

The researchers showed that the four variants "interacted like crazy such

that the combined effects of any four variants were always larger than the sum of their individual effects," Cohen says.

By developing a statistical model to account for the genetic interactions, they could genotype any combination of the four SNPs in either strain of yeast and predict with a high level of confidence their effect on sporulation.

But in that study, the yeast were grown in the same environment – glucose.

In the current study, the scientists grew the two yeast strains with all 16 combinations of four SNPs in different simple sugars: glucose, fructose, sucrose, maltose, raffinose, grape juice, galactose and a combination of sucrose, glucose and fructose.

"These were all mono- or di-saccharides, so the environments are not radically different from one another," Cohen explains. "It's not like we heated up the yeast or froze them, added acids or put them in a centrifuge. We simply changed the carbon source and measured the effects of those four SNPs in the different environments."

Surprisingly, the researchers found that the effects of the four SNPs on spore production were dramatically different in the different environments. The effects of different combinations of SNPs in one environment were not an accurate predictor of the effects of those same SNPs in other environments.

For example, one combination of the four SNPs increased sporulation efficiency by 40 percent in glucose, but that same SNP combination increased efficiency by 80 percent when the yeast were grown in raffinose.

Indeed, the relative importance of particular SNPs and their interactions were not constant but varied with the genetic background of the yeast strain and the environment.

"Having a particular combination of SNPs was never a great predictor," Cohen says. "If we didn't know the environment in which the yeast were grown, we could not accurately predict the effect of the SNPs on producing spores. And if we can't make accurate predictions about the way environment influences complex traits in yeast, then it will be exceedingly difficult to do so in people."

The new research raises many questions: what is a human's environment and how can it be measured? Is the environment a person lived in during childhood important or the environment he lives in now?

Cohen suspects that any environment that matters is likely to leave a measurable molecular signature. For example, eating a lot of fatty foods raises triglycerides; smoking raises nicotine levels; and eating high-fat, high-sugar foods raises blood sugar levels, which increases the risk of diabetes. The key, he says, is to figure out what are good metabolic readouts of the environment and factor those into statistical models that assess genetic susceptibility to disease or response to medication.

"Measuring the environment becomes crucial when we try to understand how it interacts with genetics," Cohen says. "Having a particular genetic variant may not have much of an effect but combined with a person's environment, it may have a huge effect."

Cohen says he's not hopeless when it comes to personalized medicine. As scientists conduct ever-larger studies to identify rare and common variants underlying diseases such as cancer, diabetes and schizophrenia, they will be more likely to uncover variants that have larger effects on disease. Even then, however, a person's environment will be important,

he adds.

More information: Gerke J, Lorenz K, Ramnarine S, Cohen B. Gene-environment interactions at nucleotide resolution. Sept. 2010. PLoS Genetics.

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