

The good news in our DNA: Defects you can fix with vitamins and minerals

June 2 2008

As the cost of sequencing a single human genome drops rapidly, with one company predicting a price of \$100 per person in five years, soon the only reason not to look at your "personal genome" will be fear of what bad news lies in your genes.

University of California, Berkeley, scientists, however, have found a welcome reason to delve into your genetic heritage: to find the slight genetic flaws that can be fixed with remedies as simple as vitamin or mineral supplements.

"I'm looking for the good news in the human genome," said Jasper Rine, UC Berkeley professor of molecular and cell biology.

"Headlines for the last 20 years have really been about the triumph of biomedical research in finding disease genes, which is biologically interesting, genetically important and frightening to people who get this information," Rine said. "I became obsessed with trying to decide if there is some other class of information that will make people want to look at their genome sequence."

What Rine and colleagues found and report this week in the online early edition of the journal *Proceedings of the National Academy of Sciences (PNAS)* is that there are many genetic differences that make people's enzymes less efficient than normal, and that simple supplementation with vitamins can often restore some of these deficient enzymes to full working order.

First author Nicholas Marini, a UC Berkeley research scientist, noted that physicians prescribe vitamins to "cure" many rare and potentially fatal metabolic defects caused by mutations in critical enzymes. But those affected by these metabolic diseases are people with two bad copies, or alleles, of an essential enzyme. Many others may be walking around with only one bad gene, or two copies of slightly defective genes, throwing their enzyme levels off slightly and causing subtle effects that also could be eliminated with vitamin supplements.

"Our studies have convinced us that there is a lot of variation in the population in these enzymes, and a lot of it affects function, and a lot of it is responsive to vitamins," Marini said. "I wouldn't be surprised if everybody is going to require a different optimal dose of vitamins based on their genetic makeup, based upon the kind of variance they are harboring in vitamin-dependent enzymes."

Though this initial study tested the function of human gene variants by transplanting them into yeast cells, where the function of the variants can be accurately assessed, Rine and Marini are confident the results will hold up in humans. Their research, partially supported by the Defense Advanced Research Projects Agency (DARPA) and the U.S. Army, may enable them to employ U.S. soldiers to test the theory that vitamin supplementation can tune up defective enzymes.

"Our soldiers, like top athletes, operate under extreme conditions that may well be limited by their physiology," Rine said. "We're now working with the defense department to identify variants of enzymes that are remediable, and ultimately hope to identify troops that have these variants and test whether performance can be enhanced by appropriate supplementation."

In the PNAS paper, Rine, Marini and their colleagues report on their initial analysis of variants of a human enzyme called

methylenetetrahydrofolate reductase, or MTHFR. The enzyme, which requires the B vitamin folate to work properly, plays a key role in synthesizing molecules that go into the nucleotide building blocks of DNA. Some cancer drugs, such as methotrexate, target MTHFR to shut down DNA synthesis and prevent tumor growth.

Using DNA samples from 564 individuals of many races and ethnicities, colleagues at Applied Biosystems of Foster City, Calif., sequenced for each person the two alleles that code for the MTHFR enzyme.

Consistent with earlier studies, they found three common variants of the enzyme, but also 11 uncommon variants, each of the latter accounting for less than one percent of the sample.

They then synthesized the gene for each variant of the enzyme, and Marini, Rine and their UC Berkeley colleagues inserted these genes into separate yeast cells in order to judge the activity of each variant. Yeast use many of the same enzymes and cofactor vitamins and minerals as humans and are an excellent model for human metabolism, Rine said.

The researchers found that four different mutations affected the functioning of the human enzyme in yeast. One of these mutations is well known: Nearly 30 percent of the population has one copy, and nine percent has two copies.

The researchers were able to supplement the diet of the cultured yeast with folate, however, and restore full functionality to the most common variant, and to all but one of the less common variants.

Since this experiment, the researchers have found 30 other variants of the MTHFR enzyme and tested about 15 of them, "and more than half interfere with the function of the enzyme, producing a hundred-fold range of enzyme activity. The majority of these can be either partially or completely restored to normal activity by adding more folate. And that is

a surprise," Rine said.

Most scientists think that harmful mutations are disfavored by evolution, but Rine pointed out that this applies only to mutations that affect reproductive fitness. Mutations that affect our health in later years are not efficiently removed by evolution and may remain in our genome forever.

The health effects of tuning up this enzyme in humans are unclear, he said, but folate is already known to protect against birth defects and seems to protect against heart disease and cancer. At least one defect in the MTHFR enzyme produces elevated levels in the blood of the metabolite homocysteine, which is linked to an increased risk of heart disease and stroke, conditions that typically affect people in their post-reproductive years.

"In those people, supplementation of folate in the diet can reduce levels of that metabolite and reduce disease risk," Marini said.

Marini and Rine estimate that the average person has five rare mutant enzymes, and perhaps other not-so-rare variants, that could be improved with vitamin or mineral supplements.

"There are over 600 human enzymes that use vitamins or minerals as cofactors, and this study reports just what we found by studying one of them," Rine said. "What this means is that, even if the odds of an individual having a defect in one gene is low, with 600 genes, we are all likely to have some mutations that limit one or more of our enzymes."

The subtle effects of variation in enzyme activity may well account for conflicting results of some clinical trials, including the confusing data on the effect of vitamin supplements, he noted. In the future, the enzyme profile of research subjects will have to be taken into account in

analyzing the outcome of clinical trials.

If one considers not just vitamin-dependent enzymes but all the 30,000 human proteins in the genome, "every individual would harbor approximately 250 deleterious substitutions considering only the low-frequency variants. These numbers suggest that the aggregate incidence of low-frequency variants could have a significant physiological impact," the researchers wrote in their paper.

All the more reason to poke around in one's genome, Rine said.

"If you don't give people a reason to become interested in their genome and to become comfortable with their personal genomic information, then the benefits of much of the biomedical research, which is indexed to particular genetic states, won't be embraced in a time frame that most people can benefit from," Rine said. "So, my motivation is partly scientific, partly an education project and, in some ways, a partly political project."

Marini and Rine credit Bruce Ames, a UC Berkeley professor emeritus of molecular and cell biology now on the research staff at Children's Hospital Oakland Research Institute, with the research that motivated them to look at enzyme variation. Ames found in the 1970s that many bacteria that could not produce a specific amino acid could do so if given more vitamin B6, and in recent years he has continued exploring the link between micronutrients and health.

"Looked at in one way, Bruce found that you can cure a genetic disease in bacteria by treating it with vitamins," Rine said. Because the human genome contains about 6 billion DNA base pairs, each one subject to mutation, there could be between 3 and 6 million DNA sequence differences between any two people. Given those numbers, he reasoned that, as in bacteria, "there should be people who are genetically different

in terms of the amount of vitamin needed for optimal performance of their enzymes."

This touches on what Rine considers one of the key biomedical questions today. "Now that we have the complete genome sequences of all the common model organisms, including humans, it's obvious that the defining challenge of biology in the 21st century is not what the genes are, but what the variation in the genes does," he said.

Rine, Marini and their colleagues are continuing to study variation in the human MTHFR gene as well as other folate utilizing enzymes, particularly with respect to how defects in these enzymes may lead to birth defects. Rine also is taking advantage of the 1,500 students in his Biology 1A lab course to investigate variants of a second vitamin B6-dependent enzyme, cystathionine beta-synthase.

He also is investigating how enzyme cofactors like vitamins and minerals fix defective enzymes. He suspects that supplements work by acting as chaperones to stabilize the proper folding of the enzyme, which is critical to its catalytic activity. "That is a new principle that may be applicable to drug design," Rine said.

Source: University of California - Berkeley

Citation: The good news in our DNA: Defects you can fix with vitamins and minerals (2008, June 2) retrieved 2 May 2024 from <https://phys.org/news/2008-06-good-news-dna-defects-vitamins.html>

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