Hunting for the good news in the human genome

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Genetic factors influence the body's ability to metabolize folate, which is found in dietary sources such as leafy green vegetables.

One of the most common and most disabling birth defects, spina bifida strikes about one in 1,000 births in the United States -- nearly as many as Down's Syndrome. The cause of this often devastating disorder, characterized by an incomplete closing of the back bone and spinal cord, still befuddle scientists. But UC Berkeley geneticist Jasper Rine believes his research team may be on the verge of cracking its genetic mystery.

"Our research tends to use genetic methods to study biological problems in a manner that leads to insights about what happens to cells or organisms when individual genes are damaged," says Rine, a professor of genetics, genomics and development in the Department of Molecular and Cell Biology. His studies focus in large measure on exploring human

genetic variations and determining their functional consequences.

In his efforts to understand the genetic underpinnings of spina bifida, Rine and his colleague Nicholas Marini, along with collaborators at Children's Hospital of Oakland Research Institute and the California Birth Defects Monitoring Association, zeroed in on a well-known fact about the disease: its incidence can be dramatically reduced when the mother's diet is supplemented with folic acid, the synthetic form of folate, or Vitamin B-9, which is found in leafy greens. He is trying to understand the link between the disease and this phenomenon and thereby help unravel the genetic basis of the disease.

Rine's lab has sequenced all the genes involved in folic acid metabolism in two groups of 250 children each – one born with spina bifida and a control group. He compared them and found that the two populations have about 1,400 variants in those particular genes. Still to be determined, Rine says, is which if any of these variants are, in fact, causal for the disease. But he is confident that his research is making significant headway towards making that determination.

"I think we found a genetic signature for spina bifida, at least in some groups," Rine says, noting that so far his group has only studied these gene variations in Caucasian and Hispanic populations The incidence of spina bifida appears to differ among various ethnic groups. Rine hopes to help develop a test that could tell women whether they're at risk.

Rines's interest in the genetics of spina bifida is part a much larger research effort to explore human gene variations — including those responsible for folic acid metabolism — across the entire genome and to understand their impact.

All human beings have largely the same genome sequence of three billion bases, but each individual differs from all others in three million

positions on these bases, or about 1 in 1,000.

“I think the defining challenge of human biology for this century is to understand which of these 3 million differences actually matter, and if they matter, how they matter,” Rine says.

His ultimate goal is to understand what he calls “the good news in the human genome” — variants in genes that scientists can do something about once they unravel their genetic mysteries. That’s why folic acid metabolism is such a tempting target for research. Once its genetic mechanism is deciphered and the consequences of folate deficiency understood, we may be able to prevent or treat serious medical conditions with something as simple as a nutritional supplement.

“There are about 30 human proteins that are involved in folic acid metabolism," Rine says. "We’ve described a good fraction of all the variations likely to be found in these genes among humans, and we're trying to figure out which of these variants affect the function of the gene."

These gene variations, in turn, can affect the function of certain enzymes in such a way that the enzyme needs more or less of the vitamin to work properly.

Moreover, Rine's research built on earlier studies that revealed that 9 percent of the human population has a gene variant in an enzyme that makes their ability to metabolize folic acid especially susceptible to dietary choices. Folic acid is a key nutrient leading to the synthesis of a chemical known as S-adenosylmethionine, which can donate portion of itself, known as a methyl group, to either DNA or proteins, such as the histone proteins that control the gateways to the genome. By experimenting with cells grown in low versus high folic acid conditions, Rine and postdoctoral fellow Qiaoning Guan, found a ten-fold

difference in the level of chemical modification of histone proteins at various positions across the genome as a function of nutrition.

“I think this is very interesting and probably very important for those of us who have these variants in our metabolism," Rine says. "You would not want to be a strict carnivore if you're part of this 9 percent class because plants are the best source of folic acid.”

Rine performs this type of genetic research in culture dishes of human cells, and with a yeast, Saccharomyces cerevisiae, in which a key piece of DNA is removed and replaced with the corresponding human DNA. By using this simple and easy-to-manipulate organism, he gets around the inconvenient problem of those 3 million differences between corresponding cells of any two individuals.

"How would you know which mutation was responsible for which traits in comparing two different human cell lines considering two cell lines differ at millions of positions in their genomes? So we use yeast as the interpreter of the impact of human variation," he explains.

Ready for the genomic age?

Rine’s enthusiasm at unraveling secrets of our genetic makeup is effusive and contagious — so much so that he finds it hard to understand how anyone would not partake in his joy of discovery. After all, scientists like him are giving us the tools to gain access to our unique genetic inheritance and potentially improve our lives based on that knowledge.

That is the idea behind personalized medicine — to improve medical care by tailoring patient care based on individual genetic information. The promise of this rapidly-growing field seems to be boundless. But, as is often the case with scientific and technological advances, society is not as ready as scientists to embrace them.

"I think the field of genomics and personalized medicine has suffered because our scientific glee that comes with discovering a gene variant that spells the probability of a grim medical condition is not matched by the glee of individuals to learn that about themselves. In fact, much genetic information is considered to be frightening. My goal has been to try to find genetic information that if I told you about it for yourself you wouldn't be frightened. You could something about it."

Much of this fear is understandable, Rine says. The inexorable march of scientific discovery can be daunting. Worst of all, people fear that they may be handed a medical verdict they can do little about. But science, he reminds us, is not linear, which means that advances can happen very quickly in some medical areas.

"With sickle cell anemia we have made practically no advances since Pauling figured this out in the 1950s. Marfan's Syndrome (a genetic connective tissue disease) is something I didn't think we were going to treat until gene therapy became a reality. And suddenly there are people with Marfan's in drug trials."

Ideally, Rine would like to see the individual, not the medical professional, take ownership of his or her own genetic information. "It's crazy to think that doctors should be gatekeepers to our access to our own genetic information. It is unrealistic to expect any doctor to have comprehensive knowledge of all possible variations in the human genome. I think we should all have the freedom to be able to be purveyors and consumers of our personal genetic information without necessarily involving the medical professionals. It's really important that people make this decision personally and privately."

The age of personalized medicine is already upon us, no matter what anyone may think of it. Private companies like 23andMe use DNA analysis techniques to provide individuals with information about their

risk factors for disease, their response to certain medications, and various other health-related data. Ongoing discoveries will continuously add to this extraordinary body of information. Ultimately it is up to each individual to decide if and how to use it.

Rine has already obtained his genetic profile.

“It’s a way of turning into your own genetic makeup,” he says.

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