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Map Quest

New Genetic Tools May Reveal Roots Of Everyday Ills

Rapid DNA Tests Can Search Many Variations at Once; Probing Obesity, Memory

One Worry: Statistical Errors

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In Switzerland, a group of college students and local laborers sat down for a brief memory test a couple of years ago. They were given 30 words and then asked, five minutes later, to repeat them. On average, they recalled eight.



Dietrich Stephan

Last summer, American scientists equipped with a powerful new gene-testing technology gave this simple test an extra twist. DNA samples of the best and worst word-recallers were flown to Phoenix, where their DNA was checked with machines that can scour it for 500,000 genetic variations at lightning speed.

Researchers then fed the data into a computer that compared the variations against the test scores. The goal: to identify genes that may underlie short-term memory. They hope any discoveries could be used to treat memory disorders such as Alzheimer's disease.

The project is one of dozens now using the new tools -- which include a detailed map of how DNA varies among people and sophisticated microchips that detect those differences -- to search for genetic roots of some of humanity's most common traits. Geneticists have long been able to track down DNA defects involved in certain rare disorders such as Huntington's disease. But they haven't been good at finding genes for common diseases such as diabetes. Many common afflictions are more complex, believed to involve not one gene but several, and environmental factors as well.

With a condition like Huntington's, genetic detectives could identify a guilty gene by checking families prone to it. But with more complex disorders, a conspiracy of genes could be at work hidden within the broad population, making the detective work far harder, especially using older technology.

In the new system, small microchips are coded so that DNA from a blood sample sticks to them, allowing the chips to identify a host of genetic variations in the blood's DNA. Gene chips have been around for years, but only recently have they been able to identify hundreds of thousands of DNA variants in one fell swoop. The result is to permit broad searches in thousands of patients, known as "whole-genome association," many times faster than before.

This approach has spurred hot competition among top genetics labs to be the first to study various common diseases such as autism and depression. Studies of its feasibility are awaiting publication in leading journals. Today, the journal *Science* is publishing a study that says people with a certain gene variant are 22% more likely to be obese.

The technology may quickly uncover genes that influence one's odds of getting many everyday ailments, says Francis Collins, head of genome research at the National Institutes of Health. If so, it could transform wide areas of medical research. For instance, with the most common form of diabetes, called Type II, years of study using older methods have uncovered only three genes known to influence risk.

"I expect there are about 12 genes involved," Dr. Collins says, "and that all of them will be discovered in the next two years."

But there are many caveats. It's a "big question" how well the technology will perform, says Robert Waterston, a genome expert at the University of Washington. He says the genome-association studies entail a "critical assumption" that common diseases are influenced by common gene variants. If, instead, it turns out that rare versions of genes are to blame, he says, the new approach won't detect them.

The studies are rife with statistical pitfalls, leaving a chance that genes found using a whole-genome scan won't stand up to later scrutiny. That concern has led to caution by science journals, which have delayed publication of some results. A published paper detailing 12 possible genes for Parkinson's disease, based on a whole-genome study, will soon be disputed in newer research, according to scientists familiar with the matter.

If the studies of gene variants do prove as powerful as adherents believe, they are likely to raise thorny societal issues. That's because the same tools that can find variants that raise disease risk might identify genes that influence any measurable human trait, including height, weight or even intelligence.

Despite such cautions, within the genetic research community the technology is generating excitement. "Oh my God, it's unbelievable -- the air is crackling. Every day I hear rumors about studies coming out," says Dietrich Stephan, a senior scientist at Translational Genomics Research Institute, or TGen, the nonprofit Phoenix lab that analyzed the Swiss youths' DNA.

Dr. Stephan says the word-recall test fished out several genes that scientists hadn't previously linked to memory. It has given his team new ideas for possible treatments for conditions involving impaired memory. With scientists at Arizona State University, Dr. Stephan has launched an effort to test potential memory drugs in mice.

Pfizer Inc. has paid a start-up biotech firm \$23 million to search for genes underly-

ing patients' response to anti-depressants, among other research, using the new gene chips. That firm, Perlegen Sciences Inc. of Mountain View, Calif., recently filed for an initial public stock offering. The new technology might also help pharmaceutical companies find the causes of some of their drugs' unwanted side effects.

The new approach follows years of frustration and false leads in the field of genetics. Niel Risch, a geneticist at University of California, San Francisco, says that in the 1990s, researchers publicized findings that turned out to be statistical flukes. "You had the anxiety gene, the gay gene -- the papers were full of it, and none of it was true," he says.

Statistically, it's a simple matter to check whether differences in a single gene are associated with a higher chance a person will have a particular disease. But as Dr. Risch wrote in a 1996 article, when scientists have no idea what gene to check, they need a way to check all of the genes in the body at the same time. That wasn't then feasible, but teams of scientists were busily seeking to map the whole human genome, a project that was to succeed in a few years.

DNA is composed of repetitions of four chemical building blocks, which are known by the letters A, G, C and T. The full human genome consists of a combination of three billion letters and the code is nearly identical among any two people. However, about 0.1% of the letters commonly vary. Those variations are believed to lie behind many of the differences amongst people -- what they look like and how vulnerable they are to particular diseases.

The gene variants are called "snips," shorthand for single-nucleotide polymorphisms, or SNPs. A few years after Dr. Risch's 1996 article, government and industry launched a major effort to catalog them. It turned out to be costly and slow. In the most recent phase of the effort, the U.S. government, along with China, Japan and other nations, spent nearly \$139 million cataloging how more than one million SNPs varied among several groups, including residents of Nigeria, Tokyo and Beijing, and Americans of European background.

The next step is to compare SNPs from hundreds or thousands of sick individuals with those from healthy people. That will theoretically allow scientists to zero in on genes that underlie disease.

Until recently, collecting and analyzing

such detailed DNA information from hundreds of patients' blood would have been too costly. That changed recently. Last year, gene-chip pioneer Affymetrix Inc. of Santa Clara, Calif., and Illumina Inc. of San Diego each introduced miniature chips that can detect more than 300,000 genetic markers, or SNPs, at once. While the technology is still expensive, in the past nine months the price of some chips has fallen rapidly to around \$750 each, from \$1,200, according to Dr. Stephan.

The chips spurred a frenzy of activity in academic centers. The Broad Institute, in Cambridge, Mass., is tackling genetic research that "five years ago you couldn't do...for \$10 billion," says David Altshuler, a geneticist there. The NIH plans to spend up to \$30 million a year to fund studies using the technology.

Private charities are financing studies too. The National Multiple Sclerosis Society is raising more than \$4 million to support a consortium based at the Broad Institute and Harvard University, to study blood samples from 1,000 MS patients. TGen in Phoenix received about \$3 million to study genetic predisposition to Alzheimer's from a longevity clinic in that city owned by John Sperling, a wealthy entrepreneur.

There are early indications of how quickly the landscape for patients and doctors could change as a result. Within the past 12 months, scientists discovered links between three genes and macular degeneration, the leading cause of blindness in old age, including one link found using the new method. Variation in two of the genes appears to account for 75% of the risk of developing the eye disease, experts say. That's a greater effect than known behavioral risk factors such as smoking.

"To me, it means that individuals in the future will be screened, by giving blood, to show if they are susceptible," says Timothy Schoen of the Foundation Fighting Blindness, a nonprofit in Owings Mills, Md. People at high risk could be advised to get frequent eye exams and to eat dark-green vegetables, which are believed to offer some protection. Dr. Schoen says a screening test is already in development.

Others say the biggest effects could be for drug companies, which sometimes are stymied in developing treatments for diseases because their cause is a mystery. Edward Scolnick, former head of research at Merck & Co., is helping the Broad Institute of Cambridge, Mass., organize a study of one such illness, the psychiatric condition bi-

polar disease. If the team he works with can find a gene related to it and understand the gene's role, Dr. Scolnick says, "the rest of the world will pounce on that." Outside of medicine, agricultural powerhouse Cargill Inc. is funding whole-genome-association studies in cattle to hunt for genes involved in richly marbled beef. Consumer-goods giant Unilever PLC says it is also investing, studying a human trait, which it hasn't disclosed, to help design "new consumer products."

TGen, in operation for just over three years, is housed in a \$50 million new glass-and-concrete office building in Phoenix paid for by the city as part of an effort to bolster the region's health-care sector. A medical school under construction will offer a specialty in "personalized medicine." TGen's Dr. Stephan hopes the memory study involving the Swiss youths will be among the first to be published using the newest biochips.

The project got under way when Andreas Papassotiropoulos, a psychiatrist with joint appointments at TGen and the University of Zurich, told Dr. Stephan that he and another Swiss researcher had carried out word-recall tests and also collected blood samples. The 349 subjects, tested a couple of years ago, included University of Zurich students and laborers their age. The check of word recall after a five-minute lapse measured "episodic memory," says Dr. Papassotiropoulos, which is involved in remembering things such as the names of people one has just met. It suffers in conditions such as depression and Alzheimer's.

TGen got the DNA samples and used the new chips to scan all of the samples in less than a month. Dr. Stephan says the work turned up more than 100 gene variants that seemed to show up more frequently in people with good episodic memories. The researchers then repeated the experiments in two other groups, including 256 elderly people from the retirement community of Sun City, Ariz.

TGen researchers say they've narrowed their findings to what they believe to be five memory-related genes. Some of the findings might relate to Alzheimer's. Magnetic Resonance Imaging of patients with dementia showed improved brain activity in people with the beneficial form of one of these genes, Dr. Stephan says. TGen has submitted a report of its work to a scientific journal.