

Breaking News on Drug Discovery

Previous page : [NIH puts cash behind national screening network](#)

NIH puts cash behind national screening network

20/06/2005- In the US, the National Institutes of Health has awarded \$88.9 million in grants to nine institutions over three years to establish a collaborative research network that will use high-tech screening methods to identify small molecules that can be used as research tools.

The Molecular Libraries Screening Centers Network will be the world's largest collaborative network focused on drug discovery, according to the NIH, which said that data generated from the high-throughput assays conducted at the screening centres will be made available to researchers in both the public and private sectors through the PubChem database.

Each centre will have access to a library of 2 million compounds, which will be individually tested for medicinal properties using robotic screening instrumentation.

"This tremendous collaborative effort will accelerate our understanding of biology and disease mechanisms," said Elias Zerhouni, Director of the NIH, in a statement. *"More importantly, it will, for the first time, enable academic researchers to explore novel ideas and enable progress on a broad front against human disease."*

For example, the broad-based screening effort will eventually enable researchers to explore the hundreds of thousands of proteins believed to be encoded by the approximately 25,000 genes in the human genome. To date, only a few hundred human proteins have been studied in detail using small molecule probes.

Small molecules can be valuable tools for understanding the many important cellular events involved in health and disease, which is key to identifying possible new targets for diagnosis, treatment and prevention. To date, most useful small molecules have been found serendipitously. The molecular libraries screening program is an effort by NIH to take an efficient, high-throughput approach toward the discovery of many more useful compounds.

The network is part of the NIH's 'New Pathways to Discovery' initiative, which has set out to advance the understanding of biological systems and build a better toolbox for medical researchers. It will be overseen by a project team made up of staff from NIH's 27 institutes and centres.

One of the centres in the scheme, the Burnham Institute in San Francisco, said it plans to perform screens of the 2 million library compounds against at least 20 disease-targets per year, revealing specific compounds that interact with and inhibit disease-causing proteins.

Burnham's screening centre specialises in high-throughput automated microscopy, allowing for cell-based screens using high content imaging, as well as performing methods development in nuclear magnetic resonance (NMR)-based drug design, 3D computational modeling, and combinatorial chemistry.

The other centres in the network are: Columbia University Medical Centre, Emory University, Southern Research Institute, Scripps Research Institute, the University of New Mexico Albuquerque, Vanderbilt University, Pittsburgh University and the University of Pennsylvania.

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Posted on Sun, Jun. 26, 2005

Genetic testing races toward day when diseases can be predicted

BY RONALD KOTULAK
Chicago Tribune

CHICAGO - (KRT) - Doctors can now take a few of your cells, pull out the DNA, stretch it across a screen and diagnose more than 1,100 genetic defects that could mean trouble, ranging from rare disorders to more common ones like heart disease and cancer.

Surprising even the experts, genetic testing is racing ahead faster than doctors, genetic counselors and others can keep pace, driven by scientists eager to claim the prize of predicting diseases before they happen and perhaps preventing them.

The potential of the field raises questions for a public wary of peering into the genetic future and jaded by unfulfilled medical promises. How will people handle the news that ticking away in every cell of their body are potential disease genes inherited from their parents, which they in turn may have passed on to their children?

And everybody has them. Geneticists estimate that each person may have more than 30 genes that make them susceptible to a variety of disorders. A person's risk of developing a specific disease depends on which genetic combination he or she possesses in conjunction with environmental stressors arising from lifestyle choices or chemical exposure.

"Knowledge is a good thing when you can use it productively," said Dr. Wylie Burke, chief of medical history and ethics at the University of Washington. "But sometimes it's not a good thing. This whole genetic risk era is going to push us to think very carefully about that."

Many people are especially concerned about genetic discrimination - using abnormal genes to deny jobs or health insurance - and tests for genes that cause deadly illnesses for which there currently is no treatment, such as Huntington's disease.

A test for the Huntington's gene has been available for a decade, but it has been shunned by people at risk - children of parents with the disease - who don't want to live for years knowing the illness will start destroying their brain in midlife. And although an eight-year-old test can identify a gene associated with Alzheimer's disease, few physicians offer it to patients out of fear they might become despondent.

Still, some recent studies suggest people might be more willing to take the news in stride and act on it, especially if they are told the difference between a gene that causes a disease 100 percent of the time - as with Huntington's - and a gene that only increases their susceptibility, which is far more common.

Children of Alzheimer's patients whose genes were tested overwhelmingly accepted the genetic findings without becoming depressed or anxious, Dr. Robert C. Green of the Boston University School of Medicine reported last week at an Alzheimer's conference in Washington, D.C.

Those with the faulty gene also took steps to reduce their risk of contracting the disease, including exercising more, eating better, taking vitamins and engaging in mentally stimulating tasks, he said. "We found that learning you had a genetic risk marker made this more real to people and made them want to act on it," Green said.

Genetic testing was once mostly limited to newborns and people with single-gene disorders like Huntington's, but with the discovery in 1994 of two breast cancer genes, BRCA 1 and 2, the field rapidly expanded into the common adult killer diseases.

Between 1993 and 2004, gene tests jumped more than eleven-fold to 1,148, and the number of laboratories offering genetic testing increased more than fivefold to 577, according to the University of Washington's GeneTests Laboratory Directory, a federally supported agency that lists available genetic tests.

Genetic testing costs anywhere from a few hundred dollars to thousands per test. Many health insurance companies pay for them, depending on the type of coverage.

Scientists are racing to discover disease-related genes because they promise to open a new era of predictive medicine, where each individual will eventually know the genes that increase his or her risk of illness, and what they can do to head off those health problems.

"In the next three or four years there's going to be an absolute outpouring of discoveries about gene variances that are associated with the risk of diabetes, heart disease, cancer, asthma, high blood pressure, mental illness and other conditions," said Dr. Francis Collins, director of the National Human Genome Research Institute.

"It will allow us to individualize programs of preventive medicine so that you could plan your own diet and lifestyle and medical surveillance based upon your genetic risks as opposed to some broad generic prescription of activities, which is what we currently do," he said.

"The argument against genetic testing was really, 'Well, what are you going to do about it?'" said Dr. Olufunmilayo Olopade, director of the University of Chicago's Center for Clinical Cancer Genetics. "But I think cancer presents a unique opportunity for us because we know we can cure some cancers. We can prevent them."

Gene tests are available, for example, to diagnose people at risk of developing thyroid or colon cancer in their 30s or earlier. These cancers can be prevented through the removal of the thyroid or regular screening to remove polyps from the colon, Olopade said.

When Julie Spiekhouw was diagnosed with breast cancer in August, she decided to have a genetic test and found she carries the BRCA 2 gene.

That information persuaded Spiekhouw to have her ovaries removed, since the gene also increases the risk of ovarian cancer. The disease is difficult to diagnose early enough for a cure, and two of Spiekhouw's aunts died of it.

Spiekhouw also plans to discuss the BRCA 2 gene with her 8-year-old daughter, sister and cousins so they can start mammograms early to detect breast cancer in its most curable stage or prevent it with drug therapy.

"Being diagnosed with cancer used to just be a death sentence," said Spiekhouw, 39, of Highland, Ind. "Now, I never even thought that. My first thought was, what do I have to do to fight this? Give me the information I need and I'm going to do whatever I need to do."

Susceptibility genes, such as the BRCA genes and the one linked to Alzheimer's, indicate a level of risk rather than a foregone conclusion, Green said.

"They're sort of like finding out you have elevated cholesterol," he said. "It increases your chance of getting a disease, but it doesn't mean you're definitely going to get it."

People who have one copy of the Alzheimer's gene, ApoE4, are three to five times more likely to get the disease than people without it, Green said. Those with two copies are 20 to 30 times more likely to get it.

The study presented last week involved 162 people who had a parent with Alzheimer's disease. Half were told their genetic risk and the other half were not. A year later, there was no difference psychologically between the groups, Green said.

"Under carefully controlled circumstances, we are showing that people are handling information about susceptibility genes very well," Green said.

Yet considerable uncertainty remains about the public's willingness to accept genetic testing or how they will react.

Dr. David Rubin, director of clinical education for gastroenterology at the University of Chicago, said some people at risk for a genetic disease grieve when told they don't have the gene. They suffer guilt at not being affected when other family members are.

"People react differently," said Kelly Ormand, director of the graduate program in genetic counseling at Northwestern University's Feinberg School of Medicine. "Some see genetic knowledge as valuable and that it gives you options and allows you time to prepare if you need to prepare for something like Alzheimer's disease."

"There are some people who just don't want to know," she said. "They believe it will make them anxious. ` There's nothing I can do about it. What happens, happens."

Experts also are concerned that the rate of progress in discovering new disease genes is outpacing medicine's ability to use them to help patients.

"Some discoveries are so new we don't know how to use them yet in our practice," Rubin said. "You have a generation of physicians in practice who only learned simple genetics and haven't been able to keep up with some of the more complex advancements.

"It also takes time to gather a complete family history of disease and know what to do with it," he said. "Genetic counselors are in short supply and we're going to need more of them to help us understand how to interpret risk and what to do with it."

As genetic tests for common diseases become increasingly available, a backlash may build up if federal legislation is not passed to prohibit genetic discrimination, Collins said.

HIPPA, a federal law limiting access to medical records, provides genetic privacy for people with group health insurance. But for the growing number of people who have to obtain individual policies, there is no protection, he said.

A number of states have passed anti-genetic discrimination laws, but they are usually too weak to provide adequate protection, Collins said. In February the U.S. Senate unanimously passed a bill that would ban discrimination against people because of their genes. But the proposed legislation has stalled in the House, Collins said, because of strong objections from the health insurance industry and the U.S. Chamber of Commerce.

"The promise of genetic testing, which has a great deal of potential to keep people healthy and treat disease more effectively, could end up just not happening because of people's fear that this kind of information will be used against them," he said.

Families can consider compiling their own information about family diseases.

Paula Cardinale of Hammond knew that a gene for colon cancer had been found in a second cousin, but two years ago, at age 29, she thought the disease was "an older person's problem."

Then a pain in her side led her to have a CT scan, which disclosed a large mass that turned out to be colon cancer. A blood test would reveal she had the mutated gene hMLH1 that leads to the development of colon polyps, which quickly turn cancerous, before age 30.

"It's been a huge relief for me," said Cardinale, who is being treated at the University of Chicago. "I feel like I have more control of a very scary situation. They have specific screening for me to go through to protect myself because early detection is lifesaving."

Cardinale, who now undergoes regular checks but is cancer free, knows her children, Gina, 4, and Joey, 2, have a 50 percent chance of having inherited the faulty gene.

"What this has taught me is how I'm going to raise my children to think of gene testing and screening," she said. "When you find something like that in your family, it should just be known simply as preventive maintenance to keep you healthy, like getting your teeth cleaned twice a year."

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SECTION: OP-ED; Pg. E12**LENGTH:** 1480 words**HEADLINE:** PERSONALIZED MEDICINE
A NEW APPROACH TO STAYING WELL**BYLINE:** By FRANCIS S. COLLINS**BODY:**

So, what's in it for me? That question probably crossed many minds five years ago following the news that scientists had successfully assembled the first draft of the human **genome** the genetic blueprint of a human being. The answer for most of us was "not much."

What a difference five years can make. Today, we are witnessing a revolution in the understanding of health and disease, spurred on by the sequencing of the human **genome** and the subsequent creation of a map of human genetic variation. And, like most historic movements, this revolution has been given a name: personalized medicine.

At its most basic, personalized medicine refers to using information about a person's genetic makeup to tailor strategies for the detection, treatment, or prevention of disease. That may sound like a straightforward task, but it actually poses major scientific challenges when one considers that there are 3 billion letters in the human DNA code. This "instruction book" is 99.9 percent identical between any two humans. But how do we set about analyzing the 0.1 percent differences that holds clues to the variations among humans in susceptibility to disease?

Taking aim at that crucial 0.1 percent, a six-nation consortium, led by the US National Human Genome Research Institute and involving researchers from the Broad Institute of Harvard and MIT, recently produced a map of common patterns of human genetic variation, also known as haplotypes. Though the first phase of this "HapMap" was just completed in February, early uses have already led to the discovery of genes involved in susceptibility to common diseases, including diabetes, heart disease, osteoporosis, lower back problems, and blindness. Each one of these gene discoveries sheds new light on the biological basis of disease, which in turn provides new targets for therapies and new options for prevention.

Designing new drugs

Data on human genetic variation can be used to pinpoint genes responsible for the wide variability in people's responses to many common drugs a field referred to as pharmacogenomics. For example, a recent study published in the New England Journal of Medicine identified a gene that plays a central role in determining whether someone is likely to develop a dangerous reaction to warfarin, a blood-thinning medication often prescribed for people at risk for blood clots or heart attacks. Researchers are now trying to

translate those findings into a genetic test that could help doctors adjust warfarin doses to each patient's genetic profile.

Driven by advances in biotechnology and computer software, this newfound knowledge is swiftly making its way into the clinic. Thousands of cancer patients are already benefiting from a half-dozen targeted drugs, such as Gleevec, Iressa, and Tarceva, that are known to work better in people with certain genetic profiles. In fact, researchers from Massachusetts General Hospital and Dana-Farber Cancer Institute have developed a promising genetic test to identify the lung cancer patients who could benefit most from Iressa and other drugs that attack cancer in a similar way. These therapies represent the leading edge of a wave of many similar "designer" drugs that are expected to emerge from the research and development pipeline.

In another landmark move for personalized medicine, the US Food and Drug Administration recently approved the first laboratory test designed to use genetic information to help doctors select the most appropriate medications and doses of medications for their patients. This AmpliChip test analyzes two genes that code for enzymes involved in the metabolism of about 25 percent of all prescription drugs. Common variations in the gene sequence can cause an individual to metabolize these drugs more quickly or more slowly than average.

The FDA action has implications far beyond this individual product because it clears the regulatory pathway for the development of similar "DNA micro arrays." These tests employ technology similar to a computer microchip, but contain thousands of DNA probes rather than electronic circuits.

When DNA or RNA that has been isolated from a patient's blood, tumor, or other tissue is placed on the microarray, it is possible to determine what genes are turned on or off in that sample, and even what gene variations are present in that patient, by analyzing how his or her DNA or RNA binds to the chip.

Bumps in the road

Clearly, the era of personalized medicine is underway. But are we really ready for this revolution? Many healthcare professionals have not been trained to interpret and use the results of sophisticated genetic tests. Much remains to be done to enhance the knowledge of genetics and genomics among doctors, nurses, pharmacists, and social workers, as well as to facilitate the availability of referral networks of medical geneticists and genetic counselors. Universities, hospitals, and professional societies are all vital to this effort.

The public is also in urgent need of education and guidance. Even the savviest consumer is likely to have difficulty interpreting the onslaught of advertisements from companies trying to hitch their wagons to the personalized medicine star. These ads run the gamut from established medical laboratories offering tests for genes involved in susceptibility to serious diseases, such as breast cancer, to Internet opportunists making wild claims about being able to tailor diets or face creams to a person's DNA profile.

There is no way for consumers to gauge whether a genetic test is scientifically valid, let alone whether it is appropriate for them or reimbursable by their insurance companies. The lack of oversight of such tests leaves the average person vulnerable to misuses or misrepresentation of what personalized medicine truly is.

Still, personalized medicine remains one of the most compelling opportunities we have to improve the odds of staying healthy. By 2010, it is likely that predictive genetic tests will be available for as many as a dozen common conditions, enabling individuals to take preventive steps to reduce their risks of developing such disorders. Doctors will also begin tailoring prescribing practices to each patient's unique genetic profile, choosing medications that are most likely to produce a positive response.

By 2020, the impact is likely to be far more sweeping than any of us can envision today. New gene-based designer drugs will be developed for diabetes, heart disease, Alzheimer's disease, schizophrenia, and many other conditions that take a high toll on our society.

If technological development continues at the current dramatic pace, it is possible that each of us will be able to have our genomes sequenced for \$1,000 or less, possibly right in the doctor's office using microchip technology. That information can then be used to guide prescribing patterns and develop a lifelong plan of health maintenance customized to our unique genetic profiles. Achieving the \$1,000 genome will be no small feat. Currently, it costs about \$10 million to sequence a human-sized genome, so highly innovative DNA sequencing technologies are vital to turning this dream into reality.

To realize the full potential of personalized medicine, we must venture beyond the fields of science and medicine and into the ethical, legal, and social arenas. For example, without legislative protections against genetic discrimination in health insurance and the workplace, many people will be reluctant to undergo potentially life-saving genetic tests or to participate in the clinical trials needed to develop genetically targeted therapies. In February, the Senate passed the Genetic Information Nondiscrimination Act of 2005 by a vote of 98-0. The president has indicated strong support, but the bill remains before the House of Representatives, with no hearings scheduled. Given that more than 800 genetic tests are now available and hundreds more are on the horizon, we need this legislation.

Other tough questions that we as a society need to ask ourselves are: Will access to genomic technologies be equitable? Will knowledge of human genetic variation reduce prejudice or increase it? What boundaries will need to be placed on this technology, particularly when applied to enhancement of traits rather than prevention or treatment of disease? Will we succumb to genetic determinism, neglecting the role of the environment and undervaluing the power of the human spirit?

We obviously do not have all the answers yet. It will take much thoughtful research and vigorous debate among scientists, health-care professionals, ethicists, legal scholars, patient advocates, and ordinary citizens to chart the wisest course.

NOTES:

THINKING BIG FRANCIS S. COLLINS Dr. Francis S. Collins is director of the National Human Genome Research Institute, part of the National Institutes of Health in the US Department of Health and Human Services. He led the Human Genome Project, which was the international effort to sequence the human genome.

GRAPHIC: DRAWING

LOAD-DATE: July 19, 2005

[◀previous](#) Document 3 of 30. [next▶](#)

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THE NATION

Research Shows Drugs Could Block Early-Aging Disease

Cancer-fighters may help correct problems linked with the rare syndrome, studies say.

By Rosie Mestel
Times Staff Writer

August 30, 2005

Research groups at UCLA and the National Institutes of Health have discovered a potential treatment for a rare genetic disease in which children age prematurely and usually die by the time they reach their teens.

The finding, reported online today in the Proceedings of the National Academy of Sciences, showed that a class of cancer-fighting drugs corrected abnormalities in cells taken from patients with Hutchinson-Gilford progeria syndrome, which affects one in 4 million children.

The drugs might help prolong the children's lives or block a host of problems, such as poor growth, loss of hair and body fat, and atherosclerosis, scientists said.

The finding also opens a potential avenue of research into the causes of normal aging, they said.

Children who have the progeria syndrome, which was identified more than a century ago, appear normal when born but, within the first year, their growth slows dramatically. By about age 2, they have lost their hair. They generally never reach 4 feet in height nor surpass a weight of 35 pounds.

In 2003, a team of scientists led by Dr. Francis S. Collins, director of the NIH's National Human Genome Research Institute, reported that they had found the gene causing the defect. Known as LMNA, it directs creation of a protein called lamin A.

Under normal circumstances, lamin A proteins accumulate in a layer just inside the cell nucleus.

But in Hutchinson-Gilford progeria patients, lamin A never gets to its correct destination. Instead, it builds up on the membrane of the nucleus. The nucleus becomes misshapen, with bulging projections pushing into the cell's cytoplasm.

In the two separate papers, Collins' team and that of Drs. Stephen Young and Loren Fong at UCLA reported that they had eradicated the projections in human cells by using a class of drugs known as farnesyltransferase inhibitors.

Young and Fong had earlier shown the same effect using the drugs on mouse cells containing the defective human LMNA gene.

The drugs prevent lamin A from reaching the nuclear membrane so it cannot build up there.

The scientists are uncertain if the drug treatment will translate into a useful therapy.

The next step, both teams said, would be to treat mice genetically engineered with the human gene for Hutchinson-Gilford progeria. Collins said a human clinical trial could begin as early as spring if the results were promising.

Some farnesyltransferase inhibitors have been extensively tested for safety, including in children, because of their promise in fighting certain cancers. Several are in advanced clinical trials.

"We just really are phenomenally fortunate," said Dr. Leslie B. Gordon, medical director of the nonprofit Progeria Research Foundation, assistant professor of pediatrics at Brown University in Rhode Island and a co-author on Collins' team.

Gordon, who has a child with progeria, said it is unlikely that the drugs would have undergone such costly and extensive testing for progeria itself because the disease is so rare.

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THIS STORY HAS BEEN FORMATTED FOR EASY PRINTING

DNA technology brings personal gene maps closer

The Boston Globe

By Zara Herskovits, Globe Correspondent | August 15, 2005

When his newborn son was rushed into neonatal intensive care, unable to breathe, Jonathan Rothberg feared the worst. The biotech executive remembers wishing he could read his son's genes to help figure out what was wrong.

From a couch in the hospital, Rothberg began scratching on a yellow pad of paper, dreaming of a faster way to sequence genes.

Although he completed the initial sketches in a matter of weeks -- long after his son was released from the hospital in perfect health -- Rothberg has spent the past six years transforming these hopes into reality.

The team led by Rothberg, founder and chairman of 454 Life Sciences in Branford, Conn., is one of the two independent groups of researchers who recently reported that they have found faster and more cost-effective ways of decoding DNA, an advance that could ultimately transform how doctors treat cancer, HIV, and a wide range of other diseases.

One of the larger goals of this work is to slash the costs for sequencing an individual's genome to under \$1,000. The National Human Genome Research Institute, a branch of the National Institutes of Health, announced last week that it will award \$32 million in grants this year to improve DNA sequencing technologies.

Researchers predict that with an individual patient's DNA sequences in hand, doctors will know what diseases a person is at risk for, tailor treatments to their particular set of genes, and choose the most effective types and doses of drugs.

Using a strategy called 454 sequencing, Rothberg's group reported online July 31 in *Nature* that they had decoded the genome -- mapped a complete DNA sequence -- for a bacterium in four hours, a rate that is 100 times faster than other devices currently on the market. A second group of researchers based at Harvard Medical School, published a report in last week's *Science* describing how ordinary laboratory equipment can be converted into a machine that will make DNA sequencing nine times less expensive.

Mapping the first human genome took 13 years and cost \$2.7 billion. Current estimates put the cost of a single genome at \$10 million and \$25 million.

These new methods have already proven useful in clinics -- enabling doctors to tailor more effective drug regimens to combat lung cancer and HIV. Researchers have also used one of these strategies to figure out how a drug works against tuberculosis, leading to one of the first new TB medications discovered in the past 40 years.

"Traditional sequencing would have taken too long, have been too costly, and we simply wouldn't have done it" said Peter Verhasselt, research scientist at Johnson and Johnson who used the 454 method of DNA sequencing for TB research.

Widespread genetic sequencing presents new ethical dilemmas. Because there are no regulations protecting an individual's genome there is concern that this information could give health insurance organizations additional excuses to deny treatment. But ways to regulate the use of this information could be put into place, researchers say.

"Right now you can get lots of medical tests, and genome sequencing should be treated no differently in terms of privacy," said George Church, director of the Center for Computational Genetics at Harvard and author of

the Science paper.

Scientists have been hunting for ways to make DNA sequencing faster, cheaper and more reliable for the past 25 years. The new methods are more efficient because they work on a large number of short stretches of DNA at the same time, just as computer chips perform a large number of simple calculations simultaneously. The new sequencing methods are also speedier because they use digital technology to capture the information and fast computing to process it.

One of the unexpected advantages of this new method is that it yields more complete DNA sequencing than previous strategies. When Chad Nusbaum and colleagues at the Broad Institute, a center jointly run by Harvard and MIT, used the 454 method to look at the genome of a common fungus -- previously mapped with a different method -- they found that entire pieces of this organism's genetic code had been missed.

"We picked up about another 2 percent of the genome. Whether this is a general case or a special case I don't know, but we certainly learned something that we couldn't learn previously," Nusbaum said.

Conventional sequencing chops the genome into bite-sized pieces that are fed to bacteria to make more copies of the DNA so it's easier to sequence. Unfortunately bacteria don't pick up certain kinds of sequences. The newer methods sequence the DNA directly, without bacteria.

Because the human genome project was performed using the traditional method, there may be genes that are still unknown, said Nusbaum.

Another benefit to 454 sequencing is its sensitivity. One of the major problems for HIV patients, for instance, is that they can be infected with a mixture of viruses. Because some strains are resistant to medications, knowing the sequences of all viruses in a person's blood helps doctors select the best drugs for treatment. According to Michael Kozal at the Department of Medicine at Yale University, conventional methods can only detect HIV strains that constitute more than 10 to 20 percent of the total virus in the blood.

In comparison, 454 sequencing can pick up strains that make up 1 percent of the virus circulating in a person's blood. If doctors can attack all the strains, rather than just the most common ones, they will be able to slow the disease much more effectively.

Cancer is another area in which rapid DNA sequencing may help doctors pick the most effective drug to use for treatment. Since cancers evolve rapidly, tumors can contain a mixed population of cells with different types of mutations. Sequencing the genomes of many different cells in a tumor will help doctors predict whether the cancer will respond to a particular medication.

Fast DNA sequencing has also been used to develop new medications in the battle against tuberculosis, which kills millions worldwide every year. New medications are in great demand due to the rise of resistant strains that do not respond to any of the currently available drugs.

In a study published in Science in January, researchers at Johnson and Johnson selected organisms that were resistant to the new TB medication. Using 454 sequencing, the researchers read the entire genetic code of the resistant organisms and found one gene that enabled some strains to survive treatment with the drug.

They discovered that their tuberculosis medication is working on a completely new target, and this drug is now in clinical trials, said Verhasselt. ■

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Multi-Species Genome Comparison Sheds New Light On Evolutionary Processes, Cancer Mutations

07/21/05 -- An international team that includes researchers from the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH), has discovered that mammalian chromosomes have evolved by breaking at specific sites rather than randomly as long thought - and that many of the breakage hotspots are also involved in human cancer.

In a study published in the July 22 issue of the journal *Science*, a team of 25 scientists from the United States, France and Singapore compared the organization of the chromosomes of eight mammalian species: human, mouse, rat, cow, pig, dog, cat and horse. Using sophisticated computer software to align and compare the mammals' genetic material, or genomes, the team determined that chromosomes tend to break in the same places as species evolve, resulting in rearrangements of their DNA. Prior to the discovery of these breakage hotspots, the prevailing view among scientists was that such rearrangements occurred at random locations.



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"This study shows the tremendous power of using multi-species genome comparisons to understand evolutionary processes, including those with potential relevance to human disease," said NHGRI Scientific Director Eric D. Green, M.D., Ph.D. "The dog genome map generated by NHGRI researchers and their collaborators played a key role in these new analyses. Furthermore, the team took full advantage of the wealth of human, mouse and rat genome sequence data generated by the recently completed Human Genome Project."

Chromosomes are the threadlike "packages" of DNA located in the nucleus of each cell. When cells divide, a chromosome occasionally breaks and the fragment can get stuck onto another chromosome. In addition, fragments may break off from two different chromosomes and swap places.

Chromosomal breakages, also referred to as translocations, are thought to be important in terms of evolution. When chromosomes break in egg or sperm cells, opportunities arise for the rearrangement of DNA in the resulting offspring. Such inheritable rearrangements may be lethal or cause disease. However, in some cases, the breaks may lead to the production of new or altered proteins with potential to benefit an organism. In addition to their evolutionary implications, chromosomal translocations are known to contribute to the development or progression of many types of cancer.

In their paper, researchers report that the chromosomal abnormalities most frequently associated with human cancer are far more likely to occur in or near the evolutionary breakage hotspots than are less common types of cancer-associated abnormalities. Researchers theorize that the rearrangements seen near breakage hotspots may activate genes that trigger cancer and/or inactivate genes that normally suppress cancer. However, they emphasize that far more work remains to be done to clarify the relationship between cancer and the breakage hotspots. One thing researchers have determined is that the regions immediately flanking the breakage hotspots contain more genes, on average, than the rest of the genome.

The team was led by Harris A. Lewin, Ph.D., of the University of Illinois at Urbana-Champaign, and William J. Murphy, Ph.D., of Texas A&M University in College Station.

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Mapping data for the dog genome were provided by NHGRI's Elaine Ostrander, Ph.D., and Heidi G. Parker, Ph.D., along with scientists from the French National Center for Scientific Research at the University of Rennes. Other study participants were from the National Cancer Institute, the Genome Institute of Singapore and the University of California at San Diego.

"Science tells us that the most effective tool we currently have to understand our own genome is to compare it with the genomes of other organisms. With each new genome that we sequence, we move closer to filling the gaps in our knowledge," said Dr. Ostrander, who is chief of the Cancer Genetics Branch in NHGRI's Division of Intramural Research.

The multi-species comparison published in Science also yielded surprising results about the rate at which chromosomal evolution occurs. Based on an analysis that included a computer-generated reconstruction of the genomes of long-extinct mammals, researchers found the rate of chromosomal evolution among mammals dramatically accelerated following the extinction of the dinosaurs about 65 million years ago.

Before the sudden demise of dinosaurs and many other types of animals, which is thought to have resulted from a massive comet or asteroid striking Earth, mammals shared fairly similar body plans and also fairly similar genomes. Researchers speculate that the mass extinction opened new ecological niches for mammals, spurring their diversification and the emergence of new mammalian orders. This situation would have facilitated opportunities for the isolation of mammals into more distinct breeding groups, speeding the development of species-specific chromosomes.

"This study has revealed many hidden secrets on the nature and timing of genome evolution in mammals, and it demonstrates how the study of basic evolutionary processes can lead to new insights into the origin of human diseases," said Dr. Lewin, who is director of the Institute of Genomic Biology at the University of Illinois.

To learn more about the rapidly growing field of comparative genomics, go to: <http://www.genome.gov/11509542>. The genomes of a number of organisms have been or are being sequenced by the large-scale sequencing capacity developed by the Human Genome Project, which was led in the U.S. by NHGRI and the Department of Energy. A complete list of organisms and their sequencing status can be viewed at www.genome.gov/10002154.

High-resolution photos of dog, cat, cow, rat and other organisms under study by NHGRI's Large-Scale Sequencing Program are available at: www.genome.gov/10005141.

NHGRI is one of the 27 institutes and centers at NIH, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at its Web site, www.genome.gov.

Source: National Human Genome Research Institute

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