Research Policy ALERT

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NCI/NHGRI Cancer Genome Pilot Project RFAs Expected In Fourth Quarter 2005

June 13, 2005

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The National Cancer Institute and National Human Genome Research Institute expect to issue requests for applications in the last of quarter of this year for the pilot component of the Human Cancer Genome Project.

Resulting applications would be reviewed in early 2006, NCI Deputy Director for Advanced Technologies and Strategic Partnerships Anna Barker, PhD, told the June 8 meeting of the National Cancer Advisory Board. "With the pilot, everything the cancer institute does is going to be competitive," Barker noted.

Preliminary plans for the Cancer Genome Project were unveiled at NCAB's meeting in February ("The Blue Sheet" Feb. 21, 2005, p. 3). The ultimate aim of the project is to sequence the genomes of all major cancers. The project comes out of an NCAB working group on advanced biomedical technology that is co-chaired by Fred Hutchinson Cancer Research Center President Leland Hartwell, PhD, and Broad Institute Director Eric Lander, PhD.

In preparation for developing RFAs for the pilot, NCI and NHGRI plan to hold a meeting in July to gather "broad input" from the community. "Very few people agree on how to do this, so this should be an interesting meeting," Barker commented. The institutes expect to develop an outline for the pilot in August and then present the plan to NCI's Board of Scientific Advisors and NCAB in September.

A pilot is necessary, Barker explained, because of the magnitude of the project. "It's a huge project," she said. "Absolutely the right thing to do is to go through phases with this project – do a pilot, inform and deal with the issues, and then come back and scale the project up," if appropriate.

Sequencing the major cancer genomes is the equivalent of "about 150 Human Genome Projects," Barker said. "It's going to be potentially the largest and…most important paradigm shifting initiative that anyone's going to do in terms of cancer." It will "drive sequencing technology," she predicted.

Effective analysis of cancer DNA for the project poses several significant challenges. "Potentially the biggest problem we have is tumor heterogeneity," Barker said. "It's very, very hard to get people who sequence genes to understand" that cancers differ from each other.

"This is a problem that we have to solve to get meaningful data out of this project. Otherwise you're going to get noise and it's not going to do much for us."

The lack of standard definitions of cancer subtypes is another obstacle. "When we start talking about how you genetically define subtypes, that's a whole new set of problems for us," Barker said.

In addition, "the biospecimen collection issue, and annotation and distribution, is critical here, and we don't have this well controlled," Barker added.

Issues related to DNA quantity and quality pose another problem, she noted. Quantity and quality "is not always the same, and the idea of whole genome amplification, which is what you've got to do for cancer, is not trivial or simple. Some people are actually getting to the point where they can do this pretty well, but…it remains a barrier to do on a large scale."

The sequencing technologies themselves also present a challenge. "Resequencing is one approach," Barker said, adding that "there are lots of other ways to interrogate the genome other than just sequencing."

Another area of concern is detection of epigenetic changes – heritable changes in genome function that occur without alterations in DNA sequence. "It has come to our attention that the epigeneticists are not happy because they want to do the epigenome," Barker said. "So we are trying to sort out how we actually incorporate some of these questions, and I think there is an idea floating around in that regard."

Data analysis and collection, "and even the portrayal of this data, is daunting," Barker continued. "Think about…putting multiple genome sequences in databases. We have no history of doing that, and so how are we going to actually protect patient privacy? How are we going to…protect the investigators' ability to publish?" she asked. "These are huge issues, all of which have to be dealt with."

"The good news," Barker concluded, "is that the NCI is probably the place to solve these problems because we have the synergy that I believe is going to be required to actually deal with this issue." The project "cannot occur in a vacuum," she explained. "To create this mutation atlas is going to take collaboration in all of these areas."

-- Janet Coleman

Printed By OD DER Firm:(NHGRI-NIH) on [June 13, 2005]

Next in line for genome sequencing

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Celeste Biever

Mammalian genomes

WHAT do pangolins, sloths and gibbons have in common? They are all in line to have their genomes sequenced.

Last week the National Human Genome Research Institute in Bethesda, Maryland, announced a diverse list of target species that includes nine mammals: the pangolin, 13-lined ground squirrel, megabat, microbat, tree shrew, hyrax, sloth, bushbaby and northern white-cheeked gibbon.

The idea is that by comparing the human genome to mammals that evolved from the same distant ancestor, we can identify shared or conserved DNA sequences. Conserved sequences have survived in different species because they have an important function - at least that's the theory (*New Scientist*, 5 June 2004, p 18). For the purpose of comparison, only rough, low-quality drafts of the genomes are needed.

The gibbon was chosen for a different reason. Its DNA appears to undergo 10 times as many gene rearrangements as other primates. Because such rearrangements are also common in patients with cancer and other diseases, a deeper understanding of why they occur in gibbons could reveal what causes them in diseases too.

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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 Spiekhout 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 Spiekhout 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 Spiekhout's aunts died of it.

Spiekhout 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 Spiekhout, 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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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.

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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.

"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.

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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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 mispresentation 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

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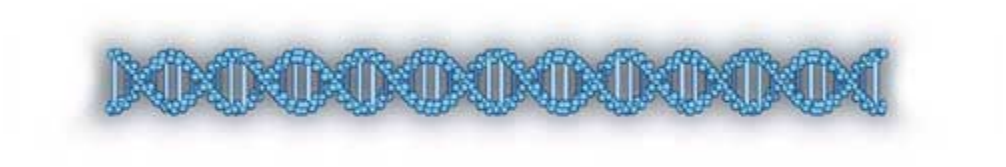
U.S. News and World Report
Science: Superfast DNA sequencing



Posted 8/4/05
By Helen Fields

The Human Genome Project took 13 years and $2.7 billion to come up with the complete sequence of human DNA. This week in the journals *Nature* and *Science,* two research groups have published the first wave of new, superfast sequencing methods; in a few years, scientists hope that these methods and others like them will let one human's DNA be sequenced for less than $100,000, ushering in a new era of data-based personalized medicine.

One new technique, published July 31 in *Nature,* is already commercially available as a $500,000 machine that uses a credit-card-size chip with about 1.6 million tiny wells; each well holds a tiny bead attached to 10 million copies of one short fragment of DNA. The machine sequences by washing the four bases that make up DNA—adenine, cytosine, guanine, and thymine—across the chip one at a time; if a base finds its partner in a fragment of DNA, it binds there and lets out a flash of light, which the chip's fiber optics detect.

Recently, this technique has managed to read more than 100 million bases in five hours. The method used now to sequence DNA can manage only about 67,000 bases in a one-hour run. Like computer chips, the method should get faster and cheaper all the time, says Jonathan Rothberg, founder and chairman of 454 Life Sciences Corp., the company that sells the machines. With one of his sequencers, he says, one person can do the work of a hundred people and millions of dollars' worth of robots, sequencing an entire genome in a few hours.

The other technique published this week uses equipment that many labs already have, says Harvard genetics professor George Church, whose team published the paper in *Science* [www.sciencexpress.org]. In their method, all four bases are marked with different colors, and are flowed across a chip simultaneously. A camera mounted on a microscope takes pictures of the different-colored bases as they attach. "Our goal is to say anybody could do this," Church says. His paper includes step-by-step instructions, although steps like "add 800ul NX2 buffer (100mM NaCl, 10mM Tris-HCl pH 7.5, 1 mM EDTA, 0.1% Triton X-100)" might be hard to follow at home—if not in the lab.

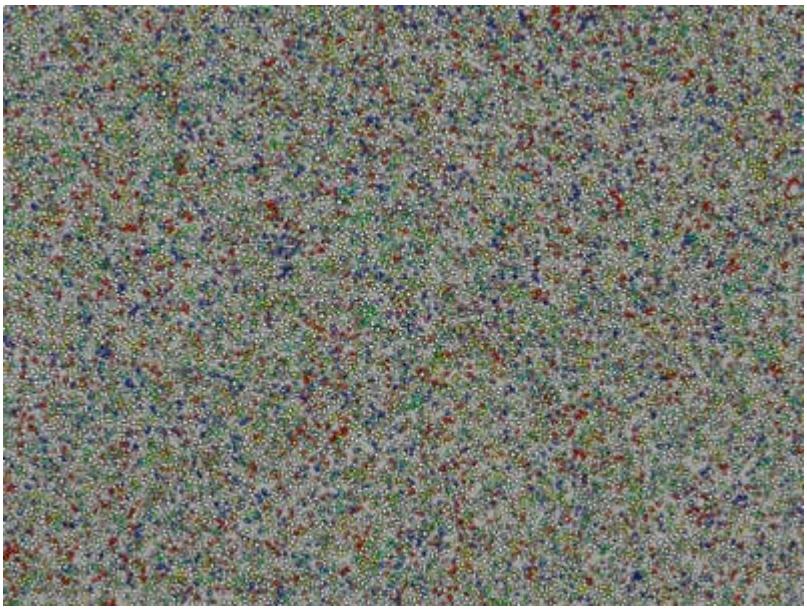
Both of these methods are part of a push by the National Human Genome Research Institute to dramatically reduce the cost of sequencing one person's genome—and improve their medical care. It's analogous to checking a patient's blood type before giving them a transfusion, says George Weinstock, co-director of the Human Genome Sequencing Center at Baylor College of Medicine. If scientists know that, say, prostate cancer patients with a particular mutation in a particular gene get better when they're given a particular cancer drug, having the sequence of that gene would help.

"Now you take all of your genes and multiply across all of the possible things we know about-diseases, responses to medicine, issues for surgery, blood types," Weinstock says. One day, he predicts, a doctor will be able to tell what's wrong with you by plugging your genome's sequence into a computer.

4 August 2005

Cut-Rate Genomes on the Horizon?

Given the exorbitant cost of deciphering genomes, most labs have given up sequencing and left that job to the big sequencing centers. But now, two groups have published methods that may make sequencing much cheaper and faster, promising small labs a chance to do it on their own.



Modern art, sequencing style. The color of each bead used in George Church's technology indicates the next identified base in a sequence. White beads have no DNA.

CREDIT: Jay Shendure and Greg Porreca/Harvard Medical School

Researchers all over the world still depend on a sequencing method introduced decades ago by Fred Sanger of the Laboratory of Molecular Biology in Cambridge, U.K. It uses bacteria to amplify the DNA and expensive reagents to label bases for identification. The cost has dropped since the mid-1990s from more than $1 to less than a 10th of a cent per base. But it's still high for many projects, including medical uses such as checking the genomes of individuals.

The new methods--one developed by George Church, a computational biochemical engineer at Harvard Medical School in Boston, and colleagues, and the other by Jonathan Rothberg, founder of 454 Life Sciences Corp. in Branford, Connecticut--save money by eliminating the need for bacteria and miniaturizing the process. In lieu of bacteria, DNA is attached to aqueous beads encased in oil,

where chemical reactions do the copying. That change alone could reduce by two-thirds the costs associated with space and personnel, says Edward Rubin, director of the U.S. Department of Energy Joint Genome Institute in Walnut Creek, California. Moreover, both methods perform many thousands of these sequencing reactions at once in miniature "reactors," further bringing down the cost.

Once the DNA is ready, the two technologies diverge: The 454 technique puts the beads on a fiber-optic chip and uses flashes of white light to identify the bases. Rothberg washes the chip surface with one base at a time, creating four light patterns that a computer puts together as a sequence. He describes 454's success in sequencing *Mycoplasma genitalium* online 31 July in *Nature*.

Church's technique employs a microscope and other off-the-shelf equipment that use bursts of different fluorescent colors to distinguish the bases. Via this method, his team sequenced a strain of *Escherichia coli* and was able to detect easy-to-miss, single-base-pair changes from an almost identical *E. coli* genome. Church's group reports its results online today in *Science*.

Neither method is up to speed yet. The accuracy of both "should be improved by at least one order of magnitude," says Mostafa Ronaghi, a biochemist at Stanford University in Palo Alto, California. Also, to sequence mammalian genomes, the length of sequence generated, the "read," should be about 700 bases, but reads with these new approaches are hovering between 26 and 110 bases.

Whatever their limitations, the two reports signal the dawn of a new era in genome sequencing and detecting changes in individual genomes. Last year, the U.S. National Human Genome Research Institute in Bethesda, Maryland, began a program aimed at decreasing the cost of sequencing mammalian genomes to $100,000 in 5 years and to $1000 5 years later. That's what many think it will take for sequencing to become affordable in small labs.

--ELIZABETH PENNISI

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Church's site
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The Seattle Times
seattletimes.com

Sunday, August 7, 2005 - 12:00 AM

Guest columnist

Exploring the frontiers of life

Francis S. Collins

By Francis S. Collins
Special to The Times

America is in the middle of a three-year commemoration of the Lewis and Clark Expedition in search of a watery Northwest Passage to the Pacific. November 2005 marks the 200th anniversary of their arrival on the Pacific Coast. A year later, in 1806, Lewis and Clark presented President Thomas Jefferson with the first map of the American Northwest, an image that defined a nation.

Another group of explorers, almost 195 years later, presented a president with a different kind of map — the map of the human genome. Another Jefferson, William Jefferson Clinton, drew a comparison to Lewis and Clark, saying of the human genome sequence: "Without a doubt this is the most important, most wondrous map ever produced by humankind," an image that defines humanity.

Both presidents knew a truth: Maps show the way. The information contained empowers. But a map alone is not enough. As in the case of western expansion, pioneers had to follow the path marked by Lewis and Clark. They had to move their families to the Pacific Northwest, till the land, and build the great industries and cities if Jefferson's vision of America were to be fulfilled.

The same is now true of the map of the human genome. The Human Genome Project, the international collaboration that produced the genomic map, was completed in April 2003, the 50th anniversary of the James Watson-Francis Crick discovery of the structure of DNA, the molecule that carries the code of heredity.

Researchers around the world now mine the genome's freely available information to understand how our bodies work and to produce new treatments when something goes wrong. Only when this medical promise is fulfilled, and appropriate policy decisions have been made that will maximize benefits, will the vision of the Human Genome Project be realized.

The Pacific Northwest is a leader in this pioneering work. The University of Washington is home to some of the most creative people in the field of genomics. That is why my organization, the National Human Genome Research Institute (NHGRI), has invested more than $30 million over five years in two Centers of Excellence in Genomic Science at UW. There are only nine such centers in the whole country, and no other institution has more than one. The two UW centers focus on understanding how cells use genomic information, how people differ at the genetic level, and why those differences lead to inherent risks of illnesses.

The federal government primarily invests in fundamental scientific questions and the new techniques necessary for this exploration. As insights and knowledge emerge from such studies, industry must convert that knowledge into medical advances that will help patients. Again, the Pacific Northwest and its vibrant biotech industry can be expected to lead.

It is safe to predict that these scientific advances and technological changes will profoundly change the future of medicine — as well as society. That is why NHGRI invests about 5 percent of its budget into the study of the ethical, legal and social implications of genomic science, what we call the "ELSI" program.

Here again, UW is a leader, receiving one of NHGRI's first Center of Excellence in ELSI Research grants — nearly $5 million for the university's Center for Gen-omic Health Care and the Medically Underserved, to understand the social factors that influence the translation of genetic information to improved human health.

Understanding the social impacts of advances in genomics is not a task for researchers alone. Communities need to find their own voices and scrutinize their own values to determine how genomic information should be used. Recently, the University of Washington partnered with NHGRI to host a community engagement at which more than 400 of your neighbors came to campus to learn about genomic science and to discuss its implications.

We all need to learn a lesson from an aspect of the Lewis and Clark expedition that did not go so well — the lesson of listening to the voices of the community. Lewis and Clark brought back knowledge that opened up the Pacific Northwest to European settlers. But the land was not vacant. American Indians already lived throughout the region. When the white settlers came, bitter conflicts arose and, in the end, many indigenous peoples were pushed aside.

We must ensure that we do not push anyone aside as genomic exploration proceeds. We need to make sure that unjust actions, such as those inflicted upon the American Indians 200 years ago, are not repeated as we strive to build a new life in this rapidly expanding gen-omic frontier.

The risks now are of a different sort, but they are compelling. Consider the current case of NBA center Eddy Curry, 22, the youngest player ever drafted by the Chicago Bulls. This spring, doctors discovered that Curry had an enlarged heart and an irregular heartbeat. There is concern that he may have a condition, called hypertrophic cardiomyopathy, that can have a genetic cause.

A gene test can detect 60 percent of people who inherit a mutation that puts them at risk, and the Bulls wanted Curry to take the test — but at what consequence? If he has the genetic mutation, is his career over? Does he lose his job because of a genetic test? How about his health insurance? And if the test is negative, does that really mean he is not at risk, since 40 percent of those with the genetic predisposition cannot be detected by the current test? Might he still suddenly die if he continues to play?

Granted, star athletes may be different as they are handsomely paid to take the risk of injury from their sport. But what about someone working on the railroad? A couple of years ago, the Burlington Northern Santa Fe Railway tested the genes of injured workers, without their permission, to try to detect a genetic predisposition to carpal tunnel syndrome. The railway, apparently, was looking for a way to avoid workman's compensation claims by using an unproven genetic test. Only media coverage and action by the U.S. Equal Employment Opportunity Commission stifled those threats.

If it can happen on the railroad, genetic discrimination can happen anywhere. Many surveys have, in fact, documented public concern about this. For Americans to benefit from the Human Genome Project without fear, we need more secure protections. We need a federal anti-discrimination law.

In 2003 and again in this 2005 session, the U.S. Senate passed a bill to prohibit discrimination on the basis of genetic information with respect to health insurance and employment. That bill — introduced by Sen. Olympia Snowe, R-Maine, but with co-sponsors including Sens. Maria Cantwell and Patty Murray, Democrats of Washington — now awaits action in the U.S. House of Representatives. The legislation is supported by the Bush administration and if enacted into law would ensure that no one in America would lose their jobs or their health insurance because of a genetic test result.

At stake is nothing less than your health and perhaps the health of the Seattle economy. The biotech companies that hope to prosper in this new era of genomic science will not get far if the public refuses to accept their products because of discrimination fears. We need to avoid the unintended consequences of the new knowledge. We need to ensure that these coming revelations about the genome provide benefits to all Americans.

Dr. Francis S. Collins is the director of the National Human Genome Research Institute, one of the 27 institutes and centers making up the National Institutes of Health, in Bethesda, Md. He was a guest speaker on May 21 at "A Community Forum on Genetics: DNA, Health and Social Justice" in William H. Gates Hall at the University of Washington Law School.

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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. ■

Los Angeles Times
latimes.com

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.

USA TODAY

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Newly decoded, chimp DNA holds promise for humans

NEW YORK (AP) — Scientists have deciphered the DNA of the chimpanzee, the closest living relative of humankind, and made comprehensive comparisons with the human genetic blueprint.

It's a step toward finding a biological answer to a key question: What makes us human?

There are no firm answers yet about how humans picked up key traits such as walking upright and developing complex language. But the work has produced a long list of DNA differences with the chimp and some hints about which ones might be crucial.

"We've got the catalog, now we just have to figure it out," said Dr. Robert Waterston of the University of Washington School of Medicine in Seattle. "It's not going to be one gene. It's going to be an accumulation of changes."

He is senior author of one of several related papers appearing in Thursday's issue of the journal Nature and being published online Thursday by the journal Science.

In the papers, Waterston presents a draft of the newly deciphered sequence of the chimp genome, in which an international team of researchers identified virtually all the roughly 3 billion building blocks of chimp DNA.

"It's a huge deal," said Dr. Francis Collins, director of the National Human Genome Research Institute, which provided some support for the project. "We now have the instruction book of our closest relative."

He said the work will help scientists analyze human DNA for roots of disease.

While the DNA comparisons don't firmly identify specific differences that played a big role in producing humans, they do indicate promising areas, said Bruce Lahn, who studies human evolution genetics at the University of Chicago but didn't participate in the project. Lahn said the research refutes a few previous ideas while providing new and better evidence for others.

Humans and chimps have evolved separately since splitting from a common ancestor about 6 million years ago, and their DNA remains highly similar — about 96% to almost 99% identical, depending on how the comparison is made.

Still, the number of genetic differences between a human and a chimp is about 10 times more than between any two humans, the federal genome institute says. It's the differences — some 40 million — that attract the attention of scientists.

Waterston and colleagues, for example, looked for genes that apparently have changed more quickly in humans than in chimps or rodents, indicating they might have been particularly important in human evolution. They found

evidence of rapid change in some genes that regulate the activity of other genes, telling them when and in what tissues to become active, for example.

It would make sense that changes in these regulatory genes could have a broad impact on how organisms develop, playing a key role in human evolution, Waterston said.

With help from the chimp DNA, his team also uncovered several regions of human DNA that apparently contain beneficial genetic changes that spread rapidly among humans within the past 250,000 years. One area contains a gene called FOXP2, which previous work has suggested is involved in acquiring speech.

Svante Paabo of the Max Planck institute for Evolutionary Anthropology in Leipzig, Germany, and colleagues report in the Science paper that genes active in the brain have changed more in the human lineage than in the chimp lineage. That wasn't the case for genes from other organs such as the heart and liver.

In a telephone interview, Paabo said that in general, "I'm still sort of taken aback by how similar humans and chimps are" in their DNA. "I'm still amazed, when I see how special humans are and how we have taken over this planet, that we don't find stronger evidence for a huge difference in our genomes."

He said he believes the key differences between the species will prove to be subtle things such as patterns of gene activity and how proteins interact.

In fact, Waterston and co-authors said they hoped documenting the overall similarity of chimp and human genomes will encourage action to save chimps and other great apes in the wild:

"We hope that elaborating how few differences separate our species will broaden recognition of our duty to these extraordinary primates that stand as our siblings in the family of life."

Find this article at:
http://www.usatoday.com/tech/science/genetics/2005-08-31-chimp-genes_x.htm

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THE NATION

Man, Chimp Separated by Dab of DNA

A new comparison of genetic blueprints shows that just a handful of mutations account for the vast differences between the species.

By Karen Kaplan
Times Staff Writer

September 1, 2005

Answering a key part of the age-old question of what makes us human, scientists on Wednesday unveiled a genetic comparison of people and chimps, revealing that changes to a mere sliver of DNA make it possible for us to walk upright, compose piano concertos and fall victim to cancer.

Those changes amount to 200,000 of the 3 billion chemical letters that make up the human genetic code that have occurred in the 6 million years since *Homo sapiens* and chimpanzees diverged from a common ancestor — a relative blip in the history of life on Earth.

Like other mammals, humans and chimps have seen rapid evolution in genes related to immune response, reproduction and smell. But humans and chimps have outpaced other mammals in evolving sophisticated genes related to hearing and brain function, the researchers found.

Researchers also identified six regions where genetic mutations appear to have spread rapidly throughout the human population in the last 200,000 years.

One of those regions contains a gene, FOXP2, that is associated with speech development in humans.

Another hot area has been associated with obesity.

In the interconnected world of genetics, the myriad mutations have also made humans susceptible to cancer, Alzheimer's disease, malaria, AIDS and other ailments that don't occur in chimps, said Dr. Robert Waterston, chairman of the Department of Genome Sciences at the University of Washington School of Medicine in Seattle and a leader in the study.

The results, published in a flurry of papers in the journals Nature and Science, provide a roadmap for studying diseases and the mechanisms by which humans evolved into the dominant species of Earth.

"This is telling us about those changes that make us human," said Eric Lander, director of the Broad Institute of MIT and Harvard University in Cambridge, Mass., one of 67 researchers in five countries who worked on the project.

The chimp DNA was taken from a male named Clint at the Yerkes National Primate Research Center in Atlanta. He died last year of heart failure at age 24.

The resulting genome overlaps with 96% of the human genome, and the corresponding sequences are 99% identical, the researchers found.

That high degree of similarity is what makes the chimp genome useful in studying human DNA.

"The human genome itself is just a parts list," Lander said. "The human genome with the chimp genome tells us how these parts have changed."

The scientists found a total of 40 million genetic differences between humans and chimps. About 35 million involved a change in a single DNA nucleotide, commonly known by the letters A, T, C and G. The remaining 5 million discrepancies involved genes that were inserted or deleted in either the human or chimp genome.

Most mutations are of little consequence, occurring in the vast regions of the genome that are not used to make proteins. Only about 200,000 of the mutations are in the functional part of the genome, Lander said.

The overwhelming similarity of the human and chimp genomes, and the incremental nature of the changes that set them on different developmental paths, validate the mechanics of evolution, project researchers said.

At a time when the theory of evolution is under attack by proponents of "intelligent design," Dr. Francis S. Collins, director of the National Human Genome Research Institute, said he could not think of a better way to prove the theory of evolution "short of a time machine."

The genome research agency, part of the National Institutes of Health, funded the study at a cost of $20 million to $30 million.

The scientists found that evolution was more flexible — and in some ways simpler — than many had previously thought.

There has been a debate about whether evolutionary advances depend on big changes in a few genes, or small changes in many genes.

Dr. Christopher A. Walsh, a neurology professor at Harvard Medical School, said the studies showed that a small number of changes were enough, demonstrating the power of evolution to respond to circumstances.

"You don't have to wait for 100 different changes to occur simultaneously for something to

happen," Walsh said.

Scientists found six areas of the human genome that were overcome with mutations during a period of rapid and widespread change, an event called a "selective sweep." These areas are remarkably similar, indicating that the changes occurred roughly within the last 200,000 years.

As an example, Landers cited the emergence of the gene for digesting lactose, which allows humans to drink milk from animals. The mutation would confer an evolutionary advantage, helping it to spread quickly and maintain its original form.

Researchers still don't know the significance of the selective sweeps they identified. But in studying them, they can make inferences about disease outbreaks and other events that would have sparked such vast genetic change, said Evan Eichler, a geneticist at the University of Washington who worked on the study.

Research groups around the world are now tackling different pieces of the human genome in the hopes of unraveling the complexities of disease and the forces that shaped human development.

"Maybe in 20, 30, 40, 50 years it will tell us why our brains are twice as big," said Richard K. Wilson, director of the Genome Sequencing Center at Washington University School of Medicine in St. Louis. "This is a place to start trying to answer those questions."

But Collins, of the National Human Genome Research Institute, cautioned that genes could not solve all of the mysteries of life.

"The real question about what it takes to be human is more than a biological question, it's also a theological question," Collins said. DNA "may not tell us 'How do we know what's right and wrong?' and 'What's the human spirit, anyway?' "

The New York Times
nytimes.com

September 1, 2005

In Chimpanzee DNA, Signs of Y Chromosome's Evolution

By NICHOLAS WADE

Scientists have decoded the chimp genome and compared it with that of humans, a major step toward defining what makes people human and developing a deep insight into the evolution of human sexual behavior.

The comparison pinpoints the genetic differences that have arisen in the two species since they split from a common ancestor some six million years ago.

The realization that chimpanzees hold a trove of information about human evolution and nature comes at a time when they and other great apes are under harsh pressures in their native habitat. Their populations are dwindling fast as forests are cut down and people shoot them for meat. They may soon disappear from the wild altogether, primatologists fear, except in the few sanctuaries that have been established.

Chimpanzees and people possess almost identical sets of genes, so the genes that have changed down the human lineage should hold the key to what makes people human.

Biologists suspect that only a handful of genes are responsible for the major changes that reshaped the apelike ancestor of both species into a human and that these genes should be identifiable by having evolved at a particularly rapid rate.

The comparison of the human and chimp genomes, reported in today's issue of Nature, takes a first step in this direction but has not yet tracked down the critical handful of genes responsible for human evolution.

One problem is the vast number of differences - some 40 million - in the sequence of DNA units in the chimp and human genomes. Most are caused by a random process known as genetic drift and have little effect. For now, their large numbers make it difficult for scientists to find the changes caused by natural selection.

But another aspect of the comparison has yielded insights into a different question, the evolution of the human Y chromosome. The new finding implies that humans have led sexually virtuous lives for the last six million years, at least in comparison with the flamboyant promiscuity of chimpanzees.

Some 300 million years ago, the Y chromosome used to carry the same 1,000 or so genes as its partner, the X chromosome. But because the Y cannot exchange DNA with the X and update its genes, in humans it has lost all but 16 of its X-related genes through mutation or failure to stay relevant to their owner's survival. However, the Y has gained some genes from other chromosomes because it is a safe haven for genes that benefit only men, since it never

enters a woman's body. These added genes, not surprisingly, all have functions involved in making sperm.

The scientific world's leading student of the Y chromosome, David Page of the Whitehead Institute in Cambridge, Mass., has been seeking to understand whether the Y will lose yet more genes and lapse into terminal decay, taking men with it.

The idea of the Y's extinction "was so delicious from the perspective of gender politics," Dr. Page said. "But many of my colleagues became confused with this blending of gender politics with scientific predictions."

Two years ago, he discovered a surprising mechanism that protects the sperm-making genes. Those genes exist in pairs, arranged so that when the DNA of the chromosome is folded back on itself, the two copies of the gene are aligned. If one copy of the gene has been hit by a mutation, the cell can repair it by correcting the mismatch in DNA units.

The 16 X-related genes are present in only single copies. Dr. Page and his colleagues thought the chimpanzee genome might show how they were protected. To their surprise, they report in Nature, the protection was not there.

The chimp Y chromosome has lost the use of 5 of its 16 X-related genes. The genes are there, but have been inactivated by mutation. The explanation, in his view, lies in the chimpanzee's high-spirited sexual behavior. Female chimps mate with all males around, so as to make each refrain from killing a child that might be his.

The alpha male nonetheless scores most of the paternities, according to DNA tests. This must be because of sperm competition, primatologists believe - the alpha male produces more and better sperm, which outcompete those of rival males.

This mating system puts such intense pressure on the sperm-making genes that any improved version will be favored by natural selection. All the other genes will be dragged along with it, Dr. Page believes, even if an X-related gene has been inactivated.

If chimps have lost five of their X-related genes in the last six million years because of sperm competition, and humans have lost none, humans presumably had a much less promiscuous mating system. But experts who study fossil human remains believe that the human mating system of long-term bonds between a man and woman evolved only some 1.7 million years ago.

Males in the human lineage became much smaller at this time, a sign of reduced competition.

The new result implies that even before that time, during the first four million years after the chimp-human split, the human mating system did not rely on sperm competition.

Dr. Page said his finding did not reach to the nature of the joint chimp-human ancestor, but that "it's a reasonable inference" that the ancestor might have been gorillalike rather than chimplike, as supposed by some primatologists.

The gorilla mating system has no sperm competition because the silverback maintains

exclusive access to his harem.

Frans B. M. de Waal of the Yerkes National Primate Research Center in Atlanta said he agreed with fossil experts that the human pair bonding system probably evolved 1.7 million years ago but that the joint ancestor could have resembled a chimp, a bonobo, a gorilla, or something else entirely.

The scientists who have compared the whole genomes of the two species say they have found 35 million sites on the aligned genomes where there are different DNA units, and another five million where units have been added or deleted. Each genome is about three billion units in length.

The chimp genome was completed in draft form in December 2003 by the Broad Institute in Cambridge and Washington University in St. Louis.

Statistical tests for accelerated evolution are not yet powerful enough to identify the major genes that have shaped humans. "We knew that this was only a beginning, but from a general standpoint we have captured the vast majority of the differences between human and chimps," said Robert H. Waterston of the University of Washington, Seattle, the senior author of the report. The genome of a third primate, the orangutan, is now in progress and will help identify the genes special to human evolution, he said.

At the level of the whole animal, primatologists have uncovered copious similarities between the social behavior of chimpanzees, bonobos and humans, some of which may eventually be linked to genes. But this rich vein of discovery may be choked off if the great apes can no longer be studied in the wild.

"The situation is very bad, and our feeling is that by 2040 most of the habitat will be gone, except for those little regions we have set aside," Dr. de Waal said.

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Male chromosome has a future after all, study says

NEW YORK (AP) — The human Y chromosome — the DNA chunk that makes a man a man — has lost so many genes over evolutionary time that some scientists have suspected it might disappear in 10 million years. But a new study says it'll stick around.

Researchers found no sign of gene loss over the past 6 million years, suggesting the chromosome is "doing a pretty good job of maintaining itself," said researcher David Page of the Whitehead Institute for Biomedical Research in Cambridge, Mass.

That agrees with prior mathematical calculations that suggested the rate of gene loss would slow as the chromosome evolved, Page and study co-authors note in Thursday's issue of the journal Nature. And, they say, it clashes with what Page called the "imminent demise" idea that says the Y chromosome is doomed to extinction.

The Y appeared 300 million years ago and has since eroded into a dinky chromosome, because it lacks the mechanism other chromosomes have to get rid of damaged DNA. So mutations have disabled hundreds of its original genes, causing them to be shed as useless. The Y now contains only 27 genes or families of virtually identical genes.

In 2003, Page reported that the modern-day Y has an unusual mechanism to fix about half of its genes and protect them from disappearing. But he said some scientists disagreed with his conclusion. The new paper focuses on a region of the Y chromosome where genes can't be fixed that way.

Researchers compared the human and chimpanzee versions of this region. Humans and chimps have been evolving separately for about 6 million years, so scientists reasoned that the comparisons would reveal genes that have become disabled in one species or the other during that time.

They found five such genes on the chimp chromosome but none on the human chromosome, an imbalance Page called surprising.

"It looks like there has been little if any gene loss in our own species lineage in the last 6 million years," Page said.

That contradicts the idea that the human Y chromosome has continued to lose genes so fast it'll disappear in 10 million years, he said.

"I think we can with confidence dismiss .... the 'imminent demise' theory," Page said.

Jennifer Marshall Graves of the Australian National University in Canberra, a gene researcher who argues for eventual extinction of the Y chromosome, called Page's work "beautiful" but said it didn't shake her conviction that the Y is doomed.

The only real question is when, not if, the Y chromosome disappears, she said. "It could be a lot shorter than 10

million years, but it could be a lot longer," she said.

The Y chromosome has already disappeared in some other animals and "there's no reason to expect it can't happen to humans," she said. If it happened in people, some other chromosome would probably take over the sex-determining role of the Y, she said.

Find this article at:
http://www.usatoday.com/tech/science/genetics/2005-08-31-y-chromosome_x.htm

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Humans, chimps almost a match

By Steve Sternberg, USA TODAY

Humans and chimpanzees share an almost identical genetic inheritance, scientists report Thursday in a landmark comparison that they call an "elegant confirmation" of Charles Darwin's theory of evolution.

Clint the chimpanzee, whose genome sequence appears in 'Nature,' helped show there's little difference between man and ape.

Yerkes National Primate Research Center, AFP/Getty Images

Although scientists have long believed that humans and chimps are related, this comprehensive analysis of their separate genomes offers the best proof of their shared genetic past.

The 3 billion genetic letters in the two genetic blueprints are 96% identical with just 40 million differences, the researchers report in the journal *Nature*.

By delving more deeply into those differences, researchers hope to explain why humans are susceptible to certain diseases; why our evolutionary paths diverged from ancestral chimps 6 million years ago; and, on an even more basic level, what makes us human.

"We can peek into evolution's lab notebook and see what went on there," says Francis Collins, director of the National Human Genome Research Institute.

The analysis offers clues to the cause of diseases such as Alzheimer's and to why chimps and humans are susceptible to different diseases.

"Evolutionary analysis is a handmaiden to human medicine," says Eric Lander of the

Broad Institute of the Massachusetts Institute of Technology and Harvard.

For example, in a discovery that could offer insights into Alzheimer's, researchers found mutations that turn off the human caspase-12 gene, which causes damaged cells to self-destruct. Those mutations weren't found in chimps, which aren't as susceptible to Alzheimer's. Knocking out caspase-12 in mice makes their brain cells more likely to survive with Alzheimer's-like damage.

Researchers also identified mutations in humans that were important for survival, including a gene associated with speech and a gene that ramps up response to sugar, an advantage in lean times but a potential ticket to diabetes today.

"Reading these two genomes side by side, it's amazing to see the evolutionary changes that are occurring," says Robert Waterston of the University of Washington. "I couldn't imagine Darwin looking for stronger confirmation of his theories."

washingtonpost.com

Scientists Complete Genetic Map of the Chimpanzee

Differences From Human DNA Pinpointed

By Rick Weiss
Washington Post Staff Writer
Thursday, September 1, 2005; A03

Scientists said yesterday that they have determined the precise order of the 3 billion bits of genetic code that carry the instructions for making a chimpanzee, humankind's closest cousin.

The fresh unraveling of chimpanzee DNA allows an unprecedented gene-to-gene comparison with the human genome, mapped in 2001, and makes plain the evolutionary processes through which chimps and humans arose from a common ancestor about 6 million years ago.

By placing the two codes alongside each other, scientists identified all 40 million molecular changes that today separate the two species and pinpointed the mere 250,000 that seem most responsible for the difference between chimpness and humanness.

"Now we can peek into evolution's lab notebook to see what went on there," said Francis S. Collins, director of the National Human Genome Research Institute, which funded the $25 million effort at 18 institutions in five countries.

On a practical level, researchers said, the work is likely to explain why chimps are resistant to several human diseases such as AIDS, hepatitis, malaria and Alzheimer's disease -- information that could lead to new ways to prevent or treat many human ills.

More profoundly, however, the achievement promises to help answer the alluring but loaded question of what, exactly, makes us truly human.

But the answer will not come easily.

"We're not going to stand up and say that these 14 things make us human," said Eric S. Lander of the Broad Institute of MIT and Harvard in Cambridge, Mass., which along with Washington University in St. Louis led the chimpanzee genome sequencing effort. "But it's not trivial to be able to say, 'Here is an inventory of the most important differences, and now go at it and figure out which of these differences contain the signatures of what is distinctively human.' "

As predicted by preliminary studies, the human and chimpanzee genetic codes are essentially 99 percent identical, a testament to how fundamentally similar the two species remain. At the same time, it is powerful evidence that seemingly modest changes in molecular code can lead to very different stations in the web of life.

Because of that 1 percent difference, experts noted, humans now dominate every ecosystem on Earth while chimpanzees and other great apes -- a group that also includes bonobos, gorillas and orangutans -- are at risk of becoming extinct within the next few decades, largely because of human activities.

Well aware of that awkward reality, several scientists yesterday used the occasion of the chimp genome's unveiling to focus attention on the creatures' plight, calling for renewed conservation efforts and new rules governing the use of great apes in research.

"There is a deep irony in the fact that the sequencing of the chimpanzee genome coincides with the potential demise of great apes in the wild," wrote Ajit Varki of the University of California at San Diego, and colleagues, in a commentary accompanying the main research report in today's issue of the journal Nature.

The DNA analysis -- the first of a non-human primate and the fourth of a mammal (after human, mouse and rat) -- was done on blood drawn from a chimp named Clint, who lived at a research center in Atlanta until dying in January from causes unrelated to the project. Key scientific findings and related commentaries fill about 100 pages in today's Nature and today's online version of the journal Science.

The human and chimpanzee genomes are distinguished by 35 million differences in individual DNA "letters" -- each the result of a tiny, random mutation -- and an additional 5 million larger differences in which entire chunks of DNA were either added to or deleted from one genome or the other.

All told, the two sequences differ by 4 percent. But three-quarters of the differences seem to be in non-functional parts of the genome, suggesting that a mere 1 percent variation makes all the difference.

Put another way, the difference between the human and chimp genomes is 10 times as great as the difference between any two humans.

Among the genes that appear unique to humans are some involved in brain development and body plan, and one that has been postulated as being crucial to the development of language. But most of the differences between chimpanzees and humans seem attributable not so much to the genes themselves but to how genes that both species share are regulated -- that is, the timing and level of intensity under which those shared genes operate.

"The class of genes that has changed the fastest in humans compared to chimps are the genes that control other genes," said Tarjei S. Mikkelsen of the Broad Institute.

Developmental changes are behind many of the differences between human and chimp brains. Human brain cells divide several more times than chimp brain cells during fetal development, a fact that contributes to the adult human brain's growth to three times the size of the chimpanzee's. Much of that increase is in the cerebral cortex, home to higher cognition.

But scientists confess to knowing little about how such changes might add up to differences in intellect and behavior.

"We are woefully ignorant about how genes build brains, and how the electrical activity of the

brain builds thoughts and emotions," wrote Marc D. Hauser, co-director of Harvard's Mind, Brain and Behavior Program, in Nature.

Chimpanzees have repeatedly toppled conceptions about the ways in which humans are purportedly unique. They fashion and use tools, including hammers, anvils, probes for fishing termites from the ground and seats to rest on, though unlike humans, they make all their tools by modifying found objects and never by putting complementary pieces together.

Chimps also medicate themselves, swallowing rough leaves and chewing on bitter stems to treat a type of intestinal infection.

And in perhaps their cheekiest aping of humanity, chimpanzees display remarkable political acumen. They form complex alliances and trade grooming services, sex and food. Like many denizens of the world's great cities, they lobby, demand bribes, repay favors and, when crossed, exact revenge.

Yet precisely because chimpanzees are so similar to humans (most medicines are absorbed, metabolized and excreted by chimps just as they are in people, for example), they make excellent stand-ins for humans in medical labs.

Medical studies on chimpanzees are no longer done in most countries other than the United States, where about 1,100 are now in research labs. Several scientists yesterday predicted that release of the chimp genome would escalate a debate as to whether U.S. research restrictions -- including an eight-year-old federal moratorium on breeding chimps for research -- should be tightened or loosened.

Pascal Gagneux of the Zoological Society of San Diego and two colleagues wrote in a Nature commentary that a stricter code of ethics for chimpanzee research is needed. They recommend rules similar to those now in place for research on humans who cannot give meaningful informed consent because of their age or mental status.

Others, recalling the initial importance of chimpanzees as research tools when AIDS first emerged, argue that newly emerging medical challenges demand renewed breeding for research.

Acknowledging recent challenges by proponents of "intelligent design," a proposition that posits the need for an intelligent creator, several scientists said the genome study offered elegant confirmation of Darwin's vision of evolution.

One analysis, for example, showed that the accumulation of deleterious mutations in the human and chimp genomes is greater than in the mouse and rat genomes in just the proportion predicted by one of the mathematical corollaries of the theory of evolution.

"I can't imagine Darwin hoping for a stronger confirmation of his ideas," said Robert H. Waterston, who led the Washington University team.

The New York Times
nytimes.com

September 9, 2005

Brain May Still Be Evolving, Studies Hint

By NICHOLAS WADE

Two genes involved in determining the size of the human brain have undergone substantial evolution in the last 60,000 years, researchers say, leading to the surprising suggestion that the brain is still undergoing rapid evolution.

The discovery adds weight to the view that human evolution is still a work in progress, since previous instances of recent genetic change have come to light in genes that defend against disease and confer the ability to digest milk in adulthood.

It had been widely assumed until recently that human evolution more or less stopped 50,000 years ago.

The new finding, reported in today's issue of Science by Bruce T. Lahn of the University of Chicago, and colleagues, could raise controversy because of the genes' role in determining brain size. New versions of the genes, or alleles as geneticists call them, appear to have spread because they enhanced brain function in some way, the report suggests, and they are more common in some populations than others.

But several experts strongly criticized this aspect of the finding, saying it was far from clear that the new alleles conferred any cognitive advantage or had spread for that reason. Many genes have more than one role in the body, and the new alleles could have been favored for some other reason, these experts said, such as if they increased resistance to disease.

Even if the new alleles should be shown to improve brain function, that would not necessarily mean that the populations where they are common have any brain-related advantage over those where they are rare. Different populations often take advantage of different alleles, which occur at random, to respond to the same evolutionary pressure, as has happened in the emergence of genetic defenses against malaria, which are somewhat different in Mediterranean and African populations.

If the same is true of brain evolution, each population might have a different set of alleles for enhancing function, many of which remain to be discovered.

The Chicago researchers began their study with two genes, known as microcephalin and ASPM, that came to light because they are disabled in a disease called microcephaly. People with the condition are born with a brain much smaller than usual, often with a substantial shrinkage of the cerebral cortex, that seems to be a throwback to when the human brain was a fraction of its present size.

Last year, Dr. Lahn, one of a select group of researchers supported by the Howard Hughes

Medical Institute, showed that a group of 20 brain-associated genes, including microcephalin and ASPM, had evolved faster in the great ape lineage than in mice and rats. He concluded that these genes might have had important roles in human evolution. As part of this study, he noticed that microcephalin and ASPM had an unusual pattern of alleles. With each gene, one allele was much more common than all the others. He and his colleagues have now studied the worldwide distribution of the alleles by decoding the DNA of the two genes in many different populations.

They report that with microcephalin, a new allele arose about 37,000 years ago, although it could have appeared as early as 60,000 or as late as 14,000 years ago. About 70 percent of people in most European and East Asian populations carry this allele of the gene, but it is much rarer in most sub-Saharan Africans.

With the other gene, ASPM, a new allele emerged 14,100 to 500 years ago, the researchers favoring a midway date of 5,800 years. The allele has attained a frequency of about 50 percent in populations of the Middle East and Europe, is less common in East Asia, and is found at low frequency in some sub-Saharan Africa peoples.

The Chicago team suggests that the new microcephalin allele may have arisen in Eurasia or as the first modern humans emigrated from Africa some 50,000 years ago. They note that the ASPM allele emerged about the same time as the spread of agriculture in the Middle East 10,000 years ago and the emergence of the civilizations of the Middle East some 5,000 years ago, but say that any connection is not yet clear.

Dr. Lahn said there might be a fair number of genes that affect the size of the brain, each making a small difference yet one that can be acted on by natural selection. "It's likely that different populations would have a different makeup of these genes, so it may all come out in the wash," he said. In other words, East Asians and Africans probably have other brain-enhancing alleles, not yet discovered, that have spread to high frequency in their populations.

He said he expected that more such allele differences between populations would come to light, as have differences in patterns of genetic disease. "I do think this kind of study is a harbinger for what might become a rather controversial issue in human population research," Dr. Lahn said. But he said his data and other such findings "do not necessarily lead to prejudice for or against any particular population."

A greater degree of concern was expressed by Francis S. Collins, director of the National Human Genome Research Institute. Dr. Collins said that even if the alleles were indeed under selection, it was still far from clear why they had risen to high frequency, and that "one should resist strongly the conclusion that it has to do with brain size, because the selection could be operating on any other not yet defined feature." He said he was worried about the way these papers will be interpreted.

Sarah Tishkoff, a geneticist at the University of Maryland and a co-author of both studies, said the statistical signature of selection on the two genes was "one of the strongest that I've seen." But she, like Dr. Collins, said that "we don't know what these alleles are doing" and that specific tests were required to show that they in fact influenced brain development or were selected for that reason.

Dr. Lahn acknowledges this point, writing in his article that "it remains formally possible that an unrecognized function of microcephalin outside of the brain is actually the substrate of selection."

Another geneticist, David Goldstein of Duke University, said that the new study was "very well done," but that "it is a real stretch to argue for example that microcephalin is under selection and that that selection must be related to brain size or cognitive function." The gene could have risen to prominence through a random process known as genetic drift, Dr. Goldstein said.

Richard Klein, an archaeologist who has proposed that modern human behavior first appeared in Africa because of some genetic change that promoted innovativeness, said the time of emergence of the microcephalin allele "sounds like it could support my idea." If the allele did support enhanced cognitive function, "it's hard to understand why it didn't get fixed at 100 percent nearly everywhere," he said.

Dr. Klein suggested the allele might have spread for a different reason, that as people colonizing East Asia and Europe pushed north, they adapted to colder climates.

Commenting on critics' suggestions that the alleles could have spread for reasons other than the effects on the brain, Dr. Lahn said he thought such objections were in part scientifically based and in part because of a reluctance to acknowledge that selection could affect a trait as controversial as brain function.

The microcephalin and ASPM genes are known to be involved in determining brain size and so far have no other known function, he said. They are known to have been under strong selective pressure as brain size increased from monkeys to humans, and the chances seem "pretty good" the new alleles are continuing that, he said.

Dr. Lahn said he had tested Dr. Goldstein's idea of alleles' spreading through drift and found it unlikely.