Professor sequences his entire genome at low cost, with small team

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Stephen Quake

(PhysOrg.com) -- The first few times that scientists mapped out all the DNA in a human being in 2001, each effort cost hundreds of millions of dollars and involved more than 250 people. Even last year, when the lowest reported cost was $250,000, genome sequencing still required almost 200 people. In a paper to be published online Aug. 9 by *Nature Biotechnology,* a Stanford University professor reports sequencing his entire genome for less than $50,000 and with a team of just two other people.

In other words, a task that used to cost as much as a Boeing 747 airplane

and required a team of people that would fill half the plane, now costs as much as a mid-priced luxury sedan and the personnel would fill only half of that car.

"This is the first demonstration that you don't need a genome center to sequence a human genome," said Stephen Quake, PhD, professor of bioengineering. "It's really democratizing the fruits of the genome revolution and saying that anybody can play in this game."

There are at least two reasons why lowering the cost and effort required to sequence all the genetic information of individuals is important. The more examples scientists have of the whole human genetic code, the more they can discern about how specific genes and mutations result in the traits that make us all different, the diseases that plague us and our response to medicines. As that understanding increases and costs drop, doctors could then sequence their patients' genomes and provide "personalized medicine" in which prevention and treatment of disease would be informed by the patient's exact genetic profile.

"This can now be done in one lab, with one machine, at a modest cost," said Quake, the Lee Otterson Professor in the School of Engineering and a member of Stanford's Cancer Center. "It's going to unleash an enormous amount of creativity and really broaden the field."

Quake's genome, one of less than a dozen sequenced so far because of the cost and resources needed, is now available to researchers worldwide. Quake's colleagues at Stanford's School of Medicine have been looking through it and sometimes examining Quake himself, mining the data for interesting connections between what they can observe about him, his DNA and his family history.

"Some of the doctors are starting to poke and prod me to see how they can couple my genome with medicine," he said.

Simpler sequencing

To sequence his genome, Quake's team used a commercially available, refrigerator-sized instrument called the Helicos Biosciences SMS Heliscope. Quake, who pioneered the underlying technology in 2003, is a co-founder of the Cambridge, Mass.-based company and chairs its scientific advisory board.

The technology—the SMS in the instrument's name—is called single molecule sequencing. While many techniques require generating thousands of copies of a subject's DNA, the single molecule technique does not, reducing the cost and effort involved. Instead, the technique requires chopping the 3 billion or so fundamental units of DNA (called bases) into strands about 30 bases long. The four bases in DNA are adenine (abbreviated A), cytosine (C), guanine (G), and thymine (T).

Each base of DNA matches with a specific other base: For example, T only matches with A. The machine captures each of the millions of strands on a specially treated glass plate, holds them there and washes successive waves of fluorescently labeled "letters" over the plate. As each complementary letter sticks next to a strand, the machine can read out the sequence of each strand. A video of the process can be seen on the Web: http://www.helicosbio.com/Technology/TrueSingleMoleculeSequencing/tabid/64/Default.aspx.

Assembling the strands back into a cohesive genome is then done by powerful computers, which compare it to the reference genomes that have been compiled before. The process is akin to assembling an enormous jigsaw puzzle by referring frequently to the picture on the box. The team said the sequencing process took about one month to complete.

Still, several tricky problems had to be solved before the machine could reliably sequence a whole human genome. Quake worked with Norma Neff, a research manager in Quake's lab, and physics doctoral student Dmitry Pushkarev to write a sophisticated algorithm that would enable them to determine how accurate the process is.

Overall, the genome is 95 percent complete, a rate comparable with other sequenced genomes, the team found. In the paper, the authors are careful to note that all genome-sequencing technologies, including the one they've demonstrated, have produced incomplete approximations of the actual genome. Still, it is enough to help produce genuine insights about a person's traits and health.

A professor's personal revelations

Quake's genome has already yielded a few interesting connections between his genetics and his health. One is that he carries a rare mutation associated with a heart disorder; the revelation, he said, sheds light on what members of his family have always wondered with regard to the health of prior generations. The good news, he said, is that he's also apparently genetically predisposed to respond well to common cholesterol-lowering statin medicines.

Quake said the information has also forced him to take heed of that history. "If you know your uncle had something, you kind of discount that you can get it, but to see you've inherited the mutation for that is another matter altogether," he said.

One amusing "revelation" is that Quake's code contains a form of a gene that has sometimes been associated with increased disagreeability, he said. The details of the code can be found on the Web at http://www.snpedia.com/index.php/Rs6832769.

"Of course, you don't need my genome to tell you that," Quake acknowledged. "My wife could have told you that and certainly the dean could have as well."

Source: Stanford University Medical Center (news : web)