Decoding leukemia patient genome leads scientists to mutations in other patients

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Decoding the complete DNA of cancer patients is giving scientists at Washington University School of Medicine in St. Louis a clearer picture of the complexity of the disease and allowing them to see intriguing and unexpected genetic relationships among patients.

Reporting online Aug. 5 in the New England Journal of Medicine, the scientists have sequenced the genome of a second patient with acute myeloid leukemia (AML), discovering a suite of genetic changes in the cancer cells. Their research has revealed that one of these mutations also is common in certain brain tumors called gliomas and that another occurred in a second patient with the same type of leukemia. Neither mutation had been previously linked to leukemia.

The fact that these genetic mistakes sometimes occur in other patients strongly suggests the mutations are relevant to the development and progression of cancer, the researchers say. Although this information does not yet point to better treatment options, it highlights the strong potential of sequencing many cancer genomes to unravel the genetic basis of cancer.

"Only by sequencing complete genomes of cancer patients are we going to find unexpected, recurring genetic mutations that are highly likely to be important for cancer to develop and grow," says hematologist and senior author Timothy Ley, M.D., the Alan A. and Edith Wolff Professor of Medicine, who led the team that sequenced the first genome of a cancer patient last year. "Gaining a genome-wide

understanding of cancer lays the foundation for developing more powerful ways to diagnose, classify and treat patients."

Interestingly, a large majority of the mutations were found in long stretches of DNA between genes in regions of the genome that may influence how genes work. These areas are not yet well understood by scientists and are only now being mined for their connections to cancer.

In an accompanying editorial, James R. Downing, M.D., of St. Jude Children's Research Hospital, says the study "opens a clear window into the rapid advancements that are being made in cancer genome-sequencing."

The new research was conducted by a large team of researchers at Washington University's Genome Center and the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.

The same team broke new ground late last year when they became the first to sequence the entire genome of a cancer patient, a woman with AML who had died of the disease. That research, published in Nature, demonstrated the feasibility of decoding the genome of a patient's cancer cells and comparing it to the genome of the patient's normal, healthy cells to find the genetic mutations unique to the person's disease. But in that study, the scientists found a completely different set of mutations than those in the current study, and none of the new mutations in that patient were found to occur in tests of almost 200 other patients with AML - a finding that underscores the genetic complexity and diversity of cancer.

"Only by sequencing thousands of cancer genomes are we going to find and make sense of the complex web of genetic mutations and the altered molecular pathways in this disease," says lead author Elaine Mardis,

Ph.D., co-director of The Genome Center. "What we find may lead us to completely restructure the way we define tumor types and subtypes."

In their latest endeavor, the scientists sequenced the genome of a man diagnosed with AML at age 38 who has been in remission for more than three years. His genome was chosen for sequencing because he had typical clinical and molecular features of the disease, including two AML-linked mutations that were already known to the researchers.

"Currently, we don't have great information about how patients with this particular subtype of AML will respond to treatment, so most of them are treated similarly up front," Ley says. "By defining the mutations that cause AML in different people, we hope to determine which patients need aggressive treatment, like a stem cell transplant, and which can be treated effectively with less intense therapies."

An estimated 13,000 cases of AML will be diagnosed in the United States this year, and some 9,000 will die of the disease. It occurs most often among those age 60 or older and becomes more difficult to treat as patients age. The five-year survival rate for adults with AML is about 20 percent.

The researchers sequenced the patient's genome using a sample of healthy skin cells. This gave the scientists a reference DNA sequence to which they could compare genetic alterations in the patient's tumor cells, taken from a bone marrow sample obtained before the patient received chemotherapy.

The scientists then looked for genetic differences - points of single base changes in the DNA, insertions and deletions of bits of genetic material, variations in gene copy number and structural changes - in the patient's cancer genome compared with his normal genome.

In all, the scientists identified about 750 mutations in the patient's AML genome. However, careful analysis indicated that the vast majority appear to be random, background mutations that were not relevant to the development of the disease.

With further study, they defined 64 mutations that were the most likely to be important for the patient's cancer. Twelve were found in genes that code for proteins, including a mutation in the IDH1 gene that has only recently been linked to gliomas, and 52 mutations were in long stretches of DNA that do not contain genes at all but potentially affect when and how neighboring genes are expressed.

"Other than the two mutations the patient was known to have before his genome was sequenced, we never would have guessed any of these mutations - they were a huge surprise," says co-author Richard K. Wilson, Ph.D., director of Washington University's Genome Center. "That so many of the mutations were found outside of protein-coding genes also underscores the need to sequence whole genomes to find all the mutations that occur in cancer. If we only look at genes with known or suspected links to cancer, we'll miss many mutations that are potentially relevant."

The investigators also tested 187 additional samples of DNA from the leukemia cells of AML patients, looking specifically for any of the 64 mutations. They found the IDH1 mutation in 15 samples, making it one of the most common mutations linked to date to AML. Another mutation in the non-coding region of the genome occurred in one other patient, which suggests to the researchers that it is important.

"Scientists tend to focus their energies on the protein-coding regions of the genome because that is the part of the genome they know and understand," Mardis says. "But it is significant that we found a mutation that occurs in another patient with AML outside of that familiar turf, in

a region of the genome that is not well understood at all."

Sequencing whole cancer genomes to find all the mutations involved in a patient's cancer now is possible because of recent advances that have made the technology faster and far less expensive. The current study took only a few months and cost about $500,000, one-third of the price tag of sequencing the first cancer patient genome less than a year ago.

The Washington University researchers are now sequencing additional genomes of patients with AML and have expanded the approach to breast, lung and ovarian cancers and glioblastomas.

Source: Washington University School of Medicine (news : web)