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## 'True landmark' reached in cancer research

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For the first time, scientists have decoded the complete DNA of a cancer patient and traced her disease, acute myelogenous leukemia (AML), to its genetic roots.

A research team at the Genome Sequencing Center and the Siteman Cancer Center at the School of Medicine sequenced the genome of the patient, a woman in her 50s who ultimately died of her disease, and the genome of her leukemia cells, to identify genetic changes unique to her cancer.

The study was reported in the Nov. 6 issue of *Nature*.

The pioneering work sets the stage for using a more comprehensive, genome-wide approach to unravel the genetic basis of cancer.

"Our work demonstrates the power of sequencing entire genomes to discover novel cancer-related mutations," said senior author Richard K. Wilson, Ph.D., director of the Genome Sequencing Center. "A genome-wide understanding of cancer, which is now possible with faster, less expensive DNA sequencing technology, is the foundation for developing more effective ways to diagnose and treat cancer."

The researchers discovered just 10 genetic mutations in the patient's tumor DNA that appeared to be relevant to her disease; eight of the mutations were rare and occurred in genes that had never been linked to AML. They also showed that virtually every cell in the tumor sample from her bone marrow had nine of the mutations, and that the single genetic alteration that occurred less frequently was likely the last to be acquired. The scientists suspect that all the mutations were important to the patient's cancer.

Like most cancers, AML, a cancer of blood-forming cells in the bone marrow, arises from mutations that accumulate in people's DNA over the course of their lives. However, little is known about the precise nature of those changes and how they disrupt biological pathways to cause the uncontrolled cell growth that is the hallmark of cancer.

Previous efforts to decode individual human genomes have looked at common points of DNA variation that may be relevant for disease risk. What's striking about the new research is that the scientists were able to sift through the 3 billion pairs of chemical bases that make up the human genome to pull out the mutations that contributed to the patient's cancer.

"Until now, no one has sequenced a patient's genome to find all the mutations that are unique to that person's disease," said lead author Timothy Ley, M.D., the Alan A. and Edith L. Wolff

Professor of Medicine. "We didn't know what we would find, but we felt that the answers to why this patient had AML had to be embedded in her DNA."

To date, scientists involved in large-scale genetic studies of cancer have not gone so far as to do a side-by-side comparison of the genomes of normal cells and tumor cells from the same patient. Rather, earlier studies have involved the sequencing of genes with known or suspected relationships to cancer, a method that likely misses key mutations.

"The determination of the first complete DNA sequence of a human cancer genome, and its comparison to normal tissues of the same individual, is a true landmark in cancer research," said geneticist Francis Collins, M.D., Ph.D., former director of the National Human Genome Research Institute. "In the past, cancer researchers have been 'looking under the lamppost' to find the causes of malignancy, but now the team from Washington University has lit up the whole street. This achievement ushers in a new era of comprehensive understanding of the fundamental nature of cancer and offers great promise for the development of powerful new approaches to diagnosis, prevention and treatment."

An estimated 13,000 cases of AML will be diagnosed in the United States this year, and some 8,800 will die of the disease. The five-year survival rate for AML is 21 percent, according to the American Cancer Society.

Based on genetic testing with traditional methods at the study's outset, the patient was known to have two mutations that are common among AML patients, an indicator she had a typical subtype of the disease, and one of the many reasons why her genome was selected for sequencing.

The researchers sequenced the patient's full genome, meaning DNA from both sets of chromosomes, using genetic material obtained from a skin sample. 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 that was comprised only of tumor cells. Both samples were obtained before the patient received cancer treatment, which can further damage DNA.

The scientists then looked for genetic differences — points of single base changes in the DNA — in the patient's tumor genome compared with her normal genome. Of the nearly 2.7 million single nucleotide variants in the patient's tumor genome, almost 98 percent also were detected in DNA from the patient's skin sample, narrowing the number of variants that required further study to about 60,000.

Using sophisticated software and analytical tools, some of which the researchers developed specifically for this project, they identified the 10 mutations (including the two previously known genetic mutations that are common to her leukemia subtype but do not directly cause the disease) by looking for single-base DNA changes that altered the instructions for making proteins.

Of the eight novel mutations discovered, three were found in genes that normally act to suppress tumor growth. Four other mutated genes appear to be involved in molecular pathways that promote cancer growth. In particular, one mutation was found in a gene family that also is expressed in embryonic stem cells and may be involved with cell self-renewal. Interestingly, the researchers note, self-renewal is thought to be an essential feature of leukemia cells.

Another gene alteration appears to affect the transport of drugs into the cell and may have contributed to the patient's chemotherapy resistance.

"We're still analyzing the patient's noncoding DNA and expect to find a number of additional relevant mutations in this portion of the genome," said Elaine Mardis, Ph.D., co-lead author of the study and co-director of the Genome Sequencing Center.

"But the role of these noncoding mutations will be more of a challenge to elucidate because we do not yet fully understand the function of this part of the genome," Mardis said.

The team is now sequencing the genomes of additional patients with AML, and they are also planning to expand the whole-genome approach to breast and lung cancers.