Scientists assemble genetic playbook for acute leukemia

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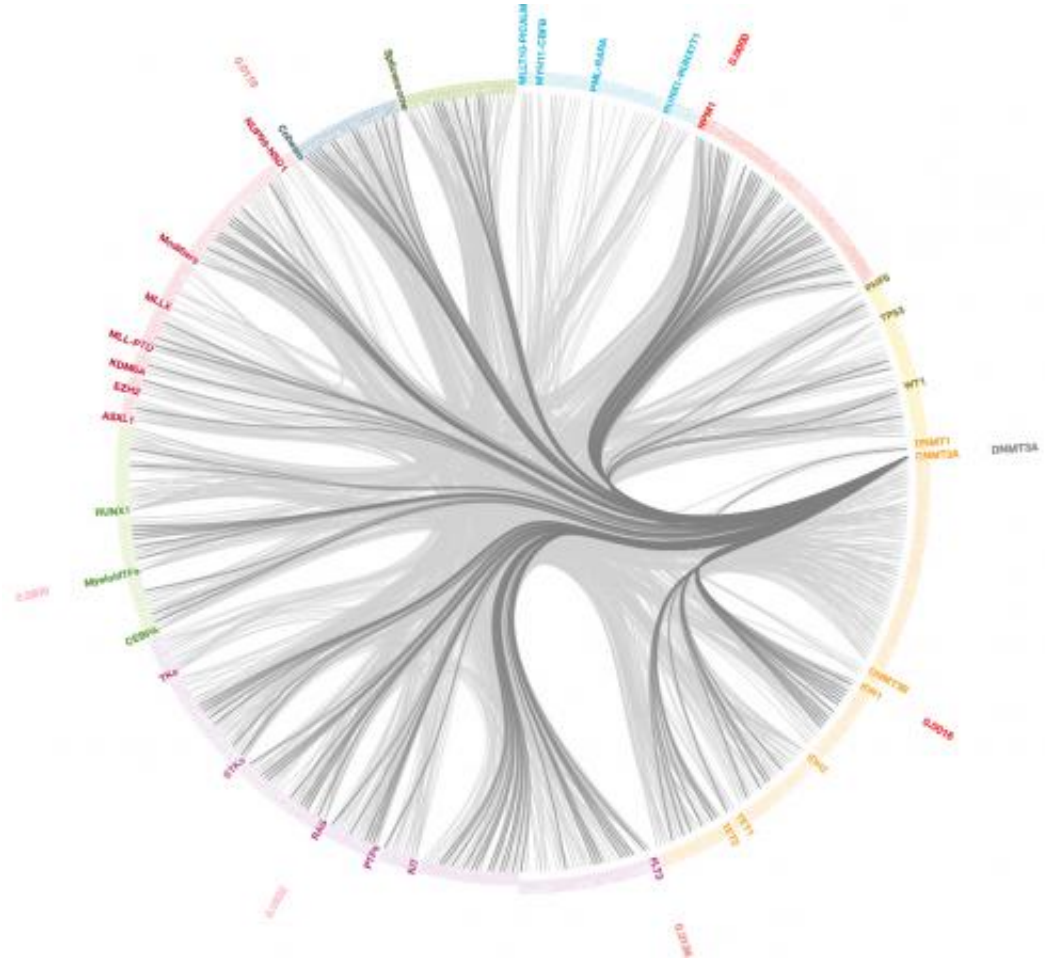

Lines in the circos plot connect major genes involved in acute myeloid leukemia with patients whose leukemia cells have mutations in those genes. An interactive version of the graphic is available at: http://compbio.cs.brown.edu/aml_tcga/. Credit: Benjamin Raphael, Brown University

A team of researchers led by Washington University School of Medicine in St. Louis has identified virtually all of the major mutations that drive acute myeloid leukemia (AML), a fast-growing blood cancer in adults that often is difficult to treat.

The findings, published online May 1 in the *New England Journal of Medicine*, pave the way for developing better treatments for AML based on the genetic profile of a patient's cancer. They also could lead to ways to more accurately predict the severity of disease in individual patients.

"We now have a genetic playbook for this type of leukemia," says study co-leader Timothy Ley, MD, associate director for cancer genomics at The Genome Institute at Washington University School of Medicine. "We don't know all the rules yet, but we know all the major players. This information can help us begin to understand which patients need more aggressive treatment right up front and which can be treated effectively with standard chemotherapy."

Some 200 patients newly diagnosed with AML were involved in the study, funded by the National Institutes of Health (NIH) as part of The Cancer Genome Atlas project. Nearly 150 researchers were involved in the effort.

A second Cancer Genome Atlas paper will be published May 2 in *Nature*. That research, also led by Washington University, shows that adding genomics-based testing to the standard diagnostic workup could change the recommended course of treatment for some women.

The scientists sequenced the DNA of each patient's leukemia cells and compared the data to DNA from that same patient's healthy cells. In this way, they found the mutations that only occurred in the cancer cells and contributed to the development and progression of AML in each patient. They also looked for defects in RNA (a close chemical cousin of DNA)

and other changes that alter the expression of genes without actually changing the DNA.

"These results provide important new insights into the genomics of a deadly and difficult-to-treat cancer, and underscore the power and scope of The Cancer Genome Atlas project," says NIH Director Francis S. Collins, MD, PhD.

Compared to other adult cancers, AML is caused by relatively few mutations, the new study shows. Cancer cells in the AML patients had an average of 13 mutated genes, far fewer than the several hundred typically found in breast, lung and other solid tumors.

By studying a large number of AML cases, the scientists predict they have found nearly all of the major mutations that occur in patients with the disease.

"If only 5 percent of AML cases have a particular gene that is mutated, there is a greater than 99 percent chance that we encountered that mutation at least once in this study," says co-leader Richard K. Wilson, PhD, director of Washington University's Genome Institute. "There are still rare mutations that remain to be discovered, but we expect they will fall into the same genetic pathways or gene sets that we identified as being very strongly associated with AML."

The researchers found more than 1,800 genes that were mutated at least once in the 200 samples, a discovery that hints at the many different routes that lead to AML. But only 23 of the genes were significantly mutated, and another 237 were mutated in two or more of the samples.

"We didn't realize how few recurrent mutations there were, and no one was thinking even a few years ago that AML was associated with a high frequency of mutations in genes that encode epigenetic modifiers," Ley

says. "This new information helps narrow the search for likely drug targets and markers that can help predict the severity of AML."

To make sense of their findings, the researchers organized the genes into nine categories based on their function or the known pathways involved. These include tumor suppressor genes, signaling genes and epigenetic modifiers, the latter of which is the most frequently mutated class of genes in the study. Epigenetic changes influence when genes are turned on and off but don't alter the DNA sequence.

To their surprise, the scientists identified patterns of cooperation and mutual exclusivity between certain genes or sets of genes. For example, a combination of mutations in three genes – FLT3, NPM1 and DNMT3A – were fairly common in patients and may represent a unique subtype of AML.

An estimated 14,600 Americans will be diagnosed with AML this year and some 10, 400 will die. Unfortunately, few good markers exist to help guide treatment decisions for many patients.

Doctors routinely assess the severity of AML by looking at patients' leukemia cells for broken or rearranged chromosomes, an indicator of very aggressive cancer. But more than half of all AML patients fall into a diagnostic category called "intermediate risk." Their cancer cells have chromosomes that look normal or have very minor changes. And while some do well on standard chemotherapy, many others do poorly, underscoring the critical need for better ways to determine prognosis.

"Anything we can do to improve risk classification in this disease is really important because there is a cure for some patients – a stem cell transplant from a matched donor – but it is risky and costly and should only be used in patients who need it," Ley says. "For these patients, it's crucial to get the transplant early in the course of the disease."

Ley, Wilson and their colleagues at The Genome Institute pioneered cancer genome sequencing. Since the Washington University team published the first cancer genome in 2008, the team has found many genetic mutations linked to AML and other tumors that never would have been suspected to be associated with cancer.

Now that scientists have a more complete list of genes altered in AML, the researchers expect other researchers will begin examining AML patient samples banked at their own institutions to understand the relationship between the mutated genes and treatment outcomes.

"We've never had such a complete picture of AML," says Wilson. "Now, researchers can mine this data to determine whether individual mutations or sets of mutations can be used to predict prognosis or be targeted by new or existing drugs."

More information: Ley, T, Wilson R, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. The New England Journal of Medicine. Online May 1, 2013.

Provided by Washington University School of Medicine