Key genetic error found in family of blood cancers

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Researchers used whole-genome sequencing to identify a critical mutation in some patients with myelodysplastic syndromes that appears to increase the likelihood they will develop acute myeloid leukemia. Credit: Robert Boston

(Medical Xpress) -- Scientists have uncovered a critical genetic mutation in some patients with myelodysplastic syndromes – a group of blood cancers that can progress to a fatal form of leukemia.

The research team at Washington University School of Medicine in St. Louis also found evidence that patients with the mutation are more likely to develop acute leukemia. While this finding needs to be confirmed in additional patients, the study raises the prospect that a genetic test could one day more accurately diagnose the disorder and predict the course of

the disease.

The research is available online in *Nature Genetics*.

The scientists discovered the mutation in a gene known as U2AF1 when they sequenced the entire genome of a 65-year old man with myelodysplastic syndrome that had progressed to leukemia and compared it to the genome of his tumor cells. They also found the genetic error in other patients with myelodysplastic syndromes, an indication of the mutation's significance.

"The mutation in this gene was not on anyone's radar screen," says senior author and hematologist/oncologist Matthew Walter, MD, assistant professor of medicine. "In many cases, the diagnosis of myelodysplastic syndromes is unclear because there isn't a straightforward diagnostic test. By understanding at the genetic level what is contributing to this disease, we hope to eventually improve the diagnosis and treatment of this disorder."

Myelodysplastic syndromes are a difficult-to-treat family of blood cancers that occur when blood cells in the bone marrow don't mature properly. About 28,000 Americans are diagnosed with the disorder each year, most of them over age 60. Drugs are available to treat the disease, but none can cure it.

In about 30 percent of cases, the disorder progresses to a form of acute myeloid leukemia that usually is fatal because chemotherapy drugs are not effective in these patients. Doctors currently assess the likelihood that a patient with myelodysplastic syndrome will develop leukemia by looking at the chromosomes in the tumor cells to determine the extent to which they have broken apart and rearranged themselves, an indicator of the severity of the disease.

“There are chromosomal patterns that indicate high risk and low risk, but the current methods to determine prognosis aren’t perfect,” says first author Timothy Graubert, MD, associate professor of medicine, who specializes in treating patients with myelodysplastic syndromes.

After identifying the U2AF1 mutation in three patients through whole-genome sequencing, the researchers scoured the gene for the mutation in another 150 patients with myelodysplastic syndromes. They identified the mutation in 13, or nearly 9 percent. The mutations were acquired during development of myelodysplastic syndromes because they were not present in normal cells obtained from each patient.

Patients were almost three times as likely to develop leukemia if they had a mutation in the U2AF1 gene. The disorder progressed to leukemia in 15.2 percent of patients with the mutation, compared with 5.8 percent of those without the genetic error.

The most common mutation results in a single letter change in the DNA at a precise location in the U2AF1 gene. Patients with the genetic error were most likely to have the amino acids phenylalanine or tyrosine substituted for a serine. The researchers say that the mutation by itself does not cause myelodysplastic syndromes but appears to be an early event in the course of the disease.

Normally, the U2AF1 gene makes a protein involved in splicing RNA, a sister molecule of DNA that carries the instructions for building proteins. Splicing brings together different sections of RNA necessary to make a protein and discards those sections that are not needed. The mutated version of the gene still produces a protein, but its splicing activity is altered, which may be important for the development of some cancers.

The new research, funded in part by a federal stimulus grant, adds to a

flurry of new findings about the genetic basis of myelodysplastic syndromes. Recent studies in Nature and the New England Journal of Medicine, along with the current study, have identified mutations in a total of eight genes involved in RNA splicing in patients with the disorder.

“Together, these findings are a real game changer,” Graubert says. “A mutation in any one of these eight genes occurs in up to 50 percent of patients with myelodysplastic syndromes. Because these changes are so common, we think there are likely to be implications for improving the diagnosis of the disorder and finding new therapeutic options.”

Whole-genome sequencing for cancer was pioneered by scientists at Washington University School of Medicine and the university’s Genome Institute, including Richard Wilson, PhD; Elaine Mardis, PhD; Timothy Ley, MD; and Li Ding, PhD, all of whom are co-authors of the study. The new research builds on their work to find novel mutations in cancer by looking across a patient’s entire genome.

More information: Graubert, TA et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. *Nature Genetics*. Advance online publication, Dec. 11, 2011

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