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# When leukemia returns, gene that mediates response to key drug often mutated

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Despite dramatically improved survival rates for childhood acute lymphoblastic leukemia (ALL), relapse remains a leading cause of death from the disease. Work led by St. Jude Children's Research Hospital investigators identified mutations in a gene named CREBBP that may help the cancer resist steroid treatment and fuel ALL's return.

CREBBP plays an important role in normal blood cell development, helping to switch other genes on and off. In this study, researchers found that 18.3 percent of the 71 relapsed-ALL patients carried alterations in the DNA sequence of CREBBP. In contrast, the gene's sequence was changed in just one of the 270 young leukemia patients whose cancer did not return.

Investigators say the gene is a potential indicator of relapse risk because of the high frequency of CREBBP mutations in relapsed patients and evidence the changes persisted from diagnosis or emerged at relapse from subpopulations of leukemia cells present from the beginning. Researchers also found evidence the changes occur in important regulatory regions of the gene and affect cell function, including how cancer cells respond to the steroids that play an important role in cancer treatment. The work appears in the March 10 issue of the scientific journal *Nature*.

"This study gives us further evidence that detailed genomic studies can identify important mutations that influence tumor response to treatment," said Charles Mullighan, M.D., Ph.D., assistant member of

the St. Jude Department of Pathology. Mullighan and Jinghui Zhang, Ph.D., an associate member of the St. Jude Department of Computational Biology, are co-first authors. Mullighan is also the corresponding and senior author.

In the same issue of *Nature*, investigators also reported that deletions and deactivating mutations in CREBBP and a related gene known as EP300 occurred in about one-third of patients identified with one of the two most common subtypes of B-cell non-Hodgkin lymphoma. Mullighan is one of that study's five St. Jude co-authors.

Previous reports have linked deletions or chromosome rearrangements involving CREBBP to rare cases of acute leukemia. But this is the first study linking changes in the gene's DNA sequence to leukemia and lymphoma, cancers of the blood and bone marrow.

ALL is the most common childhood cancer. While ALL cure rates have climbed to 90 percent, the disease is often deadly if it returns. This study was designed to advance understanding of the biological basis of treatment failure. "The results of this study emphasize that there are additional genetic changes that help determine whether a child does well or relapses," Mullighan said.

The findings stem from the largest DNA sequencing project yet for ALL, which is diagnosed in about 3,000 U.S. children annually. Researchers from St. Jude and the National Cancer Institute tracked changes in 300 genes from 23 young ALL patients. For each gene, researchers compared the DNA makeup in the patient's normal cells with the sequence at diagnosis and relapse.

The effort turned up 52 non-inherited mutations in 32 genes, many for the first time. The group included four in CREBBP. When researchers checked another 341 young leukemia patients for alteration in CREBBP,

they found that 13 of the 71 relapsed-ALL patients carried changes. In two more, pieces of CREBBP's DNA were deleted.

"The robust and accurate analytical method that we developed for processing such a large data volume made discovery of the CREBBP mutations possible," Zhang said. "This exciting finding illustrates that genomic sequencing can provide insight into not only disease initiation, but progression and prognosis as well."

Fourteen mutations were found scattered throughout CREBBP. The list includes an alteration also linked to Rubinstein-Taybi syndrome, a rare inherited multisystem developmental disorder, as well as mutations linked to the cell's steroid response. Four alterations occurred in the region of the gene that regulates DNA expression through a process of chemical modification known as acetylation. Working in mouse cells growing in the laboratory, researchers showed that CREBBP mutations disrupted acetylation of key DNA targets.

When researchers treated CREBBP-mutated leukemia cells growing in the laboratory with the steroid dexamethasone, a majority showed resistance to the drug. The study included cells from nine ALL subtypes. But researchers found most of the cells proved sensitive to another drug. That drug, vorinostat, uses a different mechanism to impact acetylation. Researchers now plan to test vorinostat in a mouse model of relapsed ALL.

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