Epigenetic factor likely plays a key role in fueling most common childhood cancer

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(Medical Xpress)—Changes in an epigenetic mechanism that turns expression of genes on and off may be as important as genetic alterations in causing pediatric acute lymphoblastic leukemia (ALL), according to a study led by scientists at St. Jude Children's Research Hospital and published in the June 10 online edition of the *Journal of Clinical Investigation*.

The results suggest the mechanism called cytosine methylation plays a previously under-appreciated role in the development of leukemia. Cytosine methylation involves adding or removing methyl groups to cytosine, which is a building block of DNA.

The study is the most comprehensive effort yet to identify and understand genetic and epigenetic factors that work together to cause ALL, the most common childhood cancer. ALL is a cancer of white blood cells known as lymphocytes. Scientists at St. Jude and Weill Cornell Medical College collaborated on the project.

Researchers used a variety of techniques to examine hundreds of thousands of methylation sites across the genome in normal and leukemic lymphocytes, including samples from more than 160 children with ALL. Investigators found that known ALL subgroups, which are defined by chromosomal alterations, have unique methylation profiles. Those profiles correlated with different patterns of gene expression.

"It is well known that different leukemia subgroups have distinct

patterns of gene expression that are important in the development of leukemia," said Charles Mullighan, MBBS (Hons), MSc, M.D., an associate member of the St. Jude Department of Pathology. Mullighan and Ari Melnick, M.D., Gebroe Professor Hematology/Oncology at Weill Cornell Medical College, are the study's co-corresponding authors.

"We have assumed that the underlying genetic changes are important determinants of those gene expression profiles. We now know that changes in methylation state also have key roles in influencing gene expression," Mullighan said.

The study used tissue samples from 137 St. Jude patients with B-cell leukemia and 30 children with T-cell leukemia. The patients represented all major ALL subgroups.

"The data show that aberrant epigenetic gene programming can now be considered a hallmark of acute lymphoblastic leukemia, occurring in all patients regardless of the presence of genetic mutations," Melnick said. "This offers the opportunity for development of epigenetic targeted therapies for patients with ALL that could be broadly applicable to many patients."

For comparison, researchers also checked B and T cells from 27 healthy children. Investigators found that leukemia cells shared a core group of abnormally methylated genes. The genes included ones involved in regulating the cell division and proliferation. "This remains to be tested, but the findings suggest that alterations in methylation are an important early step in the development of leukemia," Mullighan said.

The research provides further evidence that genetic and epigenetic events are both important in establishing different subgroups of ALL. For this study, researchers conducted genome-wide sampling of methylation, gene expression and DNA structural abnormalities,

including the gain or loss of DNA. Shann-Ching Chen, Ph.D., St. Jude Pathology, developed many of the methods used to integrate and analyze the results. Chen and Maria Figueroa, now of the University of Michigan and formerly of Cornell, are the study's co-first authors.

The study also found that more than one-third of 71 genes targeted by genetic alterations are also abnormally methylated in ALL. The methylation changes involved known tumor suppressor or oncogenes genes including CDKN2A, CDKN2B, PTEN and KRAS. "The findings suggest these genes are inactivated or deregulated more frequently than suggested by simply analyzing structural changes in the genome," Mullighan said.

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