

# Genetic hallmarks of acute lymphoblastic leukemia subtype uncovered

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A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

An international team of researchers from the St. Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project (PCGP) and the Children's Oncology Group (COG) has identified the genetic changes that underpin a subtype of the most common cancer found in children. This form of B-precursor acute

lymphoblastic leukemia (B-ALL) features genetic changes to two transcription factors known as DUX4 and ERG, proteins that closely control the activities of other crucial genes in human blood cells. The findings are published online today in the journal *Nature Genetics*.

Leukemia is the most common type of [childhood cancer](#) and ALL accounts for around 30% of cancers in children. Precursor B-cell [acute lymphoblastic leukemia](#) (B-ALL) is in turn the most common type of ALL (around 80%). In B-ALL, immature white blood cells known as B cell lymphoblasts proliferate and accumulate rapidly in the blood and bone marrow.

"Our work is motivated by a lack of information on the genetic basis of many B-ALL cases," said corresponding author Charles Mullighan, M.B.B.S., M.D., a member of the St. Jude Department of Pathology and the corresponding author of the study. "We discovered a distinct gene pattern in blood samples from some of the patients in our study and wanted to determine the underlying molecular events behind this signal."

The researchers studied a group of 1,913 patients who had B-ALL to understand the genetic basis of this subtype of B-ALL. This group of patients included children, adolescents and young adults. Microarray and transcriptome sequencing identified that 7.6% of these B-ALL patients had the distinctive genetic profile that the scientists wanted to characterize further.

The scientists uncovered a unique mechanism for how a transcription factor leads to the development of leukemia. "Our work revealed that in this type of B-ALL there is a sequence of molecular events that involves the interplay of two transcription factors," said Mullighan. Transcription factors are proteins that bind to specific DNA sequences and regulate the expression of genetic information from DNA to messenger RNA. ChIP sequencing, a method which allows researchers to analyze how

proteins interact with DNA, was crucial to reveal the link between the two transcription factors. Sequencing studies identified rearrangement of the transcription factor gene DUX4 in all cases in this subtype of ALL, resulting in high-level expression of DUX4. DUX4 was shown to bind to the gene for the transcription factor ERG, leading to deregulated expression of ERG. The deregulation of ERG compromised the function of ERG either by deletion of part of the gene, or by the expression of another form of ERG (ERGalt). In both cases, loss of activity was observed for the ERG transcription factor which led to the development of leukemia.

"The discovery of the connection between DUX4 fusion and the aberrant ERG isoform required integrating whole-genome sequencing, RNA-seq and ChIP-seq data using novel computational approaches that we developed," said Jinghui Zhang, Ph.D., chair of the St. Jude Department of Computational Biology and first author of the paper. The genomic landscape of this subtype of B-ALL can also be visualized using ProteinPaint ([pecan.stjude.org](http://pecan.stjude.org)), a powerful interactive tool developed at St. Jude to examine pediatric cancer mutations and gene expression.

Co-author Li Ding, Ph.D., assistant director of The McDonnell Genome Institute and director of computational biology in the Division of Oncology at Washington University School of Medicine in St. Louis, noted: "Our data reveal that a genetic rearrangement of DUX4 is present in all cases for patients with the distinct gene expression profile that was identified in our study. The genetic rearrangement of DUX4 is a clonal event that is acquired early in the development of leukemia."

"These findings explain the genetic defects that underlie a relatively common subset of B-ALL that was not fully understood until the DUX4 abnormalities were discovered. These results underscore that there is still more to be learned about the genetic changes in ALL, and that this knowledge can help refine treatment for patients," said co-author

Stephen Hunger, M.D., Chief of the Division of Oncology at the Children's Hospital of Philadelphia.

The researchers hope that the identification of these relationships between the two [transcription factors](#) will lead to new diagnostic tests for patients. DUX4/ERG ALL is linked with favorable outcomes even when other detrimental genetic mutations are present. At this point in time, only transcriptome or genome sequencing helps identify the DUX4 rearrangements. The scientists note that other detection methods, for example fluorescence hybridization or visual inspection of chromosomes under the microscope (karyotyping), are not sufficient to recognize genetic changes to DUX4.

Provided by St. Jude Children's Research Hospital

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