New research poised to transform approach to diagnosing and treating acute leukemia in children

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Genomic classification of ETP/ETP-like ALL. Credit: Nature (2024). DOI: 10.1038/s41586-024-07807-0

Researchers at Children's Hospital of Philadelphia (CHOP), St. Jude Children's Research Hospital (St. Jude) and the Children's Oncology Group (COG) today announced a significant paradigm shift in the understanding of T-lineage acute lymphoblastic leukemia (T-ALL), an aggressive and high-risk form of cancer, to one frequently driven by genetic changes in non-coding portions of our DNA.
The collaborative study was published today in the journal *Nature*.

Many children, adolescents, and young adult patients with T-ALL traditionally respond well to initial treatment. However, patients who relapse or have treatment-resistant disease often face a dire prognosis. Given the aggressive nature and rapid progression of the disease, and limited understanding of the genetic basis of T-ALL, researchers saw an urgent need for new and effective approaches to diagnosis and treatment.

"This paper is the first to transcend previous barriers and comprehensively profile the whole genome, uncovering critical insights in more than 1,300 children, adolescents and young adults with T-ALL," said David T. Teachey, MD, an attending physician, Director of Clinical Research at the Center for Childhood Cancer Research at CHOP and Chair of the Acute Lymphoblastic Leukemia disease committee in the COG.

"These findings are a significant clinical advancement, as the goal in treating T-ALL is to prevent relapse, which requires identifying the patients most at risk. This data now makes it possible to risk stratify patients with T-cell leukemia, identifying those with a high-risk of relapsing so we can treat them with newer or alternative medicines."

Prior studies were unable to identify important genetic changes in T-ALL, as they focused on the coding genome, the part of DNA that encodes proteins, the building blocks of cells. However, only 1% of DNA is coding, while the other 99% is termed non-coding.

Once considered useless, scientists now recognize that the non-coding region plays a key role in regulating biological processes. It signals the cell when to produce certain proteins, like a crossing guard aiding people to safely cross the street.
In this case, researchers studied more than 1,300 patients treated on the COG AALL0434 clinical trial and sequenced both the tumor and non-tumor genomes of each patient. While the researchers previously suspected that non-coding DNA in T-ALL played an important role, this study's findings are the first ever to establish that at a large scale.

The study found that approximately 60% of the genetic changes driving T-ALL cancer cells are non-coding changes. This fundamentally alters the way researchers think about T-ALL, offering a better understanding of disease biology. This leads to innovative treatments, including new immunotherapies developed at CHOP and St. Jude.

Traditionally, patients with T-All have been categorized by risk based on their therapy response and immunophenotype, which profiles cell surface proteins as part of the diagnostic workup. While cell surface protein expression helps define T-ALL subtypes, it hasn't proven effective in consistently identifying which patients have a good prognosis.

The new comprehensive data revealed why, strongly suggesting that a genomic approach replace the current immunophenotypic classification. As a result, the researchers developed models that incorporate genetics and response to treatment to risk stratify patients with T-ALL accurately and are currently in the process of validating results using patient samples from the next COG trial of T-ALL.

"It was striking how abundant these non-coding changes were and how many of them were enhancer perturbation events, whether it was hijacking or co-option of an existing enhancer, or changes that generated a new enhancer," said Charles Mullighan, MBBS, MD, St. Jude Children's Research Hospital, Comprehensive Cancer Center deputy director and Department of Pathology member.
"We now have a much stronger framework to take these alterations back to the lab and say now we've got better information to build the right models to understand the biology, and then to test therapy. We have very clear information that these are the sorts of alterations that people need to focus on to build a diagnostic test."

Researchers were able to classify T-ALL into 15 subtypes with distinct gene expression and genomic drivers, including previously undefined subtypes. They refined the classification of known subtypes and showed that driver lesions, other genetic changes, and the original cell type work together to define the genomic subtype and the clinical and biological characteristics of a condition.

They also observed a significant link between the type of gene alterations and outcomes in T-ALL. This new observation shows it is not only which gene is altered in the cancer cells, but also how it is altered, that helps define prognosis and chance of a cure.

"Future research must continue to determine broader applications for this approach," said Teachey. "These findings offer a strong a roadmap for improving patient outcomes and curing more children and adults with T-ALL."


Provided by St. Jude Children's Research Hospital

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