More accurate leukemia diagnosis expected as researchers refine leukemia classification

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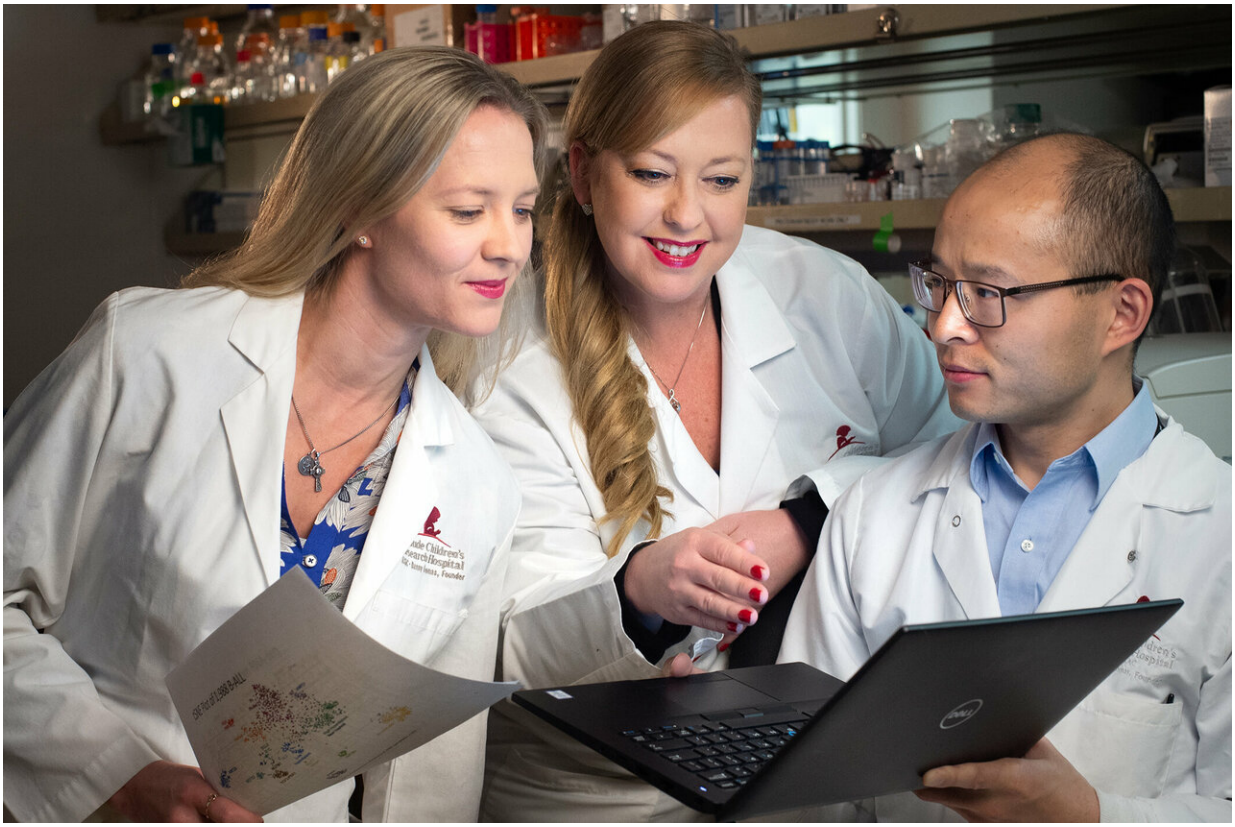

Kathryn Roberts, Ph.D., Michelle Churchman, Ph.D., and Zhaohui Gu, Ph.D., of the Mullighan laboratory, identified 23 subtypes of B-ALL, including eight new subtypes. Credit: St. Jude Children's Research Hospital

Like cartographers completing a map, investigators have identified

multiple new subtypes of the most common childhood cancer—research that will likely improve the diagnosis and treatment of high-risk patients. St. Jude Children's Research Hospital scientists led the study, which appears as an advance online publication today in the journal *Nature Genetics*.

Researchers used integrated genomic analysis, including RNA sequencing, to define the genomic landscape of B-cell acute lymphoblastic leukemia (B-ALL) in almost 2,000 children and adults. B-ALL is the most common form of ALL and the most common cancer in children. B-ALL remains the leading cause of pediatric cancer death.

Investigators identified 23 subtypes of B-ALL, including eight new subtypes, with distinct genomic and clinical features as well as outcomes. Subtype prevalence often varies with age. More than 90 percent of B-ALL cases can now be categorized by subtype compared with 70 percent a few years ago.

"B-ALL has remarkable molecular diversity, which we and others have used to refine classification and drive the development of precision medicines to improve B-ALL treatment and outcomes," said corresponding author Charles Mullighan, MBBS, M.D., a member of the St. Jude Department of Pathology. "Part of precision medicine is an accurate molecular diagnosis, which this study provides to more patients."

A novel subtype-defining alteration

Alterations of the transcription factor gene PAX5 defined two new subtypes, including PAX5 P80R, as the first lymphoblastic leukemia initiated by a point mutation. "While secondary mutations are necessary and often involve kinase signaling, we show this point mutation impairs development of B lymphoid cells and promotes development of B-ALL

in mice," Mullighan said.

The other PAX5 subtype, PAX5-altered, was defined by diverse alterations in the gene, including sequence mutations or rearrangements with one of 24 other genes. Together the PAX5 subtypes accounted for almost 10 percent of the previously uncategorized cases of B-ALL.

The new subtypes include a high-risk variety of B-ALL that occurs primarily in adults. It is defined by rearrangement of the transcription factors BCL2 with MYC or BCL6. "This subtype has a dismal diagnosis," Mullighan said. "Recognition of this subtype-defining rearrangement may lead to alternative therapy for patients." In contrast, a subtype defined by rearrangement of the gene DUX4 was associated with a good prognosis in adults, as had previously been observed in children.

Tracking gene expression

The study demonstrated the capability of RNA sequencing to identify multiple types of genomic alterations, highlighting the utility of this technique for leukemia diagnosis, particularly when whole-genome sequencing is not available. Examples in this study included chromosomal rearrangements resulting in fusion genes, gene-expression profiles and other alterations.

"Through this study, two-thirds of the previous uncharacterized B-ALL patients could be classified into different subtypes with distinct genetic alteration profiles and clinical features," said co-first author Zhaohui Gu, Ph.D., a postdoctoral fellow in the Mullighan laboratory. "That may substantially speed up the development of customized treatments for these patients.

"We also established a robust B-ALL classification pipeline based

mainly on RNA sequencing data that may be integrated into clinical diagnosis of ALL," Gu said.

"As a clinician, these data describing the diversity of subtypes of B-ALL will allow us to refine our prognostic abilities for individual patients, and ultimately, will lead to the development of new targeted therapies that will more effectively treat the leukemia with fewer side effects," said co-author Mark Litzow, M.D., professor of medicine at the Mayo Clinic and chair of the Leukemia Committee, Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network, which contributed to the study.

Additional subtypes revealed

The other newly identified subtypes include:

- NUTM1 gene rearrangement with different partner genes that researchers believe may be vulnerable to treatment
- HLF gene rearrangement to multiple genes, including TCF4 as well as the previously recognized partner TCF3.
- Three subtypes that share patterns of gene expression similar to those of established B-ALL subtypes. The classification suggests that the new subtypes, ETV6-RUNX1-like, KMT2A-like and ZNF384-like, have risk profiles and prognoses similar to the established subtype for which they are named.
- Additional subtypes driven by sequence mutations, including IKZF1 N159Y. Previous work from St. Jude and the Children's Oncology Group TARGET initiative have shown IKZF1 (Ikaros) mutations to be a marker of high risk B-ALL.

More information: PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia, *Nature Genetics* (2019). DOI: 10.1038/s41588-018-0315-5 ,

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