Prevalence of Ph-like ALL in adults underscores need for genetic testing, clinical trials

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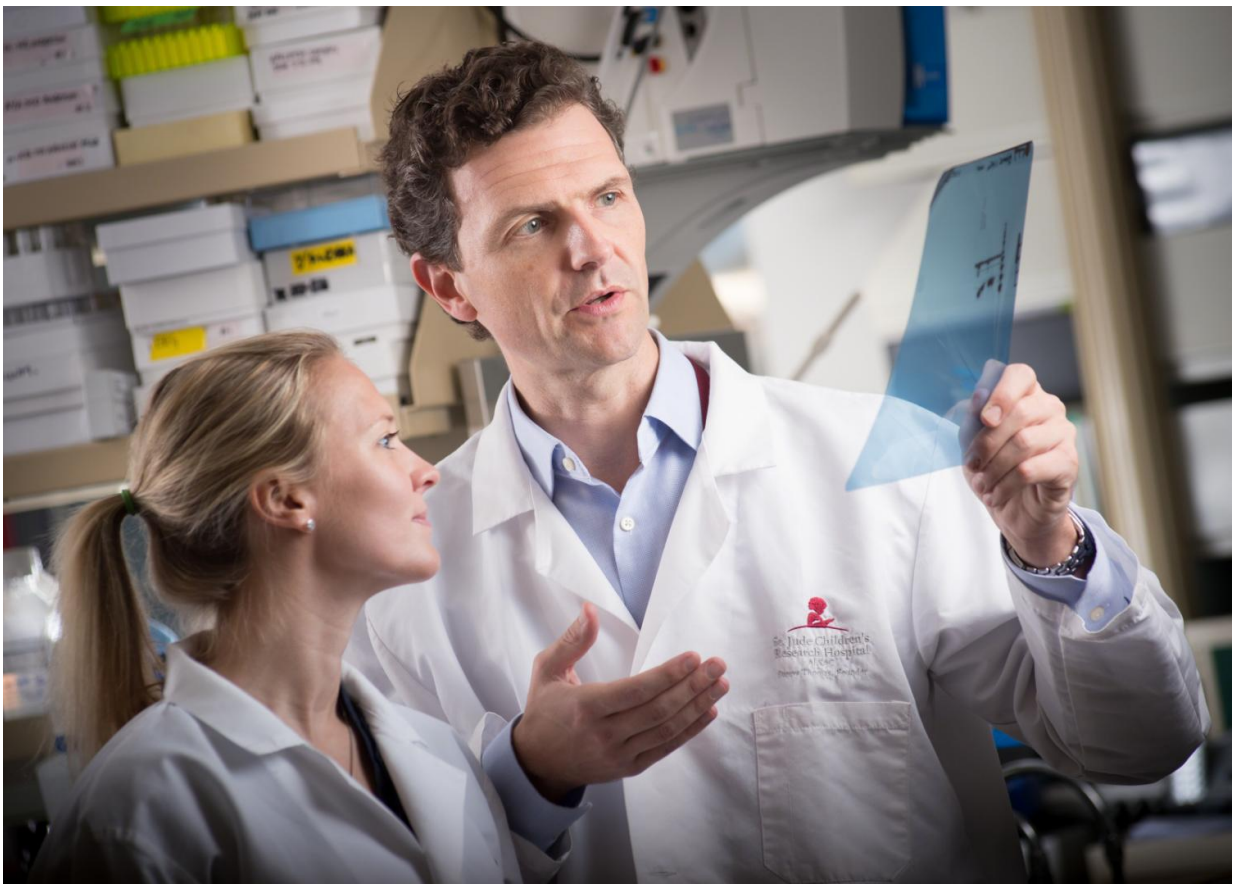

First author Kathryn Roberts, Ph.D., is pictured with corresponding author Charles Mullighan, M.D., MBBS. Researchers used gene expression profiling to identify cases of Ph-like ALL. Credit: St. Jude Children's Research Hospital / Seth Dixon

A high-risk subtype of acute lymphoblastic leukemia (ALL) first identified in children is highly prevalent in adults with ALL and is associated with a poor outcome, according to an international collaboration led by St. Jude Children's Research Hospital. The findings, published today in the *Journal of Clinical Oncology*, suggest that affected patients may benefit from treatment with available medications.

The study of 798 adults, who were between the ages of 21 and 86 years old when their cancer was diagnosed, showed that 194 patients, almost 25 percent, had the high-risk subtype Philadelphia chromosome-like ALL (Ph-like ALL). Many patients had genetic changes that suggest they may be treatable with targeted agents known as tyrosine kinase inhibitors, including dasatinib, imatinib and ruxolitinib. The drugs are already widely used to treat other types of leukemia that are common in adults.

"This study establishes that a large percentage of adults with ALL have this high-risk subtype," said corresponding author Charles Mullighan, M.D., MBBS, a member of the St. Jude Department of Pathology. "The finding provides a compelling reason to identify those with Ph-like ALL and move forward with clinical trials of these targeted therapies in combination with current chemotherapeutic regimens."

ALL is less common in adults than in children, but adults are far less likely to survive. Adults make up about 40 percent of the estimated 6,590 new cases of ALL identified annually in the U.S. At St. Jude, about 94 percent of pediatric ALL patients are alive five years after diagnosis. In this study, adults with Ph-like ALL had a five-year survival rate of 23.8 percent compared to 52.4 percent for adults with other ALL subtypes.

The study builds on previous research from St. Jude, the federally funded Children's Oncology Group and other adult cooperative groups

that identified Ph-like ALL as a distinct subtype of ALL first in children and then in young adults. "Our 2014 findings that the prevalence of Ph-like ALL increased with age and was particularly common in young adults generated tremendous interest because adult ALL is difficult to treat," Mullighan said. "In this study we determined that the prevalence remains high across the age spectrum of adults with ALL."

Researchers used gene expression profiling to identify cases of Ph-like ALL. The incidence among adults with ALL peaked at 27.9 percent in young adults between the ages of 21 and 39 years old. It remained 20 percent or more in patients between 40 and 86 years old.

Detailed genomic analysis of 180 of the Ph-like ALL cases showed that 88 percent of patients had genetic alterations fueling the cell proliferation that is a hallmark of cancer. The alterations result in abnormal activation of cell surface proteins called cytokine receptors or enzymes called kinases that cytokine receptors regulate. Tyrosine kinase inhibitors are designed to block different cytokine receptor signaling pathways. For example, dasatinib works by inhibiting ABL1 proteins while ruxolitinib targets the JAK2 protein.

"Our comprehensive sequencing showed that Ph-like ALL in adults is the most genetically diverse subtype of leukemia that has been described," said first author Kathryn Roberts, Ph.D., a St. Jude staff scientist. "Cumulatively more than 50 different chromosomal rearrangements involving 15 different kinases and cytokine receptors have been identified. In this study, we identified 11 chromosomal rearrangements that are new to Ph-like ALL."

The diversity of kinase-activating alterations in Ph-like ALL has important clinical implications, said co-author Hagop Kantarjian, M.D., of the University of Texas MD Anderson Cancer Center, Houston. "It is important that we now identify patients with Ph-like ALL at diagnosis to

provide optimal treatment with targeted agents," he said.

The findings also highlight the importance of centralized comprehensive genomic sequencing for patients, said co-author Elisabeth Paietta, Ph.D., of the Montefiore Health System and Albert Einstein College of Medicine. "Lymphoblasts from almost half of the patients with Ph-like ALL harbor a genomic rearrangement of CRLF2 (cytokine receptor-like factor 2), which can be detected by flow cytometry using an antibody to CRLF2. This is very important as it allows a quick characterization of this Ph-like ALL subtype, prior to any detailed sequencing," she said.

The study reflects a growing effort to understand cancer genetics across the age spectrum. "We have recognized for many years that childhood ALL does not exist in isolation, but is a subset of a disease that affects people of varying ages," Mullighan said.

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