Inherited gene variation tied to high-risk pediatric leukemia and greater risk of relapse

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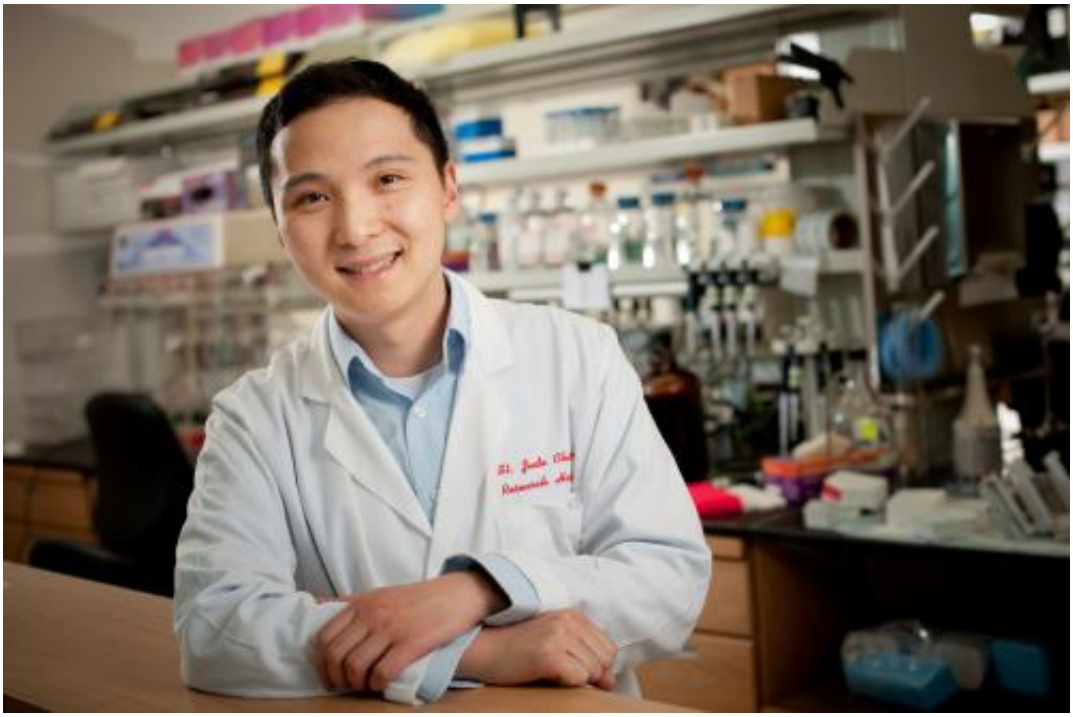

A study led by Jun J. Yang, Ph.D., of St. Jude Children's Research Hospital finds an inherited gene variation -- more common among Hispanic Americans -- is tied to increased risk of developing a high-risk form of pediatric leukemia. Credit: St. Jude Biomedical Communications

Research led by St. Jude Children's Research Hospital scientists has linked an inherited gene variation to a nearly four-fold increased risk of developing a pediatric acute lymphoblastic leukemia (ALL) subtype that is associated with a poor outcome. The study appears today in the online

edition of the scientific journal *Nature Genetics*.

The high-risk variant was found in the GATA3 gene. Researchers reported the high-risk version of the gene was more common among Hispanic Americans and other individuals with high Native American ancestry than those of other ethnic backgrounds. Forty percent of Hispanic Americans carried the high-risk variant, compared to 14 percent of individuals of European ancestry. For this study, ethnicity was defined by genetic variations associated with ancestry rather than individual self-reports.

Hispanic children are known to be at a higher risk of developing ALL and of dying from the disease. This is the latest in a series of St. Jude studies to report an association between inherited DNA variations in a handful of genes and an increased risk of childhood ALL among those of Hispanic ethnicity.

This is the first study to link an inherited genetic variation to an elevated risk of developing the leukemia subtype known as Philadelphia chromosome-like ALL (Ph-like ALL). Individuals with the high-risk version of GATA3 were 3.85 times more likely than those who inherited a different version of the gene to develop Ph-like ALL. Patients with the high-risk variant were also more likely to have a poor treatment response and have their cancer eventually return.

A significant percentage of patients with the high-risk GATA3 variant also had the tumor genetic alterations—including mutations, gene deletions and chromosomal re-arrangements—that are hallmark of Ph-like ALL. The changes occur in genes, including CRLF2, JAK and IKZF1 that regulate how blood cells grow and mature.

"Until recently, little was known about why a child develops a specific subtype of ALL in the first place and whether inherited genetic

variations that predispose an individual to a subtype also influence how he or she responds to the therapy," said corresponding author Jun J. Yang, Ph.D., an assistant member of the St. Jude Department of Pharmaceutical Sciences. "In this study, we discovered a genetic basis for susceptibility to Ph-like ALL, but even more importantly, the evidence that host and tumor genomes may interact with each other to influence the risk of developing and surviving ALL."

The study was done in collaboration with the Children's Oncology Group, a U.S.-based research cooperative study group focused on childhood cancer research and clinical trials. The research included 680 patients enrolled in COG clinical trials.

Ph-like ALL accounts for as much as 15 percent of childhood ALL and is associated with a high risk of relapse and a poor outcome. ALL is the most common childhood cancer. While overall cure rates for pediatric ALL are now about 90 percent, only 63 percent of children with Ph-like ALL are alive and cancer free after five years. Yang added that larger population studies are needed to assess risks associated with these inherited variations.

GATA3 carries instructions for assembling a protein called a transcription factor that turns other genes on and off. The GATA3 protein, and other members of the GATA gene family, plays a crucial role in normal development of a variety of blood cells. Alterations in GATA3 have been linked to other blood cancers, including Hodgkin lymphoma.

The high-risk GATA3 variation was identified using a library of 718,890 common genetic variations known as single nucleotide polymorphisms, or SNPs, to screen the DNA of 75 children with Ph-like ALL, 436 children with other ALL subtypes and 6,661 individuals without ALL. Fifty-eight percent of patients with Ph-like ALL carried the high-risk

version of the gene, compared to 29 percent of patients with other ALL subtypes and 20 percent of those without ALL. When researchers checked for the high-risk variant in additional patients with the Ph-like ALL subtype as well as other young ALL patients and individuals without the disease, they found the similar percentages carried the high-risk version.

Researchers found evidence the high-risk version of the gene was associated with significantly increased production of the GATA3 protein in cells growing in the laboratory. Investigators also found evidence that excess GATA3 activity in leukemia cells led to changes in the activity of other genes that mirrored Ph-like ALL. "Because this variant causes higher expression of GATA3 from birth, we suspect that this increased level of GATA3 may set the stage for developing Ph-like ALL later," said first author Virginia Perez-Andreu, M.D., Ph.D., a St. Jude postdoctoral fellow in the pharmaceutical sciences department.

More information: Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse, DOI: 10.1038/ng.2803

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