Discovery adds to evidence that some children are predisposed to develop leukemia

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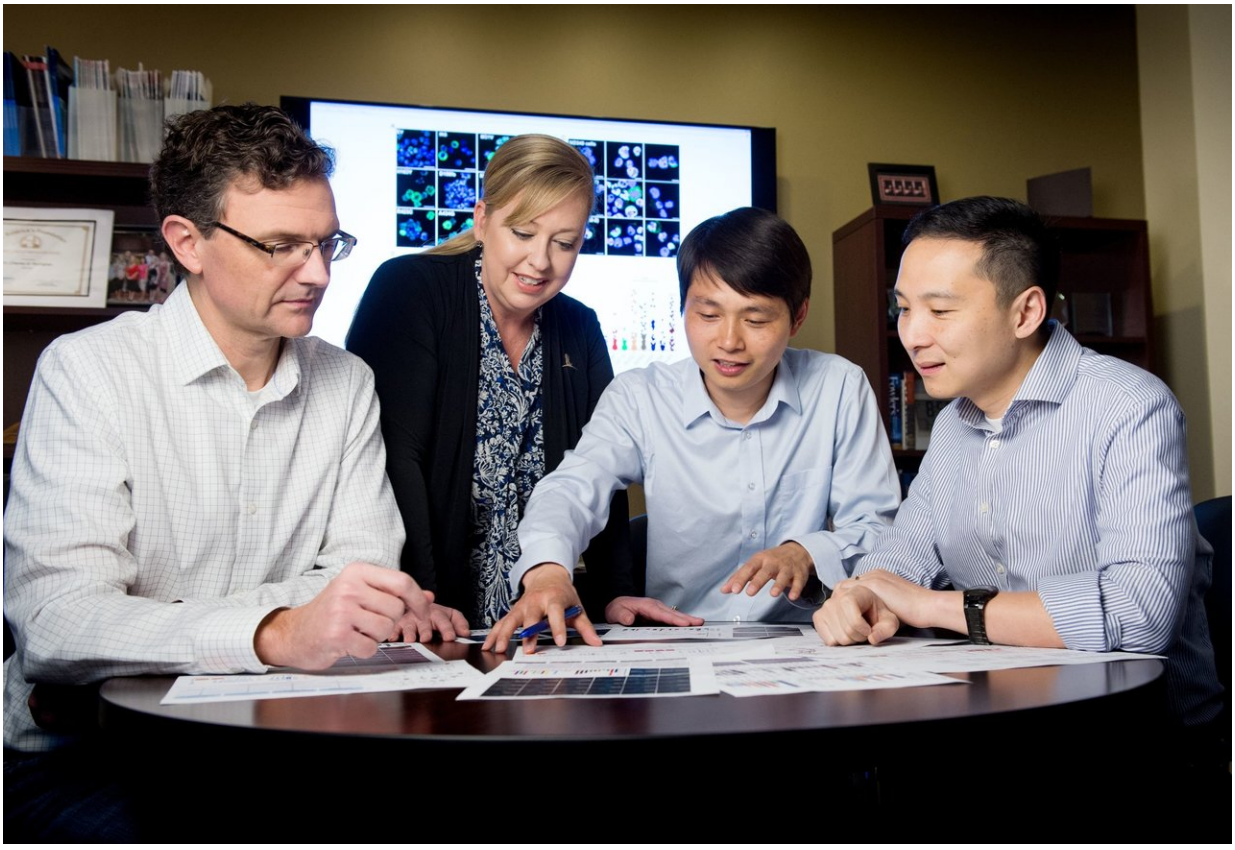

Charles Mullighan, MBBS, M.D., Michelle Churchman Ph.D., Max Qian PhD, Jun Yang Ph.D. Credit: St. Jude Children's Research Hospital / Seth Dixon

St. Jude Children's Research Hospital researchers have made a discovery that expands the list of genes to include when screening individuals for

possible increased susceptibility to childhood leukemia. The finding is reported online today in the journal *Cancer Cell*.

The gene is IKZF1, which encodes the transcription factor IKAROS that regulates gene expression. IKZF1 is the fourth gene identified that—like the genes TP53, ETV6 and PAX5—can predispose carriers to develop B-cell acute lymphoblastic leukemia (ALL). Variants in IKZF1 can also influence how some patients respond to treatment.

Researchers found a rare IKZF1 germline variant in three generations of a German family affected by pediatric ALL. St. Jude researchers then analyzed data from almost 5,000 young ALL patients and found that 0.9 percent of patients with B-cell ALL, the most common pediatric ALL, also carried germline variations in IKZF1. Germline variants are usually inherited, carried in DNA found in most cells.

"This finding adds to the growing body of evidence that, while germline variations still account for a small percentage of pediatric ALL cases overall, more children than previously recognized inherit a predisposition to develop ALL," said Charles Mullighan, MBBS, M.D., a member of the St. Jude Department of Pathology.

Jun J. Yang, Ph.D., an associate member of the St. Jude Department of Pharmaceutical Sciences and Department of Oncology, added: "The results also show that germline variants influence the response of leukemia cells to specific chemotherapeutic agents." Mullighan and Yang are the study's corresponding authors.

"This will expand the number of genes to consider when screening for predisposition to leukemia, particularly B-ALL. And while not everyone carrying a germline IKZF1 variant will develop leukemia, these results will help us educate families about the potential risk of leukemia," said co-author Kim Nichols, M.D., director of the St. Jude Cancer

Predisposition Division. As a group, Mullighan, Yang and Nichols have led research that identified the four known pediatric ALL predisposition genes.

IKZF1 frequently mutated in leukemic cells

The discovery comes a decade after Mullighan and his colleagues reported that IKZF1 was frequently mutated in leukemic cells and a harbinger of poor treatment outcomes.

The search for germline IKZF1 variants associated with ALL susceptibility began in Singapore. Nichols and Yang were there to talk about germline genetics of ALL and inherited (familial) cancer. During that visit, co-author Rupert Handgretinger, M.D., of Children's University Hospital, Tuebingen, Germany, mentioned three generations of a German family with a germline variation in IKZF1 and a family history of B-ALL.Two of the five family members with the variant had developed pediatric ALL and died. The remaining three are apparently healthy despite having reduced numbers of B cells.

Targeted sequencing of IKZF1 in 4,963 children with ALL identified 43 patients with 27 IKZF1 variants, almost exclusively patients with B-ALL. "The pattern of IKZF1 variants was surprising because many of the variants were in regions of the gene that are rarely mutated in leukemic cells; these regions of the gene have not been well characterized," Yang said.

IKZF1 variants affect IKAROS function

Extensive laboratory testing found at least 22 of the 28 variants affected protein functions. For example, IKZF1 variants resulted in IKAROS migrating outside the nucleus, which is where the protein normally functions. In other cases, variants were associated with increased cell

adhesion.

"Based on existing models, we would have predicted only 60 percent of the newly identified IKZF1 variants would be deleterious," said Michelle Churchman, Ph.D., of St. Jude Pathology. Churchman, Maoxiang Qian, Ph.D., of St. Jude Pharmaceutical Sciences, and Geertruy te Kronnie, of the University of Padova, Italy, are the first authors.

IKZF1 variants require a second "hit" to cause cancer

"In IKZF1 and the other ALL predisposition genes, cells may require an additional cooperating mutation to develop into leukemia," Mullighan said. "While familial ALL is rare, these cases can point to genes and novel biology to examine in a larger patient population.

"This study demonstrates the power of sequencing large groups of seemingly sporadic cases that reveal the genetic underpinnings of the disease," he said.

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