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Researchers identify inherited gene variation associated with pediatric acute lymphoblastic leukemia

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Researchers studying two generations of a family affected by pediatric acute lymphoblastic leukemia (ALL) have identified an inherited variation in the ETV6 gene that is associated with an increased risk of developing the disease. St. Jude Children's Research Hospital investigators led the study, which appears in the October 28 issue of the journal Lancet Oncology.

The magnitude of the risk must still be determined as well as how the variation may promote cancer. Evidence from this study suggests that the ETV6 variations alone are not sufficient to cause cancer, but may play a significant role in inherited predisposition to childhood leukemia.

Researchers discovered the association between ETV6 and childhood ALL by sequencing the whole exome of a family in which the mother and two of the three children have a history of pediatric ALL. All were treated at St. Jude and are now cancer free. The exome is the part of the genome that carries instructions for assembling the proteins that do the work of cells.

The mother and her children, including a daughter who does not have a cancer diagnosis, have an alteration in one of the two copies of ETV6. The alteration is predicted to result in the production of a shortened ETV6 protein that cannot fulfill its normal function of binding to DNA and regulating the expression of other genes. The father does not have the variant.

Researchers checked an additional 4,405 children with ALL and found 31 ETV6 variations that are potentially related to leukemia risk in 35 patients, or almost 1 percent of the patients screened. The variations were unique to ALL patients or extremely rare in the general population. The patients were enrolled in clinical trials sponsored by St. Jude or the Children's Oncology Group, an international clinical trials group focused exclusively on pediatric cancer.

"This is the latest example of the important role that genetic variation and inheritance plays in ALL risk," said corresponding author Jun J. Yang, Ph.D., an associate member of the St. Jude Department of Pharmaceutical Sciences. "That has clear clinical implications and will help us understand the biology driving this cancer."

ALL is identified in about 3,000 individuals each year aged 19 or younger in the U.S., making it the most common childhood cancer. While the cause remains largely unknown, only a small fraction of childhood leukemia is believed to involve an inherited genetic predisposition. Findings from this and other studies suggest the inherited risk for ALL may be much greater than what is thought previously, Yang said.

Additional research is needed to understand the biological effects of the ETV6 variants and to develop recommendations for monitoring and treatment, said co-first author Monika Metzger, M.D., a member of the St. Jude Department of Oncology. The other first authors are Takaya Moriyama, M.D., Ph.D., a postdoctoral fellow in Yang's laboratory, and Gang Wu, Ph.D., of the St. Jude Department of Computational Biology.

Patients with the variant tended to be older when their cancer was identified and more likely to have extra chromosomes. The variants, however, were not associated with a particular ethnicity or outcome of ALL therapy.

The family in this study has received genetic counseling through the St. Jude Cancer Predisposition Program to understand the risk and the need for continued monitoring, particularly of the currently cancer-free child with the ETV6 variation. No additional blood cancers have been reported in the extended family. "Identification of these variations has helped the family to better understand why their children developed cancer and to plan for the future," said co-author Kim Nichols, M.D., a member of the St. Jude Oncology department and director of the St. Jude Cancer Predisposition Division. Added Metzger: "In this case, the mother has been through the disease, knows the signs and symptoms and when to call."

ETV6 plays an important role in the blood system, particularly production of the platelets that help prevent bleeding. The gene works by binding to DNA and regulating the expression of other genes. An abnormal gene created by the fusion of ETV6 and the RUNX1 gene is one of the most common alterations in childhood ALL and is found in the leukemic cells of 20 to 25 percent of pediatric ALL.

This research builds on previous work from St. Jude and others that reported an association between inherited ETV6 variations and a rare inherited platelet deficiency in families with a susceptibility to blood cancers like ALL. This study further solidifies the association between ETV6 and pediatric ALL.

Almost half of the ETV6 variants identified in this study occurred in the region of the gene responsible for binding to DNA. "That suggests the loss or alteration of this DNA-binding function of ETV6 may be critical to cancer promotion," Yang said.

Source:
St. Jude Children's Research Hospital