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Inherited risk factors for childhood leukemia are more common in Hispanic patients

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Hispanic children are more likely than those from other racial and ethnic backgrounds to be diagnosed with acute lymphoblastic leukemia (ALL) and are more likely to die of their disease. Work led by St. Jude Children's Research Hospital scientists has pinpointed genetic factors behind the grim statistics.

Researchers studying a gene called ARID5B linked eight common variants of the gene to an increased risk of not only developing pediatric ALL but of having the cancer return after treatment. Two more ARID5B variants were tied to higher odds of developing the disease. Investigators found that Hispanic children were up to twice as likely as their white counterparts to inherit a high risk-version of ARID5B.

"For years we have known about ethnic and racial disparities in ALL risk and outcome, but the biology behind it has been elusive. Therefore, it is truly exciting to be able to not only pin down the biological basis but to find that the same gene might be responsible for both differences. Children who inherit high-risk versions of ARID5B are more likely to develop ALL in the first place and then more likely to fail therapy," said Jun Yang, Ph.D., an assistant member of the St. Jude Department of Pharmaceutical Sciences and the paper's corresponding author.

The work was done in collaboration with the Children's Oncology Group (COG), a U.S. based research cooperative study group focused on childhood cancer research and clinical trials. The study appears in the January 30 online edition of the *Journal of Clinical Oncology*.

Multiple factors contribute to cancer development, and inheriting a high-risk version of ARID5B is not enough to cause the disease, Yang said. These findings set the stage for exciting research in understanding how genetic, environmental and other factors combine in ALL, especially in the context of racial and ethnic disparity, he said.

"These and other genomic studies suggest we are poised to finally make significant progress in eliminating racial disparities in this catastrophic disease," Yang said. Additional work is needed to translate these findings into new clinical tools, he added.

Each year ALL is found in about 3,000 U.S. children, making it the most common childhood cancer. The incidence varies by self-declared race and ethnicity with rates for Hispanic individuals 50 percent higher than for non-Hispanic white individuals. For this study, researchers used genetic variations rather than individual self-report to define ancestry. White children were defined as having greater than 95 percent European ancestry and Hispanics children as having greater than 10 percent Native American ancestry.

Although the work of St. Jude researchers and others is helping to close the survival gap, Hispanic children are still less likely than children from other racial or ethnic backgrounds to be alive five years after diagnosis.

This study builds on the earlier St. Jude research that linked different versions of the ARID5B gene to ALL risk.

St. Jude and COG investigators partnered to see if variations in the ARID5B gene help to explain differences in either the incidence or the outcome of ALL in white and Hispanic patients. ARID5B belongs to a family of genes called transcription factors. They play a role in the normal development of white blood cells, which are targeted in ALL. Evidence suggests the gene also influences how methotrexate, a key anti-

leukemia drug, is metabolized.

To find ARID5B variants related to ALL, the study compared the gene in 330 Hispanic children with ALL and 541 Hispanic individuals without ALL. Researchers also checked ARID5B in 978 white ALL patients and 1,046 white individuals without the cancer.

Although the high-risk versions of ARID5B were found in both white and Hispanic patients, those variants were 1.5 to two times more common in Hispanic children than in white children.

Individuals inherit two copies of every gene, one from each parent. Children with one high-risk version of ARID5B were up to 80 percent more likely to develop ALL than others. Inheriting two copies of a high-risk version of the gene translated into a 3.6-fold increased ALL risk.

Researchers also found evidence linking ARID5B variants to relapse risk in 1,605 pediatric ALL patients enrolled in COG studies. Yang and his colleagues previously linked that level of Native American ancestry to a higher relapse risk in Hispanic ALL patients. Patients in this study who inherited a high-risk version of ARID5B were 50 percent more likely to relapse than other patients. They were also more likely to die of their cancer.

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