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Inherited risk factors increase odds of developing childhood acute lymphoblastic leukemia

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Scientists at St. Jude Children's Research Hospital have identified inherited variations in two genes that account for 37 percent of childhood acute lymphoblastic leukemia (ALL), including a gene that may help predict drug response.

The findings stem from the first complete search of the human genetic blueprint or genome to look for inherited risk factors for ALL, the most common childhood cancer. Published in the August 16 advance online issue of *Nature Genetics*, the work offers the first proof based on a complete survey of the human genome that inheritance plays a role in childhood ALL.

Mary Relling, Pharm.D., St. Jude Pharmaceutical Sciences chair and the paper's senior author, estimated that individuals who inherited variations in genes known as ARID5B or IKZF1 are almost twice as likely to develop ALL as those without the variations. Even then, she said, the risk remains low. ALL strikes roughly one in every 75,000 Americans. Sixty percent are children and teenagers.

"The genetic variations alone are not enough to cause the cancer. Like all cancers, pediatric ALL is a multi-factor disease," Relling explained. "But these findings may give us a handle on the mechanism of the disease and drug responsiveness to it."

Exactly the same genes, ARID5B and IKZF1, were confirmed to be altered in British children with ALL. That study was published by the Institute of Cancer Research in Surrey, England, in the same issue of *Nature Genetics*.

In the St. Jude study, researchers collaborated with colleagues from the Children's Oncology Group (COG), who provided additional cases for genetic analysis. COG is an international group of medical institutions that cooperate in research studies and clinical trials of childhood cancer treatment.

Researchers scanned the genomes of 441 children with ALL and a control group of 17,958 cancer-free individuals for more than 300,000 common genetic variations known as single nucleotide polymorphisms or SNPs.

The search found 18 SNPs that differed significantly in frequency between individuals with and without ALL. Six of the 18 SNPs were associated with one of the four main subtypes of ALL.

The six included two SNPs linked to the ARID5B gene. About 11 percent of those in the control group inherit the leukemia-risk ARID5B variations from both mother and father, Relling said. In comparison, the same high-risk ARID5B SNPs were found in 38 percent of patients with a type of ALL known as hyperdiploid ALL. That subtype accounts for about 20 percent of ALL patients.

Three more SNPs were traced to the genes IKZF1 and DDC, which are next to each other on chromosome 7. IKZF1 is also known as IKAROS. Earlier research from St. Jude and COG linked acquired changes in IKZF1 to an increased risk of ALL relapse. The new evidence tying inherited variation in IKZF1 to an increased risk of developing ALL underscores the need for medications targeting variations in this gene,

Relling said.

Both ARID5B and IKZF1 play important roles in normal development of lymphoid or white blood cells, she said. ARID5B belongs to a family of genes that make transcription factors, which help regulate gene activity. "If they have an inherited variation that affects the function of those genes, these are plausible pathways for how a normal lymphoid cell could be disrupted and transformed into a cancer cell," Relling said.

Inherited variations in ARID5B might also influence patient response to chemotherapy, particularly to the drug methotrexate. "We found this same inherited variation also affected accumulation of the drug in leukemia cells. It accumulates better. That allows us to use a lower dose and still cure the leukemia," Relling explained. "These findings may identify a new marker that could be used to help decide on doses of methotrexate in patients with varying ARID5B status."

Scientists are not sure how the SNPs they identified influence cancer risk. But studies of variation in gene expression associated with the ARID5B gene indicate the inherited variations have a biological function. Researchers must still determine what it is.

Source: St. Jude Children's Research Hospital