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Inherited genetic variations have a major impact on childhood leukemia risk

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Humans have between 20,000 and 25,000 genes that carry instructions for assembling the proteins that do the work of cells. Work led by St. Jude Children's Research Hospital found that children who inherit certain variations in four particular genes are at much higher risk of developing acute lymphoblastic leukemia (ALL).

The study also showed that Hispanic patients were more likely than patients of European or African ancestry to inherit high-risk versions of two of these genes. ALL rates are known to be higher among Hispanic children than those of European or African ancestry, this discovery points to at least one reason for that difference.

Each person's genome includes two copies of each gene, one from each parent. Thus, individuals could inherit up to eight high-risk versions of the four genes tied to an increased ALL risk. In this study, researchers found that having more than five copies of the risk genes resulted in a nine-fold greater risk of developing ALL in childhood than inheriting no more than one copy.

The report appears online March 19 in the *Journal of the National Cancer Institute*.

The findings stem from one of the largest multi-ethnic studies of genetic variation and ALL susceptibility ever conducted. The work included 2,450 pediatric ALL patients and 10,977 individuals from diverse racial and ethnic backgrounds without the disease.

The study's senior author, Jun J. Yang, Ph.D., an assistant member of the St. Jude Department of Pharmaceutical Sciences, said that the absolute risk for a particular child of developing ALL remains low. "ALL is a complex disease that likely involves many genes," he said. "The discoveries we are reporting in this paper are an important step forward in terms of understanding why children develop ALL in the first place, particularly for those with African or Hispanic ethnicity. However, this is probably still just a small part of the complete picture."

Along with providing insight into ethnicity and ALL risk, the study also offered clues to understanding the age pattern of ALL, which peaks in children ages 2 to 4. These findings suggest that younger patients might be most vulnerable to the effects of the high-risk gene variations.

This year about 3,000 children in the U.S. will be diagnosed with ALL, making it the most common childhood cancer. It is also among the most curable. Evidence that inheritance plays a role in childhood ALL risk has been building in recent years, but previous studies focused almost exclusively on patients of European ancestry. Thanks in part to new statistical methods for studying genetic variation in more diverse populations, this study expanded the quest to understand the genetic basis of ALL risk to include patients of African and Hispanic as well as European ancestry.

The effort involved ALL patients treated at St. Jude and through the Children's Oncology Group, the world's largest cooperative pediatric cancer research organization, As a comparison, investigators also screened DNA from individuals without ALL. Researchers used an automated system to check each person's DNA for 709,059 gene variations. In this study, ethnicity was assigned based on gene variations representative of European, African and Native American ancestry.

Previous studies from St. Jude and others linked pediatric ALL risk to

common differences in the ARID5B, IKZF1, CEBPE and CDKN2A/2B genes. All play a role in normal blood and immune system development. ALL is a cancer of certain immune cells. In this study, researchers also discovered several variations in the gene PIP4K2A, which were associated with an elevated pediatric ALL risk. Hispanic patients were more likely than others in this study to inherit high-risk versions of the ARID5B and PIP4K2A genes, while African-American patients were less likely to have these variants.

Provided by St. Jude Children's Research Hospital