Rare, inherited mutation leaves children susceptible to acute lymphoblastic leukemia

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(Medical Xpress)—Researchers have discovered the first inherited gene mutation linked exclusively to acute lymphoblastic leukemia (ALL) occurring in multiple relatives in individual families. The discovery of the PAX5 gene mutation was led by St. Jude Children's Research Hospital and others. The work appears in the current advance online edition of the scientific journal *Nature Genetics*.

The mutation was identified in two unrelated families in which pediatric ALL has been diagnosed in multiple generations. The mutation involved a single change in the DNA sequence of PAX5, a gene that is known to be deleted, mutated or rearranged in some B cell tumors, including ALL. This is the first time changes in PAX5 have been linked to an inherited cancer risk.

"Pioneering work from St. Jude and others has identified inherited variations in other genes that modestly increase the risk of developing ALL, but few had been identified in familial leukemia," said co-corresponding author Charles Mullighan, MBBS(Hons), MSc, M.D., an associate member of the St. Jude Department of Pathology. "Prior studies had identified inherited mutations in families with multiple types of cancer including leukemia, but not in families with ALL alone."

While inherited mutations have been linked to an increased risk of breast, colon and other cancers, particularly adult cancers, very few have been tied to childhood tumors. ALL affects about 3,000 children nationwide annually, making it the most common childhood tumor.

"For families with several generations of cancer patients, it means a lot to know that scientists and clinicians are working together to better understand the genetic factors that explain their family's increased risk," said co-author John T. Sandlund, M.D., a member of the St. Jude Department of Oncology. "They are hopeful that other families, as well as their own, might benefit from this research."

The mutation was found in the normal cells and leukemia cells of eight ALL patients from several generations of two unrelated families. The work was led by researchers at St. Jude, Memorial Sloan-Kettering Cancer Center in New York and the University of Washington, Seattle.

The newly identified mutation is a single letter change in the DNA sequence of PAX5. The change results in the amino acid glycine being substituted for serine at amino acid 183 in the PAX5 protein. While PAX5 sequence mutations are common in sporadic cases of ALL, this mutation is the first identified at this location in the protein.

Genes are segments of DNA that determine the sequence of the amino acid chains that fold into proteins. These protein-coding regions of DNA are known collectively as the exome.

The mutation was discovered by sequencing the exome of normal cells from seven ALL patients in the two families and the exomes of the leukemic cells of four of these patients. The exomes from three relatives unaffected by leukemia were also sequenced.

Researchers reported that the leukemia cells all carried a single copy of PAX5 that included the mutation. The patients had all lost the normal version of the gene due to the partial deletion of chromosome 9, where PAX5 is located. The loss resulted in a marked reduction of normal PAX5 activity in the leukemia cells. In contrast, family members who carried the mutant gene, but who had not developed leukemia, retained

the normal copy of the gene.

Researchers studied 39 other families with a history of multiple tumors, including leukemia, without finding additional inherited PAX5 mutations. The researchers also examined more than 500 additional cases of non-inherited B cell ALL and found mutations at the same position of the PAX5 gene in two more patients. These two individuals had also lost the other copy of PAX5 through partial deletion of chromosome 9 in their leukemic cells. The findings suggested that the PAX5 mutation and deletion of the second, non-mutated copy of PAX5 contribute to the development of leukemia.

The PAX5 gene encodes a transcription factor, which is a protein that regulates the activity of other genes. Working in cells growing in the laboratory, investigators found evidence that the newly identified PAX5 mutant resulted in reduced expression of genes normally regulated by PAX5 in developing and mature B cells.

Researchers used a technique called transcriptome sequencing to examine the patterns of gene expression in leukemic cells from two of the patients with familial leukemia and 139 patients with non-inherited ALL. The results also associated the PAX5 mutation to deregulation of the genes that the PAX5 protein controls.

"The study clearly shows that the inherited PAX5 mutation is an important event in the development of leukemia. More work is needed to define the full range of inherited mutations in ALL," said first author Esmé Waanders, Ph.D., a St. Jude postdoctoral fellow who is affiliated with Radboud University Medical Center, Nijmegen, the Netherlands.

Provided by St. Jude Children's Research Hospital