a gene mutation linked with a rare inherited form of childhood acute lymphoblastic leukemia (ALL), the most common cancer occurring in children. The finding could potentially be used to prevent ALL in leukemia-prone families by prenatal testing.

Clinical Genetics Service Chief Kenneth Offit

"This is the first genetic susceptibility specific to childhood ALL that has ever been seen, so this is a new syndrome," says Kenneth Offit, Chief of the Clinical Genetics Service and lead investigator of the study, which was published online by the journal *Nature Genetics* on September 8. "When you look at this story, there's also the human context of a family with small children who have more than their share of medical challenges."

The gene, known as *PAX5*, works as a transcription factor or "master gene" by regulating the activity of numerous other genes and is essential for maintaining the identity and function of mature immune cells called B cells, which are integral to the development of ALL.

Dr. Offit's work focuses on defining genetic factors that cause an increased susceptibility to cancer. In 1996, the same gene-sequencing approach used in the new research helped his team identify *BRCA2*, the most common mutation associated with an increased risk of breast and ovarian cancer among individuals of Ashkenazi Jewish ancestry.

"Like Lightning Striking Multiple Times"

About five years ago, Memorial Sloan Kettering physicians became aware that a family being cared for by their team had multiple members from several generations diagnosed with ALL in childhood. Despite ALL's high cure rate — due in large part to several successful treatment protocols developed at Memorial Sloan Kettering — the family had lost one child to the disease.

Family members were strongly committed to helping with this research, Dr. Offit recalls. Seeing so many cases of the same cancer in the same family "was like lightning striking multiple times — there's a sense of bewilderment when this calamity repeats itself."

By analyzing their DNA through genome sequencing, and comparing thousands of genes from people with and without ALL, the researchers discovered that all members of the family who had the disease and were involved in the study carried the *PAX5* mutation.

Scientists from St. Jude Children's Research Hospital, the University of Washington, and the Broad Institute of Harvard and MIT were the lead collaborators on the study, and were joined by other institutions around the globe. The researchers also identified a second leukemia-prone family unrelated to the family treated at Memorial Sloan Kettering.

"In this second family, it was the same exact gene mutation," Dr. Offit says. "The chances of that happening are incredibly small. It's like a single misspelling in the entire encyclopedia."

In addition, the researchers carried out a series of experiments that confirmed that the gene mutation caused significant changes in the gene's function.

Back to top

Additional Contributing Factors under Investigation

Beyond the mutated *PAX5* gene, other factors led affected children to develop ALL. In all family members who developed ALL, one of the two copies of the *PAX5* gene was missing, leaving only the mutated version. Some family members who didn't develop ALL — such as a parent of a child who had the disease — carried the mutation without becoming ill, however.

The researchers believe additional factors — which are currently under examination but as yet unknown — played a role in the development of ALL in these children.

"It's clear we need additional genetic events to happen for this disease to take over," says Cornelius Miething, a research associate working with biologist Scott W. Lowe, chair of Memorial Sloan Kettering's Geoffrey Beene Cancer Research Center, and a senior coauthor of the study.

Back to top

Preventing Future ALL in Affected Families

Dr. Offit hopes that ongoing research will determine what percentage of childhood ALL patients have the *PAX5* mutation. Current estimates suggest that the gene mutation is quite rare, and Memorial Sloan Kettering will again team with the St. Jude group led by physician-scientist Charles Mullighan to address the question.

But even before such information is ascertained, an immediate application of the research is the prevention of ALL in families in which leukemia is already prevalent. Concerned prospective parents can seek in vitro fertilization that includes preimplantation genetic diagnosis, also known as PGD, a technique that can identify embryos with genetic defects before pregnancy is attempted.

"It could provide a way to preemptively allow parents to check for the mutation so they can make better-informed reproductive decisions," says medical geneticist Kasmintan Schrader, who is a postdoctoral researcher in Dr. Offit's lab.

Additionally, the newly discovered gene mutation may someday help scientists determine how to target transcription factors to treat other, more common forms of leukemia, Dr. Offit says, since the *PAX5* mutation is also present in some non-inherited leukemias.

"Our focus is understanding why the cancers occur," Dr. Offit says. "With better understanding, we're better able to target prevention as well as therapy. We want to test this idea that there may be more typical forms of leukemia that do not appear to be hereditary but may in fact have these same genetic alterations occurring spontaneously and lead to cancer forming in the first place. That research is in progress now, and if this model proves correct, these findings will have much broader relevance to childhood leukemia and possibly other cancers."

Back to top

This research was supported by the Starr Cancer Consortium and by the National Institutes of Health under grant CA21765.