

# Cancer sequencing project identifies potential approaches to combat aggressive leukemia

January 11 2012

---

Researchers have discovered that a subtype of leukemia characterized by a poor prognosis is fueled by mutations in pathways distinctly different from a seemingly similar leukemia associated with a much better outcome. The findings from the St. Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project (PCGP) highlight a possible new strategy for treating patients with this more aggressive cancer.

The work provides the first details of the genetic alterations fueling a subtype of acute lymphoblastic leukemia (ALL) known as early T-cell precursor ALL (ETP-ALL). The results suggest ETP-ALL has more in common with acute myeloid leukemia (AML) than with other subtypes of ALL. The study appears in the January 12 edition of the journal *Nature*.

ALL is the most common childhood cancer and about 12 percent of patients have T-ALL. T-ALL arises from T-lineage white blood cells that make up one branch of the immune system. ETP-ALL was discovered by St. Jude researchers and accounts for about 12 percent of T-cell ALL. Many ETP-ALL patients fail to respond to current therapy and never enter remission. Only 30 to 40 percent of these patients become long-term survivors, compared to about 80 percent of children battling other T-ALL subtypes.

"The mutations and gene expression profile we identified in this study suggest that patients with ETP-ALL might benefit from treatment that includes drugs developed for treatment of acute myeloid leukemia," said Charles Mullighan, M.D., Ph.D., an associate member of the St. Jude Department of Pathology and one of the study's corresponding authors.

Mullighan said ETP-ALL was selected for inclusion in the [pediatric cancer genome project](#) due to the poor outcome and the lack of information on the genetic lesions that underlie this aggressive subtype of leukemia. "St. Jude is a pioneer in increasing overall ALL survival rates, which today exceed 90 percent for St. Jude patients. Now we are working toward similar progress against this rare form of the disease," he said.

The human genome is the complete set of instructions needed to assemble and sustain human life. Leukemia and other cancers develop when normal cells accumulate mutations in the genome that cause the unchecked cell growth that is a hallmark of cancer. The three-year Pediatric Cancer Genome Project is sequencing the genomes of tumor cells and matched normal DNA samples of 600 children with some of the most poorly understood and aggressive cancers. Investigators believe the findings will be the foundation for the next generation of clinical tools.

For this study, researchers sequenced and analyzed the normal and cancer genomes of 12 St. Jude patients with ETP-ALL. Investigators then checked for some of the same mutations in an additional 94 young [leukemia](#) patients with either ETP-ALL or other types of T-cell ALL.

"We found mutations unique to ETP-ALL that are not seen in other forms of ALL," said co-author Richard Wilson, Ph.D., director of The Genome Institute at Washington University. "The results provide new targets for therapy and a way to use genetic tests to identify ETP-ALL

patients early and earmark them for more aggressive therapy."

The pattern of mutations identified in ETP-ALL was reminiscent of changes associated with AML, Mullighan said. The alterations were concentrated in genes in the cytokine receptor and RAS signaling pathways that are involved in the type of cell regulation disrupted in cancer. The mutations, which included NRAS, FLT3, JAK3, IL7R and other genes, were found in about 67 percent of patients with ETP-ALL, but in only 19 percent of other T-ALL patients.

In addition, mutations in genes known or predicted to disrupt normal development of blood stem cells or lymphocytes were identified in 58 percent of ETP-ALL patients, but in just 17 percent of other T-ALL patients. The affected genes included ETV6, RUNX1, IKZF1 and GATA3. GATA3 helps regulate the early stages of T cell development, and mutations in the gene were found exclusively in ETP-ALL patients.

Epigenetic mutations, which are alterations affecting genes that indirectly influence the activity of other genes, were also more common in ETP-ALL patients. These genes, including EZH2 and SUZ12, were mutated or deleted in 45 percent of ETP-ALL patients, but in just 11 percent of the comparison group. The targeted genes modify proteins known as histones, which control gene activity through DNA binding.

Researchers also showed that ETP-ALL includes recurring mutations in about a half-dozen genes not previously linked to blood cancers. The list includes the genes RELN and DNMT2. "The pattern of [mutations](#) we found in those genes suggests they function as tumor suppressors and their loss contributes to the malignant transformation of developing blood cells," Mullighan said.

Mullighan said work is underway to develop laboratory models of human ETP-ALL and to use these models to identify AML drugs that are most

likely to benefit ETP-ALL patients. The list of possible drugs includes high-dose cytarabine and targeted chemotherapy agents that inhibit activity in the cytokine receptor and JAK signaling pathways found in this study to be disrupted in ETP-ALL [patients](#), researchers said. Those pathways help regulate cell division and normal development of the blood system.

"This is the first of a series of important discoveries on the genomic basis of childhood cancers that are emerging from the Pediatric Cancer Genome Project, which is on schedule to fully sequence 600 pediatric cancer genomes by 2013," said Dr. William E. Evans, St. Jude director and CEO. James Downing, M.D., St. Jude scientific director, St. Jude PCGP site leader and a corresponding author of the study, added: "This study highlights how the genome project is generating new insights into the genetic alterations that underlie some of the most aggressive childhood cancers and in turn is pointing us toward new therapeutic options that may increase the survival rates for children with these cancers."

[Another PCGP study](#) that advances understanding of the genetic underpinnings of the malignant childhood eye tumor retinoblastoma is scheduled to appear in the January 11 online edition of *Nature*. Data from both studies are available at no cost to investigators on the PCGP Explore website, which can be accessed at <http://explore.pediatriccancergenomeproject.org>.

Provided by St. Jude Children's Research Hospital

Citation: Cancer sequencing project identifies potential approaches to combat aggressive leukemia (2012, January 11) retrieved 8 May 2023 from <https://medicalxpress.com/news/2012-01-cancer-sequencing-potential-approaches-combat.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.