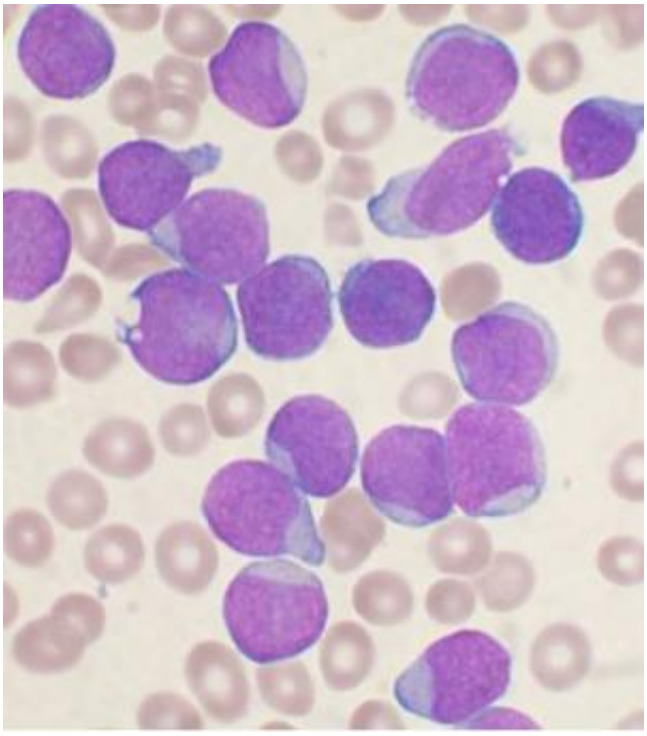
Chromosomal rearrangement is the key to progress against aggressive infant leukemia

March 6 2015



A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

The St. Jude Children's Research Hospital—Washington University Pediatric Cancer Genome Project reports that a highly aggressive form of leukemia in infants has surprisingly few mutations beyond the chromosomal rearrangement that affects the MLL gene. The findings suggest that targeting the alteration is likely the key to improved

survival. The research appeared online ahead of print this week in the scientific journal *Nature Genetics*.

The study is the most comprehensive analysis yet of this rare but aggressive subtype of pediatric acute lymphoblastic leukemia (ALL) that occurs during the first year of life and is sometimes diagnosed at birth. The leukemia cells of up to 80 percent of infants with ALL have a chromosomal rearrangement that fuses the MLL gene to a gene on a different chromosome. The resulting MLL fusion gene encodes an abnormal protein. The fusion protein plays a key role in transforming normal blood cells into leukemia cells.

Researchers used whole genome sequencing and other techniques to identify the genetic alterations in 65 infants with ALL, including 47 with the MLL rearrangement. Scientists were surprised to find that despite being an aggressive leukemia, the MLL rearranged subtype had among the lowest mutation rates reported for any cancer.

"These results show that to improve survival for patients with this aggressive leukemia we need to develop drugs that target the abnormal proteins produced by the MLL fusion gene or that interact with the abnormal MLL fusion protein to shut down the cellular machinery that drives their tumors," said senior and co-corresponding author James R. Downing, M.D., St. Jude president and chief executive officer. "That will not be easy, but this study found no obvious cooperating mutations to target."

St. Jude researchers are working to identify compounds and develop combination therapies to improve cure rates for infants with the MLL rearrangement. Nationally, 85 percent of pediatric ALL patients now enjoy long-term, cancer free survival compared to 28 to 36 percent of infants with the high-risk subtype.

"We frequently associate a cancer's aggressiveness with its mutation rate, but this work indicates that the two don't always go hand-in-hand," said co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis. "Still, our findings provide a new direction for developing more effective treatments for these very young patients."

The other corresponding authors are Tanja Gruber, M.D., Ph.D., assistant member in the St. Jude Department of Oncology, and Anna Andersson, Ph.D., formerly of St. Jude and now of Lund University, Sweden. Andersson and Jing Ma, Ph.D., of the St. Jude Department of Pathology, are co-first authors.

Almost half of infants with MLL rearranged ALL had activating mutations in a biochemical pathway called the tyrosine kinase-phosphoinositide-3-kinase (PI3K)-RAS pathway. Surprisingly, the mutations were often present in only some of the leukemic cells. Researchers analyzed leukemia cells in infants whose cancer returned after treatment and found that at the time of relapse the cells lacked the pathway mutations. "The fact that the mutations were often lost at relapse suggests that patients are unlikely to benefit from therapeutically targeting these mutations at diagnosis," Downing said.

Researchers also found that older pediatric leukemia patients with the MLL rearrangement had significantly more mutations than infants. Almost half of the older children had mutations in genes that encode epigenetic regulatory proteins. Epigenetic proteins influence activation of other genes. "While MLL belongs to a family of genes that encode epigenetic regulatory proteins, there was a striking difference between infants and older children regarding the frequency of mutations in other epigenetic regulatory genes," Andersson said.

Gruber added: "This observation raises the possibility of a fundamental

difference in the cell targeted for transformation in infants versus older patients. Our working hypothesis is that in infants the MLL rearrangement occurs in a developing blood cell, a prenatal progenitor cell, which requires fewer additional mutations to fully transform into leukemia. In contrast, in older patients the MLL rearrangement isn't enough on its own."

Provided by St. Jude Children's Research Hospital