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Comprehensive look at rare leukemia finds relatively few genetic changes launch disease

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The most comprehensive analysis yet of the genome of childhood acute myeloid leukemia (AML) found only a few mistakes in the genetic blueprint, suggesting the cancer arises from just a handful of missteps, according to new findings from St. Jude Children's Research Hospital. The research appears in the July 27 online edition of the *Proceedings of the National Academy of Sciences*.

"Our data raise the possibility that the development of AML may require fewer genetic alterations than other cancers and that a very limited number of biological processes may need to be altered in hematopoietic stem cells, multi-potential progenitors or committed myeloid progenitors to convert them from a normal cell to AML," the authors noted, referring to several types of immature and maturing cells that give rise to this cancer. James Downing, M.D., St. Jude scientific director and the paper's senior author, said the findings highlight questions about what it takes to transform a normal cell into a cancer cell. "The complement of genetic lesions varies across the different genetic subtypes of AML, but there are very few lesions in total. That is surprising. Most cancers have lots of alterations," he explained.

AML accounts for about 20 percent of childhood leukemia. This year it will be diagnosed in about 500 U.S. children. About 60 percent of young AML patients become long-term survivors.

This study reflects the push to chart the genetic changes that free cells from normal controls and allow the uncontrolled cell division that is a

hallmark of cancer. Downing said the findings underscore the need to survey the entire genome of childhood AML and take a more detailed look at particular AML subtypes.

Added Ina Radtke, Ph.D., the paper's lead author: "This rigorous systemic genome-wide study was an important step to direct our future efforts to the most effective strategies to pinpoint lesions in AML." She is a postdoctoral fellow in Downing's laboratory.

For this study, researchers analyzed leukemia cells from 111 St. Jude AML patients representing the seven most common subtypes of the disease. The scientists used several techniques to catalog the changes, including single-nucleotide-polymorphism (SNPs) microarrays to chart genome-wide regions of DNA gain or loss, which are known as copy number alterations (CNAs). To identify point mutations, the researchers also performed DNA re-sequencing of 25 genes that are commonly mutated in adult AML. Point mutations involve a single chemical change in the molecular building blocks of DNA.

The data demonstrated that, in contrast to pediatric acute lymphoblastic leukemia (ALL), AML is characterized by a very low burden of mutations. The researchers found slightly more than two CNAs per AML patient, and less than one point mutation per patient in the genes sequenced. The scientists also reported just 21 percent of AML patients had six or more lesions. By comparison, an earlier St. Jude study reported 77 percent of young ALL patients, a more common cancer, had that much DNA damage. Even more surprising, 34 percent of patients in this study lacked any apparent CNA, and 28 percent of those with a translocation lacked additional DNA abnormalities. Certain chromosomal re-arrangements are known as translocations.

The investigators also found no association between CNAs and patient outcome. Despite the low overall number of lesions in the patients

studied, novel recurring regions of genetic alteration were identified that harbor known and potential new cancer genes.

The study also reports cryptic chromosomal translocations in 14 percent of patients in this study who, based on standard testing, appeared to lack such re-arrangements. Cryptic translocations are too small to be detected by conventional testing. Downing said the analysis identified focal CNAs adjacent to genes previously linked to chromosomal translocations. Those genes are MLL, MLLT4, NUP98 and NSD1. These data suggest that chromosomal translocations are more frequent in AML than was previously thought. Identifying the abnormality during diagnostic testing will require additional, more sophisticated screening, Downing said.

Source: St. Jude Children's Research Hospital