Medical Xpress

Study finds new genetic defects in high-risk childhood leukemia subtypes with chromosomal loss

January 20 2013

Research led by St. Jude Children's Research Hospital scientists has identified a possible lead in treatment of two childhood leukemia subtypes known for their dramatic loss of chromosomes and poor treatment outcomes.

The findings also provide the first evidence of the genetic basis for this high-risk leukemia, which is known as hypodiploid acute lymphoblastic leukemia (ALL). Normal human cells have 46 chromosomes, half from each parent, but hypodiploid ALL is characterized by fewer than 44 chromosomes. Chromosomes are highly condensed pieces of DNA, the molecule that carries the inherited instructions for assembling and sustaining a person. The research appears in the January 20 advance online edition of the scientific journal *Nature Genetics*.

The study, the largest ever focused on hypodiploid ALL, confirmed that this tumor has distinct subtypes distinguished by the number of chromosomes lost and the submicroscopic genetic alterations they harbor. Researchers found evidence suggesting more than one-third of patients with a subtype known as low hypodiploid ALL have Li-Fraumeni syndrome. Families with Li-Fraumeni syndrome harbor inherited mutations in the TP53 tumor suppressor gene and have a high risk of a range of cancers. Hypodiploid ALL had not previously been recognized as a common manifestation of Li-Fraumeni syndrome.

Researchers reported that the major hypodiploid subtypes are both sensitive to a family of compounds that block the proliferation of cancer cells. The compounds include drugs already used to treat other cancers. The subtypes are low hypodiploid ALL, characterized by 32 to 39 chromosomes, and near haploid ALL, which has 24 to 31 chromosomes.

"This study is a good example of the important insights that can be gained by studying the largest possible number of patients in as much detail as possible. This approach led us to key insights about these leukemia subtypes that we would otherwise have missed," said the study's senior and corresponding author, Charles Mullighan, MBBS(Hons), MSc, M.D., an associate member of the St. Jude Pathology Department. Mullighan is a Pew Scholar in Biomedical Sciences.

The near haploid and low hypodiploid ALL subtypes represent 1 to 2 percent of the estimated 3,000 pediatric ALL cases diagnosed annually in the U.S. But they account for a much larger number of ALL treatment failures. Today more than 90 percent of young ALL patients will become long-term survivors, compared to 40 percent for patients with these two high-risk subtypes. St. Jude researchers led the study in collaboration with investigators from the Children's Oncology Group, the world's largest organization devoted exclusively to childhood and adolescent cancer research.

"The cure rate for hypodiploid ALL is only about half that obtained overall for children with ALL. The findings of this study are very important and have the potential to impact how this high-risk subset of childhood ALL is treated," said Stephen Hunger, M.D., chair of the Children's Oncology Group ALL committee and one of the paper's co-authors. "This study grew out of the efforts of Hank Schueler, a teenager who died from hypodiploid ALL. He wanted to find ways to help treat other children with this type of leukemia. After he passed away, his

parents established a foundation to support research in hypodiploid ALL. We thought that one way to do this was to conduct the genomic analyses reported in this paper. These findings would not have been possible without Hank's idea and without support from the Schueler family."

Researchers used a variety of laboratory techniques to look for genetic abnormalities in cancer cells from 124 pediatric patients missing at least one chromosome. The patients included 68 with near haploid ALL and 34 with low hypodiploid ALL. Investigators also checked white blood cells collected when 89 of the 124 patients were in remission. The study included whole-genome sequencing of the entire cancer and normal genomes of 20 patients with near haploid or low hypodiploid subtypes. For another 20 patients, investigators deciphered just DNA involved in protein production. Researchers also screened cancer cells from 117 adult ALL patients, including 11 with the low hypodiploid subtype.

The whole genome sequencing was done in conjunction with the St. Jude Children's Research Hospital – Washington University Pediatric Cancer Genome Project. The project has sequenced the complete normal and cancer genomes of more than 600 children and adolescents with some of the most aggressive and least understood cancers.

Near haploid ALL was characterized by alterations in six genes and increased activity in key pathways that help regulate cell division and development. Disruption of these pathways, known as Ras and PI3K, has been linked to other cancers. The changes were found in 71 percent of near haploid ALL patients and included deletion of the NF1 gene. The gene had not previously been linked to high-risk leukemia. Other alterations involved the genes NRAS, KRAS, MAPK1, FLT3 and PTPN11.

Low hypodiploid ALL in both adults and children was linked to mutations in the TP53 tumor suppressor gene. The gene was altered in

91 percent of pediatric patients with the ALL subtype and in 10 of the 11 adults with low hypodiploid ALL included in the study. Other common alterations involved RB1, another tumor suppressor gene.

About 38 percent of children with low hypodiploid ALL also carried TP53 abnormalities in non-cancerous blood cells. The mutations included many previously linked to Li-Fraumeni syndrome, which is characterized by changes in TP53.

Further evidence linking low hypodiploid ALL to Li-Fraumeni syndrome came when researchers found the same TP53 mutation in two generations of the same family. The father was 31 years old when he was found to have a brain tumor associated with Li-Fraumeni syndrome. His son later developed low hypodiploid ALL.

"Identification of children with low-hypodiploid ALL and inherited TP53 mutations could help expand the use of life-saving cancer screening," said Linda Holmfeldt, Ph.D., a St. Jude postdoctoral fellow. She and Lei Wei, Ph.D., of the St. Jude Department of Computational Biology and formerly of Pathology, are the study's co-first authors. "Screening helps save lives by finding cancers much earlier when the odds of a cure are greatest," Holmfeldt said.

Investigators also reported deletions involving Ikaros gene family members that are rare in other ALL patients. The genes play a role in normal immune system development. The IKZF3 gene, also known as AIOLOS, was deleted in 13 percent of near haploid ALL patients. IKZF3 was deleted in nearly 53 percent of patients with low hypodiploid ALL.

Despite such differences, when researchers tested a variety of compounds against cells from both subtypes growing in the laboratory, they found compounds that targeted the PI3K pathway inhibited

proliferation. Researchers are testing the effectiveness of these drugs in mouse models.

Provided by St. Jude Children's Research Hospital

Citation: Study finds new genetic defects in high-risk childhood leukemia subtypes with chromosomal loss (2013, January 20) retrieved 24 April 2024 from https://medicalxpress.com/news/2013-01-genetic-basis-high-risk-childhood-cancer.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.