Researchers reveal genomic landscape of core-binding factor acute myeloid leukemia

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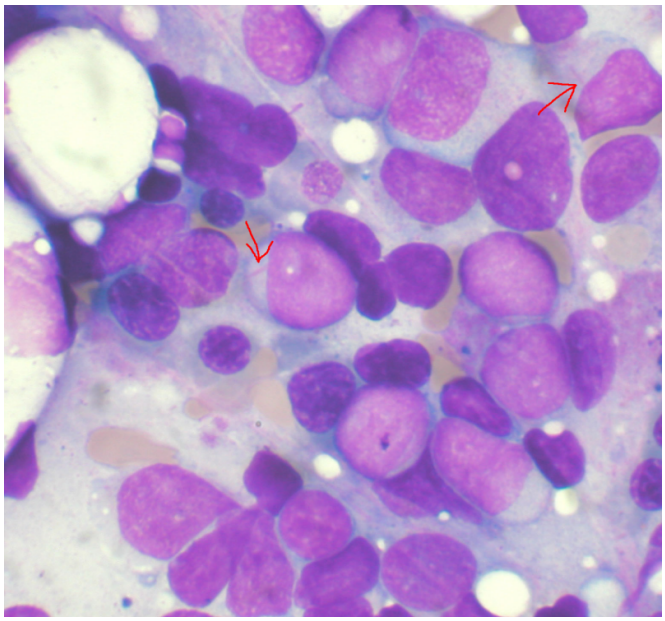

Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

An international team of researchers from the St. Jude Children's Research Hospital - Washington University Pediatric Cancer Genome Project (PCGP) has completed a detailed map of the genomic landscape for core-binding factor acute myeloid leukemia (CBF-AML). The work reveals differences in the landscape of mutations that contribute to the diversity of CBF-AML. The findings are published online today in the journal *Nature Genetics*.

"We set out to understand the genetic variations that contribute to the development of CBF-AML using whole-exome and whole-genome sequencing," said Jeffery Klco, M.D., Ph.D., assistant member of the St. Jude Department of Pathology and one of the lead authors of the study along with James R. Downing, M.D., and Jinghui Zhang, Ph.D., of St. Jude and Lars Bullinger, M.D., Ph.D., of the University of Ulm in Germany. "Our goal was to define a detailed mutational landscape to understand better the genetic changes that contribute to disease."

CBF-AML accounts for approximately 30 percent of pediatric AML and 15 percent of adult cases. The researchers sequenced samples from 87 children and 78 adults and found a similar mutational landscape in both groups. In 17 cases, full genome sequences were obtained. Whole-exome sequencing was carried out on the remaining 148 samples.

Scientists have known for some time that two genes, RUNX1 and CBFB, can be affected by chromosomal rearrangements in AML. These genes encode for proteins that are part of the core-binding factor (CBF) complex, a transcriptional complex essential for normal blood cell development. CBF-AML arises by chromosomal rearrangements that impair the activity of the CBF complex. While patients with CBF-AML have a massive accumulation of abnormal cells known as myeloid blasts and an acute shortage of mature blood cells, it is clear that these chromosomal rearrangements are not sufficient for the development of cancer. This has prompted scientists to search for other mutations that can work together with the genetic rearrangements to cause leukemia.

"One or more cooperating mutations are needed for leukemia to take hold," Klco said. "Our analysis showed dramatic differences in the genetic landscapes of these cooperating mutations for CBF-AML with rearrangements involving RUNX1 compared to those that involve CBFB."

The researchers identified several mutations that may contribute as cooperating mutations, including changes in CCND2, a gene that makes a protein involved in the cell cycle. New recurrent mutations were also identified, including alterations in DHX15,

which has a role in modifying certain types of RNA.

"Mutations that shortened the length of CCND2 were clustered around one end of the protein, the C-terminus, and resulted in stabilization of cyclin D2 and cell cycle activation," said Zhang, chair of the St. Jude Department of Computational Biology. "Many of the mutations we identified interfered with molecular signaling or epigenetic factors."

Other genes identified that may contribute to CBF-AML included ASXL2, ZBTB7A and MGA. "Some of the mutations, like ASXL2, are epigenetic regulators that modify the local state of chromatin. Others, like ZBTB7A, appear to act like tumor suppressors," Klco said.

Co-author Li Ding, Ph.D., assistant director of The McDonnell Genome Institute and director of computational biology in the Division of Oncology at Washington University School of Medicine in St. Louis, noted: "We continue to uncover genetic alterations and mutations that underpin different types of AML. This speaks to the value of this rigorous type of genetic analysis in defining the genomic landscape and learning how specific genes and mutations contribute to disease."

Patients with CBF-AML have a relatively good prognosis. However, the disease recurs in some patients. "In some cases we were also able to look at the types of mutations in CBF-AML at diagnosis and relapse to understand how the disease changes over time, and we hope to build on this work moving forward," said Klco.

"This study highlights how the Pediatric Cancer Genome Project continues to generate new insights into genetic alterations and cooperating mutations that give rise to diseases like AML," said Downing, St. Jude president and chief executive officer. "The results suggest a number of new components that may have a functional role in CBF-AML and also highlight genes that may be crucial for patients at risk of relapse."

While the findings suggest that these new components play a role in disease, the next step is to confirm their precise function in this type of leukemia. Further studies are already underway to fully evaluate the contributions of the different genes as well as the roles of the newly identified genetic alterations in CBF-AML.

More information: The genomic landscape of core-binding factor acute myeloid leukemias, *Nature Genetics*, DOI: 10.1038/ng.3709

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