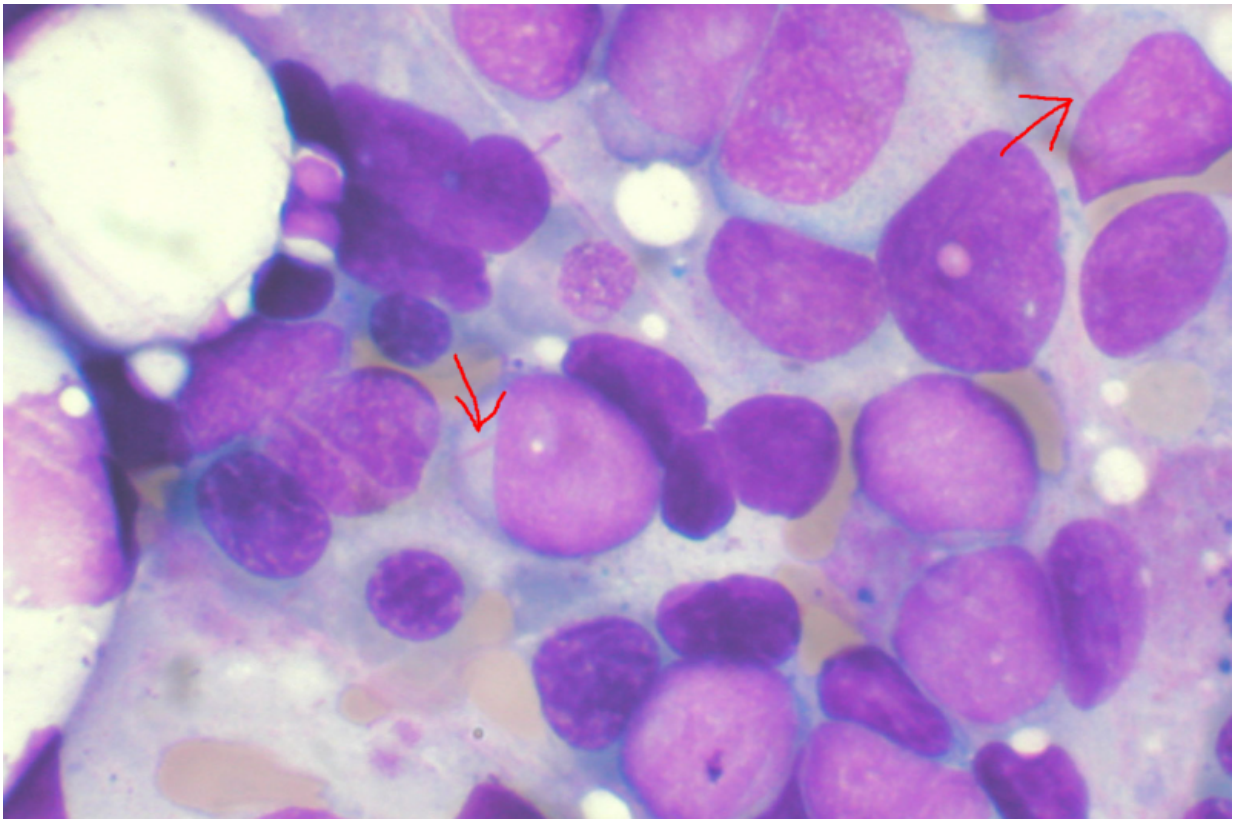
MedicalXpress

Two genetic mutations discovered in subset of acute myeloid leukemia

December 7 2016



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

Two genetic mutations known to play a role in many solid cancers might also help explain why a subset of acute myeloid leukemia (AML)

patients develop the disease, according to new research from The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James).

The mutations (which occur in the CCND1 and CCND2 genes) have been previously implicated in solid tumors but this new report represents some of the first data describing the role of these mutations in core binding factor acute myeloid leukemia (CBF-AML), a form of cancer that affects blood-forming tissue (bone marrow).

It is well-established that the two primary types of CBF-AML—called t(8;21) and inv(16)—are related on a molecular level and are both identified by the presence of a merged genetic mutation, or fusion gene. Researchers know, however, that the fusion gene alone is not capable of causing leukemia independently.

"The hematology community has long sought to determine what other factors in addition to the fusion genes occur in this special type of leukemia. We are now the first to describe that mutations in CCND1, and among the first to describe that mutations in the sister gene CCND2 are unique features of CBF-AML with t(8;21)," says Ann-Kathrin Eisfeld, MD, first author of the study, Internal Medicine resident in the Physician-Scientist-Training program of OSU and researcher with the OSUCCC-James Leukemia Research Program in the laboratories of Clara D. Bloomfield, MD, and Albert de la Chapelle, MD, PhD.

"In addition, we have collected the first evidence that mutations in CCND2 lead to more aggressive growth of leukemia cell lines. Based on those results, we can now test if they actually provide a transformative 'second hit' that propels the cells carrying the fusion gene to progress into cancer," adds Eisfeld.

The OSUCCC - James team reports its findings online ahead of print Nov. 15, 2016, in the journal *Leukemia*. Additional insights were also presented at the American Society of Hematology meeting on Sunday, Dec. 4, 2016.

Study Design and Results

A previous comprehensive study of gene mutations in CBF-AML reported the presence of at least one genetic mutation in 85 percent of the patients studied, leaving the remaining 15 percent of patients to harbor other, as yet not discovered mutations. For this new study, Eisfeld and colleagues searched a large cohort of CBF-AML samples for the missing mutations that, together with the fusion genes, might contribute to the leukemia in this subgroup of cases.

The team analyzed pretreatment bone marrow and peripheral blood samples from a 177 adult CBF-AML patients who received similar medical treatment through a national clinical trial conducted at multiple centers across the United States.

Using a customized, targeted next-generation sequencing approach, the team looked for mutations in 84 leukemia- and/or cancer-associated protein-coding genes. Laboratory tests were also performed on blood or bone marrow cells to look for chromosomal irregularities.

Researchers discovered two significant new mutations in the cyclin D1 (CCND1) and cyclin D2 (CCND2) genes, representing the first dual evidence of these recurrent genetic mutations in patients with t(8;21) AML.

CCND1 and CCND2 mutations were found in 15 percent of patients with t(8;21), making it the third most common mutation among this subgroup of AML patients.

"This is extremely valuable information that was previously unknown and it might help us develop targeted therapies more likely to help patients with this disease in the near future," adds Eisfeld.

Researchers say this enhanced understanding of molecular alterations in CBF-AML could help explain the differences in clinical features between patients in the two subtypes of the disease, and especially also to patients with other types of leukemias.

More information: A-K Eisfeld et al, Mutations in the CCND1 and CCND2 genes are frequent events in adult patients with t(8;21)(q22;q22) acute myeloid leukemia, *Leukemia* (2016). DOI: 10.1038/leu.2016.332

Provided by Ohio State University Medical Center