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Inherited DNA change explains overactive leukemia gene

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A small inherited change in DNA is largely responsible for overactivating a gene linked to poor treatment response in people with acute leukemia.

The study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) focused on a gene called BAALC. This gene is often overactive, or overexpressed, in people with acute myeloid or acute lymphoblastic leukemia, and it indicates that the disease is likely to respond poorly to standard therapy.

This study discovered that BAALC overexpression is caused by a small change called a single nucleotide polymorphism, or SNP (pronounced "snip") in the gene's DNA. The SNP alters the gene's "On" switch, allowing a different molecule to keep it "running" when it shouldn't.

"We want to emphasize," says principal investigator Dr. Albert de la Chapelle, professor of medicine, the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research, and co-leader of the Molecular Biology and Cancer Genetics Program, "that this SNP does not raise an individual's risk of developing leukemia, but it does predispose to overexpression of the BAALC gene, which is associated with leukemia development and poor response to treatment."

The findings, published recently in the *Proceedings of the National Academy of Sciences*, suggest that this SNP could be a useful marker of

prognosis and for guiding therapy in acute leukemia patients.

Specifically, the DNA change caused by the SNP creates a binding site for an activating molecule called RUNX1, which is also involved in the formation of normal and malignant blood cells. The researchers showed that patients with high levels of RUNX1 protein also had high levels of BAALC gene expression, while those with low RUNX1 protein had low BAALC gene expression.

For this study, de la Chapelle and his colleagues used DNA sequencing to examine the genomic region of BAALC in 253 patients with cytogentically normal AML (CN-AML) treated in Cancer and Leukemia Group B clinical trials. The analysis revealed nine SNPs of interest, but the researchers focused only on one – called rs62527607[T] – which creates a RUNX1 binding site in the BAALC promoter region.

The researchers validated the findings in 105 CN-AML patients enrolled in the German-Austrian AML Study Group trials for adult patients. The validation group findings supported the association of high BAALC expression with the SNP, and high RUNX1 expression with high BAALC expression.

"We doubt that this SNP is entirely responsible for BAALC overexpression, but we do believe it is a major contributor to the overactivity," de la Chapelle says.

Provided by Ohio State University Medical Center