Study pinpoints genetic cause of increased leukemia risk

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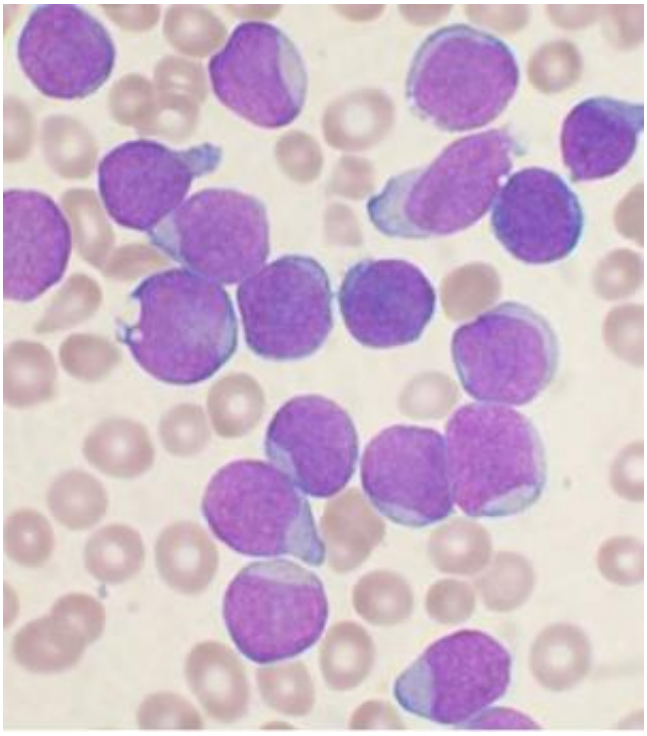

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A University of Colorado Cancer Center study published today in the journal *Nature Genetics* describes a newly-discovered, heritable genetic cause of acute lymphoblastic leukemia (ALL), namely mutation of the gene ETV6. Much like mutation of the gene BRCA marks people at risk to develop breast and ovarian cancers, identification of mutations in the

gene ETV6 may allow doctors to predict the development of ALL, allowing increased monitoring and in the future, perhaps strategies to prevent the disease. There are just over 30,000 cases of ALL diagnosed in the United States each year, with the majority of those cases being in children ages 2-5.

"These people are born with a broken gene and it sets them up for leukemia," says Chris Porter, MD, investigator at the CU Cancer Center and associate professor in the Department of Pediatrics at the CU School of Medicine.

The finding started with a family that had an abnormally high rate of ALL.

"All of them had big red blood cells, low platelet counts and propensity to bleed," Porter says.

This familial link to abnormal blood dynamics and predisposition to ALL implied a common genetic denominator. The question was what, exactly, in this family's genes created these blood problems. To answer the question, the group performed "whole exome sequencing" of family members to, effectively, take snapshots of each protein-producing gene in the chromosomes of these people predisposed to ALL.

Working at the CU Cancer Center, bioinformaticist Ken Jones, PhD, sifted through the data to compare these high-risk genomes with normal-risk genomes. The key difference between healthy genomes and those predisposed to develop ALL was mutation of the gene ETV6.

The gene is involved in the development of blood cells. "Somatic" mutations of the gene, meaning mutations that are not present in the genome at birth but develop later, have previously been implicated in the development of blood cancers. In fact, somatic ETV6 translocation is the

most common gene rearrangement in childhood leukemia. Porter explains that somatic mutation of the gene ETV6 requires the presence of other "helper" mutations to cause ALL.

This study is one of two new reports to show that "germline" mutation of ETV6, meaning abnormality that is heritable and present in the genome at birth, can also cause cancers. (Thus the mutation and the risk can run in families.) Unlike somatic mutation of the gene, it seems as if the germline mutation puts the patient one important step closer to the development of leukemia from the time of birth.

Porter and colleagues hope that future work will show the prevalence of this mutation.

"It's not common in a general population," Porter says, "but we think it might be much more common in people who develop ALL."

This means that of people who develop ALL, heritable mutation of the gene ETV6 may be a cause in some cases.

"The paper highlights this gene in the development of leukemia," Porter says. "By studying this mutation, we should be able to gather a better understanding of how leukemia develops."

More information: Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia, DOI: 10.1038/ng.3253

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