Genetic variants tied to increased risk of bone complications in young leukemia patients

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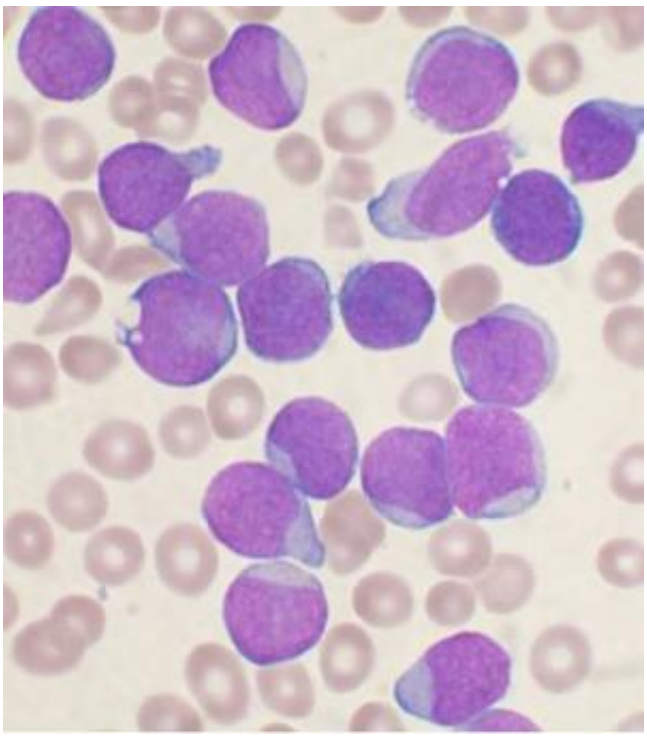

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Variations in genes involved in normal bone development are associated with an 8-to 15-fold increased risk for osteonecrosis in young patients with acute lymphoblastic leukemia (ALL), according to research led by St. Jude Children's Research Hospital and Children's Oncology Group

investigators. The results were discussed today at the 57th Annual Meeting of the American Society of Hematology.

Osteonecrosis is a major side effect of ALL treatment with chemotherapy. About 15 percent of ALL patients develop the complication, which is caused by reduced blood flow to bones in the hips and other joints and leads bone to break down faster than it is replaced. For patients, the results may include stiffness, pain, disability and joint-replacement surgery. ALL patients aged 10 to 20 years old are at particularly high risk for osteonecrosis.

This study is the first to focus on genetic risk factors for osteonecrosis in ALL patients less than 10 years old, an age group that accounts for about 75 percent of newly identified ALL patients and about half of ALL patients who develop osteonecrosis. Researchers used genome-wide association studies to check the DNA of 1,186 ALL patients less than 10 years old for single changes in the 3.2 billion 'letters' or chemical bases that make up the human genetic code.

Researchers checked for genetic variations that were more common in 82 young ALL patients who developed osteonecrosis than in 287 who did not. The screening was then repeated with an additional 817 ALL patients younger than 10 years old. The patients were treated in clinical trials of the Children's Oncology Group, an international clinical trials group focused exclusively on pediatric cancer.

Patients with osteonecrosis were eight to 15 times more likely to have genetic variations located near BMP7, a gene important for normal bone development.

"The goal of this and earlier studies is to identify and understand genetic and other risk factors for osteonecrosis so we can identify patients at high risk for the side effect and develop interventions to prevent the

disease," said first author Seth Karol, M.D., a St. Jude Physician Scientist Training Program fellow. Karol works with the study's senior author Mary Relling, Pharm.D., chair of the St. Jude Department of Pharmaceutical Sciences.

A variation in the glutamate receptor gene GRID2 was also associated with a greater likelihood of osteonecrosis in ALL patients younger than 10. GRID2 belongs to a family of genes that carries instructions for assembling receptor proteins on the cell membrane that cells rely on to respond to the chemical messenger glutamate. The finding confirms previous research that reported variations in other glutamate receptor genes were associated with an elevated risk of osteonecrosis, with the prior study primarily identifying the risk in patients aged 10 and older.

"The finding that the genetic variations that affect osteonecrosis risk differ by age was unexpected," Karol said. "The results suggest that as children age, particularly when bone growth is accelerated during adolescence, certain gene variants may become more or less important."

More information: S. E. Karol et al. Genetic risk factors for the development of osteonecrosis in children under age 10 treated for acute lymphoblastic leukemia, *Blood* (2015). DOI: 10.1182/blood-2015-10-673848

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