New insights into why people with Down syndrome are at higher risk for leukemia

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Scientists from Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago were the first to examine endothelial cells—one of the main sources of blood

production—for clues as to why people with Down syndrome have higher prevalence of leukemia. They identified a new set of genes that are overexpressed in endothelial cells of patients with Down syndrome. This creates an environment conducive to leukemia, which is characterized by uncontrolled development and growth of blood cells. Their findings, published in the journal *Oncotarget*, point to new potential targets for treatment and possibly prevention of leukemia, in people with Down syndrome and in the general population.

"We found that Down syndrome, or Trisomy 21, has genome-wide implications that place these individuals at higher risk for leukemia," says co-lead author Mariana Perepitchka, BA, Research Associate at the Manne Research Institute at Lurie Children's. "We discovered an increased expression of leukemia-promoting genes and decreased expression of genes involved in reducing inflammation. These genes were not located on chromosome 21, which makes them potential therapeutic targets for leukemia even for people without Down syndrome."

Down syndrome is a congenital genetic disorder caused by additional genetic material from an extra copy of chromosome 21. The condition occurs in about one in 700 babies. In addition to developmental and physical impairments, people with Down syndrome have a 500-fold risk of developing acute megakaryoblastic leukemia (AMKL) and a 20-fold risk of being diagnosed with acute lymphoblastic leukemia (ALL).

"Our discovery of leukemia-conducive gene expression in endothelial cells could open new avenues for cancer research," says co-lead author Yekaterina Galat, BS, Research Associate at the Manne Research Institute at Lurie Children's.

The study used skin samples from patients with Down syndrome to create induced pluripotent stem cells (iPSC) that were then

differentiated into endothelial cells. Impairment in endothelial cell genetic expression was found to produce altered endothelial function throughout the cell maturation.

"Fortunately, advances in iPSC technology have provided us with an opportunity to study cell types, such as endothelial cells, that are not easily attainable from patients," says senior author Vasil Galat, Ph.D., Director of Human iPS and Stem Cell Core at Manne Research Institute at Lurie Children's and Research Assistant Professor of Pathology at Northwestern University Feinberg School of Medicine. "If our results are confirmed, we may have new gene targets for developing novel leukemia treatments and prevention."

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago

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