Genes related to Down syndrome abnormalities may protect against solid tumors

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Scientists from Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago discovered that a set of genes with decreased expression in individuals with Down syndrome may lead to clinical abnormalities in this population, such as poor muscle development and heart valve problems. Impairment in these same genes may also protect people with Down syndrome from developing solid tumors. Their findings were published in *Scientific Reports*.

"Our promising preliminary data carries strong potential for ultimately developing gene-targeted therapies to inhibit solid tumor growth in the general population," says co-lead author Yekaterina Galat, BS, Research Associate at the Manne Research Institute at Lurie Children's. "Our findings may also provide gene targets for therapies aimed at alleviating the clinical abnormalities in people with Down syndrome."

Down syndrome is a congenital genetic disorder that is associated with cognitive impairment, reduced muscle tone, heart defects, and other clinical anomalies. At the same time, individuals with Down syndrome have lower prevalence of solid tumor formation.

The study used skin samples from two patients with Down syndrome to create induced pluripotent stem cells that were then differentiated into endothelial cells, which build blood vessels and the vascular system, and mesodermal cells, which are responsible for connective tissues and muscle development. During the process of differentiation, in the progenitor phase, Manne Research Institute scientists discovered down-regulated genes that appear to be involved in the abnormal muscle

development and heart problems that are common in people with Down syndrome.

By studying the role of these genes in biochemical pathways relevant to solid tumor development, they found that the decreased expression of such genes interferes with the processes needed for solid tumor formation and growth. These genes produced impeded cell movement, slower proliferation and reduced inflammatory response—creating a microenvironment that is not conducive to solid tumors. Genome-wide analyses was then performed to confirm these findings, using publicly available data from 11,000 patients.

"When we performed genomic analyses comparing mesodermal and endothelial cell lines, we were surprised to find that trisomy 21 impacted gene expression across the entire genome. Furthermore, the decreased expression of the genes we studied was consistent, and the large extent of their down-regulation was notable as well," says co-lead author Mariana Perepitchka, BA, Research Associate at the Manne Research Institute at Lurie Children's. "This significant down-regulation potentially creates conditions that are opposite of what solid tumors would need to take hold. So in a way, Down syndrome provides us with a non-traditional lens to study cancer development."

"We still need to validate our findings in an animal model," 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. "The potential for gene-targeted therapies is very exciting, especially since it could help individuals born with Down syndrome and the general population battling cancer."

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