Discovery may explain high risk of leukemia in children with Down syndrome

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Children with Down syndrome are 20-times more likely to develop acute lymphocytic leukemia (ALL) and 150-times more likely to develop acute myeloid leukemia (AML) compared to their typical peers. According to a new study by researchers at the Linda Crnic Institute for Down Syndrome, the reason could be that children with Down syndrome are more likely to present with clonal hematopoiesis (CH), a process in which a blood stem cell acquires a genetic mutation that promotes replication.

The findings, published online by *Blood Advances*, add to a growing body of evidence, much of which has been established by the Crnic Institute, linking immune dysregulation to a dramatically different disease spectrum, whereby people with Down syndrome are highly predisposed to some diseases (e.g., leukemia, autoimmune disorders, and Alzheimer's disease) and highly protected from others (e.g., solid tumors).

"We found a higher-than expected rate of CH in individuals with Down syndrome between the age of one to 20 years old," says study author Dr. Alexander Liggett, who spearheaded the study as a doctoral candidate in the lab of Dr. James DeGregori, Professor of Biochemistry and Molecular Genetics. "It is a surprising finding, as the phenomenon is typically only observed in elderly people."

To perform the study, Liggett and DeGregori and colleagues applied an advanced sequencing technique they developed, called FERMI, to blood samples from the Crnic Institute Human Trisome Project BiobankTM. Not only were mutations detected more often in young individuals with Down syndrome, but those mutations were more likely to be oncogenic, or potentially cancerous. In the typical elderly population, oncogenic mutations are commonly found in the genes DNMT3A, TET2, ASXL1, TP53, and JAK2. Interestingly, in the Down syndrome cohort, oncogenic CH was dominated by mutations of the TET2 gene.

"Given the increased risk of leukemia that accompanies clonal expansion of blood cells carrying oncogenic mutations, these expansions may become an important biomarker of cancer risk in the future," says Dr. Liggett.

The study also found that CH in Down syndrome is associated with biosignatures of immune dysregulation that are linked to diseases that commonly co-occur with Down syndrome, including thyroiditis, Alzheimer's disease, and leukemia. This discovery opens new lines of investigation to understand how CH impacts a variety of health outcomes in Down syndrome and how to potentially counteract its effects.

"This is truly transformative. This team has identified a new trait of Down syndrome that has strong implications for understanding the appearance of comorbidities more common in this population, such as leukemia and premature ageing," said Dr. Joaquin Espinosa, Executive Director of the Crnic Institute. "The next step is to

define the long-term impacts of this precocious clonal hematopoiesis and how to prevent its harmful effects."

More information: L. Alexander Liggett et al, Precocious clonal hematopoiesis in Down syndrome is accompanied by immune dysregulation, *Blood Advances* (2021). DOI: 10.1182/bloodadvances.2020003858

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