Researchers clarify role of blood cell mutations in disease

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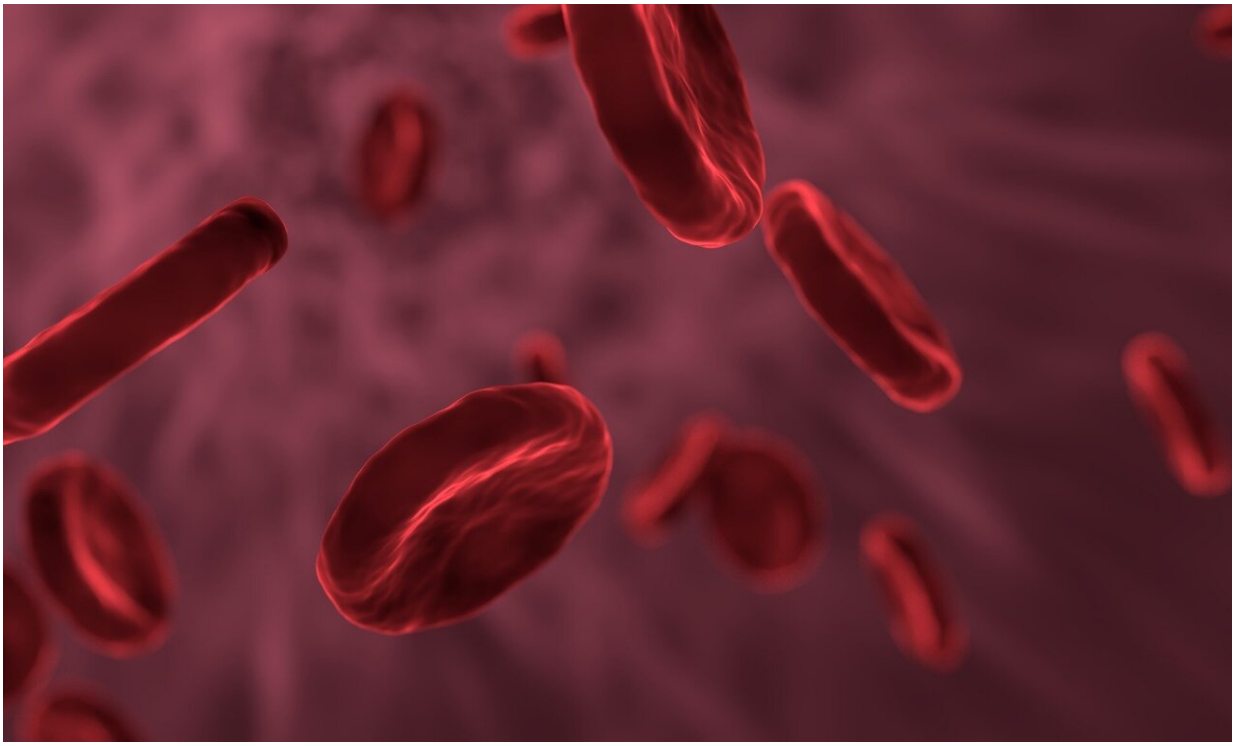

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More than 10% of older adults develop somatic (non-inherited) mutations in blood stem cells that can trigger explosive, clonal expansions of abnormal cells, increasing the risk for blood cancer and cardiovascular disease.

Multiple DNA sequencing methods have been used to identify what is called "clonal hematopoiesis of indeterminate potential," or CHIP, but it has been difficult to distinguish true mutations from artifacts.

Reporting in the journal *Blood*, a research team at Vanderbilt University Medical Center led by Alexander Bick, MD, Ph.D., detailed a stepwise method for analyzing large data sets (more than 550,000 individuals) that can improve dramatically the accuracy of CHIP determination.

By combining genomics, demographics and computational biology, this approach has "refined our understanding of what mutations most increase the risk of blood cancers," said Bick, assistant professor of Medicine in the Division of Genetic Medicine and director of the Vanderbilt Genomics and Therapeutics Clinic.

In a separate research letter published in the journal *Circulation*, Bick and his colleagues reported that genetic variations in the receptor for interleukin-6 (IL-6), a signaling protein involved in inflammation, spurred development of "incident" coronary artery disease (resulting in hospitalization, heart attack or death).

"We showed how a subset of these clonal hematopoiesis mutations give rise to heart disease and provided genetic evidence that these patients could benefit from IL-6 inhibitor medicines," he said.

"We knew very little on how to counsel patients with clonal hematopoiesis when I started the VUMC CHIP Clinic five years ago," said co-author Michael Savona, MD, director of Hematology Research and section head of Hematology, Cellular Therapy and Stem Cell Transplantation in the Vanderbilt-Ingram Cancer Center.

"This new research clarifies the genetic variants involved in CHIP and will allow us to better personalize care we provide these patients," he

said.

A professor of Medicine and Cancer Biology, Savona holds the Beverly and George Rawlings Directorship in Hematology Research at VUMC.

In 2020, he co-founded CHIVE (Clonal Hematopoiesis and Inflammation in the Vasculature), a registry, biorepository and think tank representing multiple medical specialties, genetics, data science and molecular biology. The goal: understand and develop new therapies to block the pathological consequences of clonal hematopoiesis before they start.

First author of both papers was Caitlyn Vlasschaert, MD, MSc, a resident physician at Queen's University in Kingston, Ontario, Canada, who was a visiting research fellow at VUMC last year.

The researchers ascertained CHIP in more than 450,000 individuals whose genomic information is stored in the UK (United Kingdom) Biobank, and—for the paper published in *Blood*—another 98,500 participants in the All of Us precision medicine research program of the National Institutes of Health.

"We show how large data sets with paired genomic and demographic information can be leveraged to identify CHIP more accurately for both clinical and research applications," the researchers concluded.

More information: Caitlyn Vlasschaert et al, A practical approach to curate clonal hematopoiesis of indeterminate potential in human genetic datasets, *Blood* (2023). DOI: 10.1182/blood.2022018825

Caitlyn Vlasschaert et al, Interleukin-6 Receptor Polymorphism Attenuates Clonal Hematopoiesis-Mediated Coronary Artery Disease Risk Among 451 180 Individuals in the UK Biobank, *Circulation* (2023).

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