CeMM

St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

Mechanism of leukemia predisposition unraveled

Teaser (Website): (Vienna, 24.06.2026) – **Spontaneous genetic mutations can disrupt normal blood development and drive pediatric leukemia. In addition to these acquired mutations, inherited genetic variants can also increase leukemia risk, but the underlying molecular mechanisms remain poorly understood. A new study reveals how the protein ARID5B controls gene expression to safeguard B cell development and how genetic variants in this protein might contribute to leukemia susceptibility. Published in Nucleic Acids Research, the study provides the first detailed characterization of ARID5B's function and offers new insights into how its loss may predispose children to the development of B cell leukemia.**

Like many childhood cancers, leukemia begins when normal development goes awry. Genetic alterations trap cells in an immature state, where they continue to divide uncontrollably instead of developing into fully functional cells. For decades, scientists have studied how spontaneous genetic mutations can drive leukemia development. However, inherited genetic variants that can predispose to leukemia remains poorly understood.

In particular, small variations associated with ARID5B are some of the most significant risk factors for developing B cell acute lymphoblastic leukemia (B-ALL), the most common subtype of childhood leukemia. However, ARID5B's normal function—and more importantly, how it contributes to leukemia development—remained unknown.

A new study led by Ana Kutschat in the laboratory of Davide Seruggia at St. Anna Children's Cancer Research Institute (St. Anna CCRI) and CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences now sheds light on how ARID5B works. By combining advanced molecular analyses with AI-based predictions of protein structure and interactions, the researchers dissected ARID5B's function for the first time and uncovered how ARID5B may set the stage for leukemia to develop.

A Close Partnership

One of the study's key findings was the identification of ARID5B's closest molecular partners. The team discovered that ARID5B forms a previously unknown protein complex together with MIER1, C16ORF87, and either HDAC1 or HDAC2. Using the AI-based tool AlphaFold, the researchers predicted how these proteins interact, providing important clues about how the complex functions. They also showed that removing ARID5B causes the entire complex to fall apart.

The researchers found that this protein complex binds to key genes that control how B cells function and develop. ARID5B acts as a bridge, recruiting HDAC1 and HDAC2 to switch B cell specific genes.

Without ARID5B, HDAC1 and HDAC2 can no longer perform their function. As a result, B cell function is impaired. This may explain why certain ARID5B variants make B cells more vulnerable to becoming leukemic when pro-cancer mutations occur.

First Step Toward Understanding Leukemia Predisposition

While the study reveals for the first time how ARID5B works in healthy cells, further research will investigate how specific ARID5B variants alter B cell behavior and increase leukemia risk.

"This is an important first step," says Ana Kutschat, first author of the study. *"Now we understand what ARID5B normally does, we can begin to study how its function is disrupted, and what effects it has."*

Understanding ARID5B's role in creating the conditions for leukemia development could also open new therapeutic opportunities.

"*Understanding the molecular mechanisms behind leukemia predisposition has two main benefits. On one side, we identify new factors contributing to the disease, adding up new potential targets for therapy,*" explains Davide Seruggia. "*At the same time, we learn new biology regarding how normal B cells develop.*"

More broadly, the findings highlight that cancer-driving mutations alone may not be enough to trigger leukemia—cells must first be primed for the disease to take hold.

Publication

Kutschat, A. P., Frommel, F., Santini, B. L., Müller, S., Batty, P., Awasthi, A., Karbon, G., Superti-Furga, G., Seruggia, D. Leukemia risk factor ARID5B Coordinates HDAC-Mediated Transcriptional Repression. *Nucleic Acids Res* 44, 224 (2026). https://doi.org/10.1093/nar/gkag628

Commented [SD1]: doi pending

Funding: This work was supported by the Austrian Science Fund (FWF) and the European Research Council (ERC).

CeMM

St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE

About St. Anna Children's Cancer Research Institute

St. Anna Children's Cancer Research Institute (CCRI) is an international and interdisciplinary research institution dedicated to developing and improving diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Taking into account the specific characteristics of childhood tumors, dedicated research groups in tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics, and clinical research work together to align the latest scientific and experimental findings with the clinical needs of physicians and sustainably improve the well-being of young patients. www.ccri.at www.kinderkrebsforschung.at

About CeMM

CeMM is an interdisciplinary research institute of the Austrian Academy of Sciences committed to advancing the understanding of human diseases through basic and biomedical research. Located in a tailor-made building in the midst of the campus of the Medical University of Vienna, CeMM is dedicated to its mission statement to pioneer science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM currently hosts 9 principal investigators, 12 adjunct principal investigators and 2 facilities. Focusing on medically relevant questions, CeMM researchers concentrate on human biology and diseases like cancer and inflammation/immune disorders and rare diseases. An additional focus lies on aging research. In support of scientific pursuits and medical needs, CeMM provides access to cutting-edge technologies and has established a strategic interest in personalized medicine.

Editor
Manel Llado Santaeularia
Editor Science Communication
St. Anna Children's Cancer Research Institute
Zimmermannplatz 10, 1090 Vienna, Austria
M: +43 664 5477295
E: manel.llado@ccri.at
www.ccri.at

Contact:
Lisa Huto
Head of Marketing & Communication
St. Anna Children's Cancer Research Institute
1090 Vienna, Zimmermannplatz 10
M: +43 664 847 66 87
E: lisa.huto@kinderkrebsforschung.at