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New method predicts childhood hyperdiploid B-ALL relapse risk

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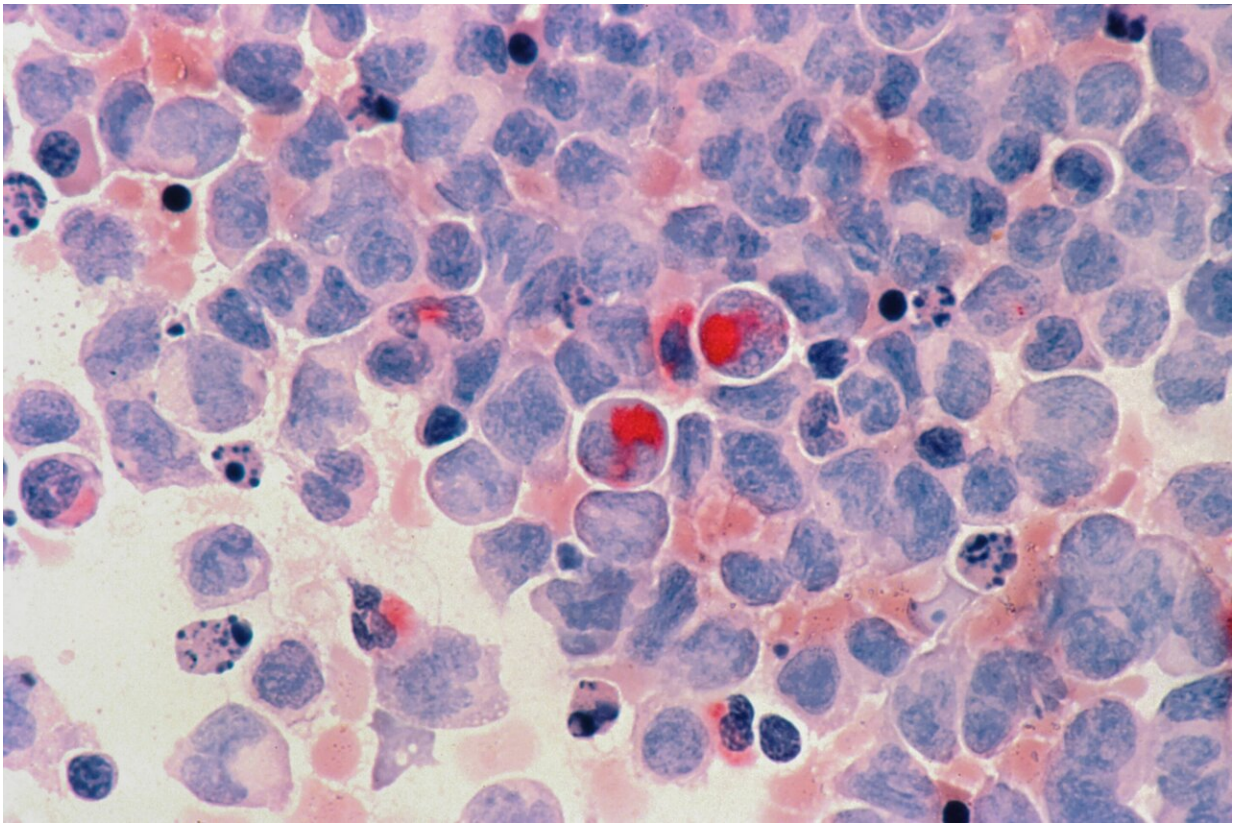

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An international research team coordinated by Dr. Oscar Molina and Dr. Pablo Menéndez, from the Josep Carreras Leukaemia Research Institute, identifies chromosomal abnormalities associated with relapse in a

frequent subset of B-cell Acute Lymphoblastic Leukemia (B-ALL), a severe condition that especially affects children. This finding may help identify those patients at a higher risk of relapse at diagnosis to direct them to more appropriate treatment options and anticipate the cancer comeback.

The research, published in the specialized journal *Molecular Oncology*, confirmed that hyperdiploid B-ALL, a frequent subtype of childhood B-ALL, is associated with a high genetic heterogeneity with variable chromosome numbers in leukemic cells. Results demonstrated that chromosome 10 and 18 trisomies are good prognosis markers that can be used to predict the relapse risk and to decide the most appropriate treatment strategies for these patients.

In addition, the research also found that clonal genetic variability is responsible of the appearance of specific chromosomal combinations that become predominant and demonstrated that lower clonal heterogeneity can thus be used as another marker to predict relapse risk in hyperdiploid B-ALL patients.

According to the lead authors, Mireia Ramos from the Autonomous University of Barcelona and Juan L. Trincado, from the Josep Carreras Institute, classical karyotyping misses the high genetic variability observed and other techniques like iFISH and single cell sequencing would be advised to refine the initial cytogenetic diagnosis in the childhood high-hyperdiploid B-ALL entity.

B-ALL is the most common blood malignancy in children, with almost 3 out of 4 cases affecting kids under 6 years old. It is characterized by the accumulation of B-cell progenitors in the bone marrow, leading to the underproduction of mature B-cells, an essential part of our defense system, and other types of blood cells. A usual feature of this type of cancer is the presence of aberrant gains or losses of entire chromosomes

in the leukemic cells.

When gains are too high, like over 5 extra chromosomes, clinicians regard this as hyperdiploidy (diploidy refers to the usual array of chromosomes, coming in pairs in most human cells), a good prognosis marker and patients with these features tend to show complete response after treatment.

However, relapses from cells escaping treatment are not uncommon, meaning that part of the chromosome instability seen in hyperdiploid B-ALL may benefit the malignant cells in some way. To find out how, researchers wanted to know whether any specific chromosomal gains were associated with the appearance of resistant clones and a higher probability of relapse.

They analyzed cells from 72 Hyperdiploidy B-ALL patients, 62 coming from first diagnosis and 10 after relapse. The computational analysis of single-cell genetic data from those samples allowed the researchers to identify new prognostic markers to improve the relapse risk assessment of patients employing techniques widely used by clinical hematoncology laboratories. Results showed that, while extra 10 and 18 chromosomes were associated with good prognosis, low clonal heterogeneity—resulting from clonal selection of the "fitter" clones—meant higher risk of relapse and lower chances of survival.

Overall, this new research offers a new perspective on high hyperdiploid B-ALL and proposes new tools so clinicians can better understand the future outcomes of their patients and improve individual survival.

More information: Mireia Ramos-Muntada et al, Clonal heterogeneity and rates of specific chromosome gains are risk predictors in childhood high-hyperdiploid B-cell acute lymphoblastic leukemia, *Molecular Oncology* (2022). DOI: 10.1002/1878-0261.13276

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