3-D genetic structure in blood cancer important beyond DNA code changes

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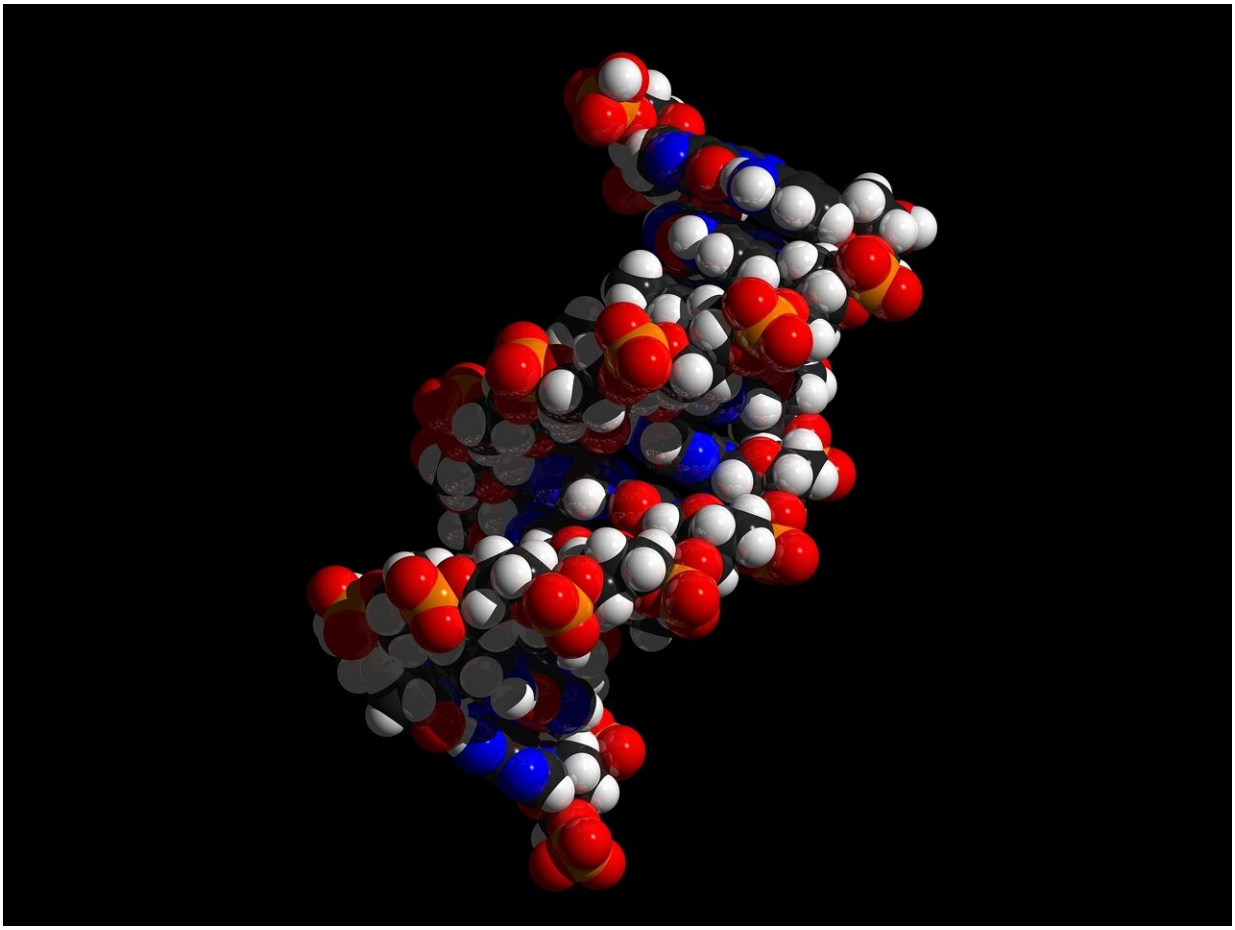

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Children with aggressive blood cancers have differences—not just in the

DNA code of their blood cells—but also in the heavily twisted protein superstructure that controls access to genes.

Led by researchers at NYU Grossman School of Medicine, a new study showed that whether T cell acute lymphoblastic leukemia takes off or worsens depends on structural changes in the layout of protein bundles called chromosomes. Upon receiving the right signal, this arrangement changes to expose the gene-reading machinery to only those bits of DNA code needed for the job at hand in each cell.

The new work builds on the discovery that DNA chains exist, not in vast tangles of chromosomes, but in organized "neighborhoods" called topographically associated domains, or TADs. Specifically, DNA snippets, called enhancers, are known to turn up or down the action of genes, but normally only those housed only in their own TADs. Within TAD boundaries, DNA is free to fold back on itsself in 3-D loops, bringing together enhancers and other elements (e.g., promoter DNA) that must interact for a given stretch of code to be read.

The new study showed that key TAD boundaries are lost in this form of leukemia, enabling parts of DNA to interact with enhancers from the wrong neighborhoods, turning up the action of the wrong genes and encouraging cancer growth and spread. Researchers say their findings suggest that these 3-D changes in chromosome structure are as important as changes in the order of molecular letters making up the DNA code itself (mutations), with both mechanisms encouraging cancer onset and progress.

"Our study is the first to show that the naturally 'looped' structure of genetic material in blood cells is changing in T cell leukemia," says study co-lead investigator Palaniraja Thandapani, Ph.D., a postdoctoral fellow at NYU Langone Health and its Perlmutter Cancer Center. "With this in mind, the most effective treatment for this type of leukemia may be a

combination of a drug that targets the disease's cancer-causing, genetic mutations and another that counters any changes to chromosomal 3-D structure."

In childhood leukemia, the most common code changes or mutations or changes in activity occur in two genes, NOTCH1 and MYC, says study co-senior investigator Iannis Aifantis, Ph.D., the Hermann M. Biggs Professor and chair of the Department of Pathology at NYU Langone and Perlmutter.

Existing drug therapies designed to block NOTCH1 and MYC, he says, work well but are not foolproof. When testing them in blood cell samples from people undergoing therapy, the research team found that part of the explanation may reside in the failure of single-drug therapies to correct the epigenetic changes that come with the disease.

Experiments with one drug that successfully blocked NOTCH1 activity showed that it did not effectively block access to the exposed MYC neighborhood, which could explain, Aifantis says, why NOTCH1 inhibitors do not work for most patients.

However, a second experimental drug (targeting molecular, or epigenetic, changes in these DNA neighborhoods) effectively corrected DNA looping in the MYC neighborhood, restoring normal chromosomal structure and gene regulation, and dramatically decreasing MYC action and cancer spread.

The findings, publishing in the journal *Nature Genetics* online March 23, were made possible by advanced genetic and imaging techniques developed in recent years. These include such experimental methods as RNA sequencing and Hi-C that lets researchers track step-by-step genetic activity in cancer cells and reveal the 3-D architecture of chromosomes by comparing small fragments of genetic material to each

other.

For the new study, researchers compared the genetic material in blood samples from eight children between the ages of 1 and 16, including some with advanced-stage disease, to blood samples of healthy children.

Co-senior investigator Aristotelis Tsirigos, Ph.D., says the changes in DNA looping observed in these blood cells were "quite unique" to this severe form of leukemia and its related mutations. This suggests that looping alterations may be different in other cancers that are closely tied to different mutations.

Moving forward, Tsirigos says, the team has plans to describe the changes in chromosomal looping involved in other blood cancers, such as lymphoma, as well as for other subtypes of leukemia.

"Once these 3-D genetic changes are fully described, we should be able to test existing and new drugs based on their ability to correct any malformations and better predict the chances for patient survival from cancer," says Tsirigos, an associate professor at NYU Langone and Perlmutter. Tsirigos also serves as director of NYU Langone's applied bioinformatics laboratories, where the computer analysis is performed

The American Cancer Society estimates that more than 1,500 Americans, mostly children, die each year from T cell acute lymphoblastic leukemia. This type of cancer accounts for roughly one-quarter of all leukemias.

More information: Three-dimensional chromatin landscapes in T cell acute lymphoblastic leukemia, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-0602-9 , nature.com/articles/s41588-020-0602-9