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To understand chromosome reshuffling, look to the genome's 3D structure

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That our chromosomes can break and reshuffle pieces of themselves is nothing new; scientists have recognized this for decades, especially in cancer cells. The rules for where chromosomes are likely to break and how the broken pieces come together are only just now starting to come into view. Researchers at Children's Hospital Boston and the Immune Disease Institute (IDI) have helped bring those rules into clearer focus by discovering that where each of the genome's thousands of genes lie within the cell's nucleus – essentially, the genome's three-dimensional organization – holds great influence over where broken chromosome ends rejoin, knowledge that could shed light on fundamental processes related to cancer and normal cellular functions, for example in immunity.

The study team, led by Frederick Alt, PhD, director of the Program in Cellular and Molecular Medicine at Children's Hospital Boston and the IDI; and Job Dekker, PhD, co-director of the Program in Systems Biology at the University of Massachusetts Medical School, reported their results online on February 16 in the journal *Cell*.

In cancer cells, the process of chromosome rearrangement, or translocation – marked by stretches of DNA physically breaking and swapping – often results in the creation of new cancer-promoting "fusion" genes. Similarly, when a naïve B cell starts to produce antibodies for the first time, it establishes its choice of target by breaking and recombining genes for antibody diversity.

"While chromosomal breaks and translocations are fundamental to many cancers, historically we've had no approaches to systematically study how they are generated," said Alt, who is also a Howard Hughes Medical Institute investigator and the Charles A. Janeway Professor of Pediatrics and Professor of Genetics at Harvard Medical School. "About five years ago, our group set out to generate a high-throughput approach to address this important problem in cancer biology."

To accomplish this goal, the Alt lab developed high-throughput genome-wide translocation sequencing (HTGTS, which maps "hot spots" in the genome where chromosome breaks and translocations are more likely to occur) and at a level of resolution not previously thought possible. In early HTGTS studies, they found that broken chromosomes often rearrange within themselves, as opposed to sharing pieces across different chromosomes.

To probe these findings more deeply, his laboratory joined forces with Dekker's to combine HTGTS with a method called Hi-C. Developed by Dekker's group, Hi-C measures how all the sequences in the genome are organized relative to one another in three dimensions.

The combined data revealed several related but distinct principles of how genomic organization governs chromosome rearrangements. The first is based on the slight differences in how each cell organizes its genome compared to its neighbors (referred to as cellular spatial heterogeneity of genome organization). While the genome is organized in an average fashion that is largely common across all cells of a population, each individual cell harbors small deviations from that average. This latter property allows many genes to be physically close to each other in just a small subset of cells, even if they are not close to each other in the majority of cells.

The second principle involves proximity. If two broken chromosome

strands lie in close proximity within the three-dimensional space of a given cell's nucleus, they are more likely to connect. This finding is of particular importance for translocations involving DNA sequences that do not break frequently, such those involved in translocations found in various non-lymphoid tumors.

The third principle applies the first two to DNA sequences that do break frequently (such as those that drive antibody gene rearrangements during B cell development). Such sequences tend to reshuffle with the same partner sequences in those subsets of cells where the partners lie physically close together, even if the partners do not within most cells. This can fuel recurrent translocations like those seen in many lymphoid tumors.

Together, the principles highlight the relationship between proximity, genomic organization, and break frequency. "Two sequences have to be broken and physically proximal to join," Alt explains. "If two sequences are together in most cells and frequently broken, they will translocate in many cells. If they are frequently together but one of them doesn't break, or if they both break frequently but always lie on opposite sides of the nucleus, the chances that they will translocate are very low or zero. However, if both sequences break very frequently and are close together in a subset of cells, they will very frequently translocate in that subset, contributing to recurrent translocations."

"Our finding that broken chromosome segments are more likely to join with other segments within the same chromosome, rather than other, more physically distant segments from other chromosomes, likely has great relevance to cancer genomes," Alt continued. "For example, cancer treatments that cause breaks may preferentially lead to intra-chromosomal rearrangements. It may also have relevance for 'chromothripsis,' a recently discovered phenomenon in many cancers in which the sequences of one chromosome become scrambled."

The new understanding of the roles of physical spatial proximity and overall three-dimensional genome structure in chromosomal translocations opens up new avenues for deciphering how the way a cell's nucleus is organized affects the genomic disarray found in cancer and other diseases characterized by chromosome reshuffling. The study also shows the power of combining two high-throughput genomic assays – Hi-C and HGTGS – for studying how the organizational plan within the nucleus influences fundamental biological processes.

"We feel that our findings and the application of our approaches will provide a new lens through which to view the genomes of many different types of cancer," Alt concluded.

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