

New technology helps reveal inner workings of human genome

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Weill Cornell Medicine and New York Genome Center researchers, in collaboration with Oxford Nanopore Technologies, have developed a new method to assess on a large scale the three-dimensional structure of

the human genome, or how the genome folds. The genome is the complete set of genetic instructions, DNA or RNA, enabling an organism to function.

Using this method, the researchers demonstrated that [cell function](#), including [gene expression](#), may be affected by groups of simultaneously interacting regulatory elements in the [genome](#) rather than pairs of these components. Their findings, published May 30 in *Nature Biotechnology*, may help shed light on the relationship between [genome structure](#) and cellular identity.

"Knowing the three-dimensional genome structure will help researchers better understand how the genome functions, and particularly how it encodes different cell identities," said senior author Dr. Marcin Imieliński, associate professor of pathology and laboratory medicine and computational genomics in computational biomedicine at Weill Cornell Medicine and a core member of the New York Genome Center. "The ways that we've had to study genome structure have given us amazing insights, but there have also been key limitations," he said.

For example, previous technology to assess the genome's three-dimensional structure has allowed researchers to study how frequently two loci, or physical locations on the genome, interact with one another. Traditionally, pairs of loci called enhancers and promoters—components in the genome that interact with one another to influence gene expression—have been observed.

Information about these pairings offers incomplete insight into genome structure and function. For instance, linking a folding pattern to how the genome encodes for a specific cell identity—like a liver, lung or epithelial cell—has been difficult, said Dr. Imieliński, who is also a member of the Englander Institute for Precision Medicine and the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

Scientists have theorized that this folding influences gene expression. "But how cell types are encoded, particularly in the structure of DNA, has been a mystery," he said.

Dr. Imieliński and his research team, including first author Aditya Deshpande, a recent graduate of the Tri-Institutional Ph.D. Program in Computational Biology & Medicine working in Dr. Imieliński's lab, developed a new genome-wide assay and algorithm that allows them to study groups of loci, not just pairs.

They adapted a traditional technology, Hi-C (chromatin conformation capture), which assesses a mixture of DNA and protein to analyze three-dimensional genome structure, to nanopore sequencing, or the high-throughput sequencing of long, continuous strands of DNA molecules. The resulting assay, which the researchers called Pore-C, enabled them to observe tens of millions of three-dimensional locus groupings.

They also developed [statistical methods](#) to determine which locus groupings were important, based on whether they interacted cooperatively to affect gene expression. "Many three-dimensional interactions of the genome are not important," Dr. Imieliński said. "Our analytic methods help us prioritize the group interactions that are likely to matter for genome function." As a key finding of the study, the researchers found that the most significant cooperative groupings of DNA elements occurred around genes associated with cell identity.

Future experiments will explore which specific groupings of genomic components are essential for various aspects of cell identity. The new technology may also help researchers to understand how [stem cells](#), the immature, master [cells](#) of the body, differentiate into different [cell types](#)

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In addition, researchers may be better able understand abnormalities in

[cancer cells](#). "In the future, this technology may be really helpful in understanding how cancer cell genomes are rearranged, and how those rearrangements drive the altered cell identities that enable cancers to grow and spread" Dr. Imieliński said.

More information: Aditya S. Deshpande et al, Identifying synergistic high-order 3D chromatin conformations from genome-scale nanopore concatemer sequencing, *Nature Biotechnology* (2022). [DOI: 10.1038/s41587-022-01289-z](#)

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