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GENOMICS

Radial genome organization

Sequencing gradually digested chromatin along the nuclear radius enables the mapping of radial organization of chromatin in human cells.

Three-dimensional genome organization is critical to genome function.

Microscopy techniques like DNA fluorescence in situ hybridization (FISH) have been applied to visualize this spatial organization of chromosomes in the nucleus.

Magda Bienko from Karolinska Institutet in Sweden says, “When you stare at chromosomes under the microscope, you cannot help but be astounded by how the shape and localization of individual chromosomes differ from one cell to another. You develop a sense that our nucleus is a place of chaos, yet you know that this is not the case.”

Using DNA FISH, previous work has shown that large and gene-poor chromosomes tend to preferentially localize close to the nuclear periphery, whereas small and gene-rich chromosomes tend to localize toward the center of the nucleus. This radial organization of chromosomes is considered relevant to transcriptional activity. Yet genome-wide tools that explicitly explore how radial nuclear organization associates with gene regulation at high resolution remain lacking.

The Bienko group and their collaborators — Nicola Crosetto's group, also from Karolinska Institutet — sought to develop a sequencing-based approach to infer nuclear radiality with improved resolution. In their approach, the diffusion gradient of restriction enzymes gradually digests genomic DNA from the nuclear lamina to the center, generating successive DNA fragments for sequencing. Bienko comments that “it was not obvious to us how to achieve a controllable diffusion of restriction enzymes into the meshwork of chromatin.” To obtain reliable digestion, they tested a range of cell fixation and permeabilization conditions, as well as developed a Y-shape adapter-based FISH assay to monitor the progress of restriction digestion.

To infer the radial distance from sequencing data, Bienko and colleagues tested about forty different radiality estimates and defined a GPSeq score by comparing the calculation results with their DNA FISH measurements. Based on the calculation of a digestion probability, the GPSeq score provides information about the radial location of individual chromosomes.

chr1	chr7	chr13	chr19
chr2	chr8	chr14	chr20
chr3	chr9:22	chr15	chr21
chr4	chr10	chr16	chr22:9
chr5	chr11	chr17	chrX
chr6	chr12	chr18	

A two-dimensional map of radial location of individual chromosomes. Reprinted with permission from G. Girelli et al. *Nat. Biotechnol.* doi:10.1038/s41587-020-0519-y (2020), Springer Nature.

Furthermore, the researchers developed an algorithm, named chromflock, to integrate GPSeq with Hi-C measurements for improving single-genome 3D structure modeling. As expected, the generated genome structures retain a resolution of 100 kb and recapitulate the radial organization of A and B subcompartments obtained from bulk GPSeq.

In the current study, GPSeq reveals similar radial profiles in two cell lines, HAP1 and GM06990. However, Bienko notes that “our ongoing work in the lab, where we apply GPSeq to various cell lines, is revealing cell-type and differentiation-stage-specific radial features of genome organization.” Bienko expects that the radial arrangement of chromatin will vary across cells. Thus, they are working towards a single-cell version of GPSeq.

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