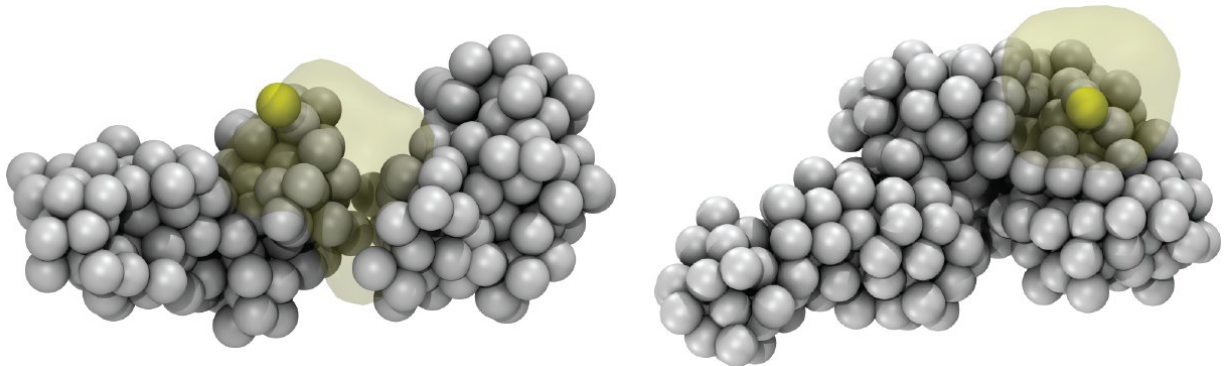


# The surprising role of gene architecture in cell fate decisions

January 16 2018

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Credit: Centre for Genomic Regulation

Scientists read the code of life—the genome—as a sequence of letters, but now researchers have also started exploring its three-dimensional organisation. In a paper published in *Nature Genetics*, an interdisciplinary research team of scientists from the Centre for Genomic Regulation (CRG) in Barcelona, Spain, shows that the three-dimensional organisation of the genome plays a key role in gene expression and consequently in determining cell fate.

It all began with the 4-D Genome project, an ambitious and innovative research initiative aimed at understanding how the spatial organisation of the [genome](#) contributes to decisions made by cells. What scientists wanted to find out was whether genome architecture plays an active

function or whether it is a mere side effect of the genome's activity. The model that the 4-D Genome team used was [cell reprogramming](#), a process that allows the scientists to revert [white blood cells](#) back to a state of pluripotency in which they can differentiate into any other cell type. Proteins that control gene activity (known as [transcription factors](#)) play a key role in this process, which the 4-D Genome team studied in great detail, assessing how they induce changes in [gene expression](#), modifications of chromatin (the structure around which DNA is wrapped), and changes in the 3-D organisation of the genome.

Understanding how stem cells are formed and how they can convert into different cell types is a major challenge in modern biology. It has been known since the 1950s that all specialized cells in the body contain the same genome. So what then distinguishes one cell type from another? The answer is that different cells read the information contained in different parts of the genome. The machinery required to achieve this selective information recall resides primarily in so called transcription factors, molecules that switch genes on or off. Many other molecules are also involved in this process, including epigenetic regulators that help to densely pack the genome into the nucleus of a cell, or locally unpack it to allow gene expression. The scientists used a reprogramming method discovered by CRG senior researcher Thomas Graf and his team. With this precision tool in hand, they were able to study the dynamics of genome organization by comparing the changes in genome architecture and transcription at different times during reprogramming.

"We expected that transcription factors would first switch on certain genes, which then afterwards may force a re-organisation of the 3-D structure of the chromosome. Surprisingly, what we found is that in a large proportion of the genome, the transcription factors were actually promoting this re-organisation before the genes were switched on," explains Ralph Stadhouders, co-first author of the paper together with computational biologist Enrique Vidal.

"Our paper shows that transcription factors may play a completely new role in cell reprogramming. They do not only switch [genes](#) on and off, but also promote the architectural changes necessary to modify gene expression," says Thomas Graf, senior CRG group leader and lead investigator of this study. "It may have relevant implications for researchers worldwide studying gene regulation in general since we know now that the large-scale organization of the genome cannot be ignored. It also raises new questions about how these large changes can be brought about: possibly new mechanisms, perhaps even new machineries that are necessary to change certain areas of the genome," says Graf.

The findings, reported in *Nature Genetics*, indicate that [genome architecture](#) has important informational value for controlling gene expression during cell reprogramming, and is thus required for the specialized functions of a cell. "We are only scratching the surface of what could be critical, as-yet unrecognized mechanisms by which [cells](#) regulate gene expression," says co-principal investigator Marc A. Martí-Renom. "The new discovery might also be fundamental for development and for some development-related diseases and cancer," he concludes.

**More information:** Ralph Stadhouders et al. Transcription factors orchestrate dynamic interplay between genome topology and gene regulation during cell reprogramming, *Nature Genetics* (2018). [DOI: 10.1038/s41588-017-0030-7](https://doi.org/10.1038/s41588-017-0030-7)

Provided by Centre for Genomic Regulation

Citation: The surprising role of gene architecture in cell fate decisions (2018, January 16) retrieved 27 March 2023 from <https://medicalxpress.com/news/2018-01-role-gene-architecture-cell-fate.html>

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