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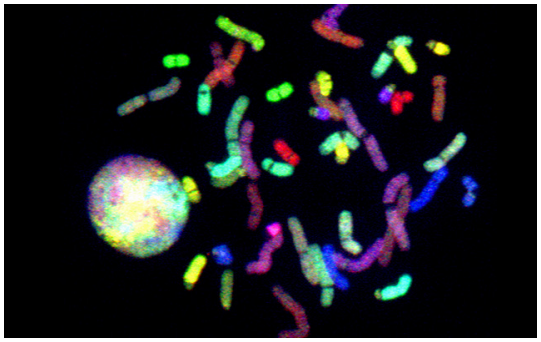
New Insights into 3D Genome Organization and Genetic Variability

Two NIH Roadmap Epigenomics studies answer longstanding questions about the differences between chromosome pairs and how chromosome folding influences gene expression

While genomics is the study of all of the genes in a cell or organism, epigenomics is the study of all the genomic add-ons and changes that influence gene expression but aren't encoded in the DNA sequence. A variety of new epigenomic information is now available in a collection of studies published Feb. 19 in *Nature* by the National Institutes of Health (NIH) Roadmap Epigenomics Program. This information provides a valuable baseline for future studies of the epigenome's role in human development and disease.



Cell nucleus and chromosomes stained by spectral karyotyping, a technique that allows scientists to visualize all of the human chromosomes by "painting" each pair of chromosomes in a different fluorescent color. Credit: National Human Genome Research Institute.

Two of these studies, led by researchers at University of California, San Diego School of Medicine and Ludwig Cancer Research, address the differences between chromosome pairs (one inherited from mom, the other from dad) and how chromosome folding influences gene expression.

"Both of these studies provide important considerations for clinicians and researchers who are developing personalized medicines based on a patient's genomic information," said Bing Ren, PhD, professor of cellular and molecular medicine at UC San Diego, Ludwig Cancer Research member and senior author of both studies.

The first paper by Ren's group takes a look at differences in our chromosome pairs. Each of us inherits one set from our mother and the other from our father. Chromosome pairs are often thought to be identical, one just a backup for the other. But this study found widespread differences in how genes are regulated (turned on and off) between the two chromosomes in a

pair. It turns out that we all have “biases” in our chromosomes. In other words, different traits have a stronger contribution from one parent than the other. The study also suggests that these biases are rooted in inherited sequence variations and that they are not randomly distributed. These findings help explain why, for example, all kids in a family may have their father’s hair but their mother’s eyes.

The second paper by Ren’s group tackles how the genome is organized and how it changes as stem cells differentiate (specialize). DNA strands in every cell are tightly wound and folded into chromosomes. Yet chromosomal structures, and how they influence gene expression, are not well understood. In this study, Ren and team mapped chromosomal structures in stem cells and several different differentiated cell types derived from stem cells. First, they induced differentiation in the stem cells. Then they used molecular tools to examine how the structure of the cells’ chromosomes changed and how that change is associated with gene activity. The team found that chromosomes are partitioned into relatively stable structural units known as topologically associating domains (TADs), and that TAD boundaries remain constant in different cell types. What’s more, the researchers found that the changes in chromosomal architecture mostly take place within the TADs in a way that correlates with changes in the epigenome.

“The epigenome — chemical modifications to chromosomes and 3D chromosomal structure — is not just a linear object,” Ren said. “The epigenome is a 3D object, folded in a hierarchical way, and that should affect how we think about many aspects of human development, health and disease.”

Co-authors on the paper “Integrative Analysis of Haplotype-Resolved Epigenomes Across Human Tissues” include Danny Leung, Inkyung Jung, Nisha Rajagopal, Anthony Schmitt, Siddarth Selvaraj, Ah Young Lee, Chia-An Yen, Yunjiang Qiu, Samantha Kuan, Lee Edsall, Ludwig Cancer Research; Shin Lin, Yiing Lin, Stanford University and Washington University School of Medicine; Wei Xie, formerly at Ludwig Cancer Research and now at Tsinghua University; Feng Yue, formerly at Ludwig Cancer Research and now at Pennsylvania State University; Manoj Hariharan, Joseph R. Ecker, Howard Hughes Medical Institute and Salk Institute for Biological Studies; Pradipta Ray, University of Texas; Hongbo Yang, Neil C. Chi, UC San Diego; and Michael Q. Zhang, University of Texas, Dallas and Tsinghua University.

Co-authors on the paper “Chromatin Architecture Reorganization during Stem Cell Differentiation” include Jesse R. Dixon, Siddarth Selvaraj, Ludwig Cancer Research and UC San Diego; Inkyung Jung, Yin Shen, Ah Young Lee, Zhen Ye, Audrey Kim, Nisha Rajagopal, Yarui Diao, Ludwig Cancer Research; Jessica E. Antosiewicz-Bourget, Morgridge Institute for Research; Wei Xie, Tsinghua University; Jing Liang, Huimin Zhao, University of Illinois at

Urbana-Champaign; Victor V. Lobanenkov, National Institute of Allergy and Infectious Diseases; Joseph R. Ecker, Howard Hughes Medical Institute and Salk Institute for Biological Studies; James Thomson, Morgridge Institute for Research, University of Wisconsin and University of California, Santa Barbara.

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