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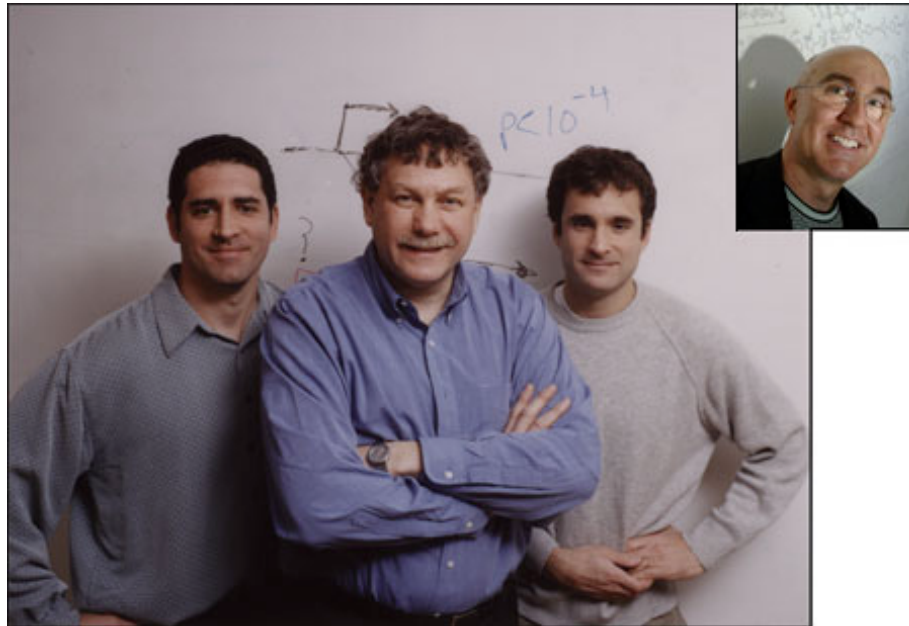
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Using new tools they developed for mapping chromatin modifications across entire chromosomes, researchers have identified novel structures that package and regulate the genome. The structures' association with genetic regions that are critical for development and disease and their presence in both human and mouse genomes hint at an important role in controlling how the genome is translated into living cells.



In the most detailed examination to date of histone modifications in human chromosomes, researchers (from left) Michael Kamal, Eric Lander, Bradley Bernstein, Stuart Schreiber (inset), and their colleagues found novel chromatin structures, some of which may function independently of the underlying DNA sequences. The work was a collaboration of HMS, the Harvard Faculty of Arts and Sciences, the Broad Institute, and other institutions. (Photo by Graham Ramsay; inset photo by Marc Berlow)

The study is the most detailed examination to date of the histone proteins at the core of DNA's chromatin packaging and, more specifically, of the chemical modifications that regulate histone function. The results, published in the Jan. 28 *Cell*, underscore the significance of the emerging field of epigenetics, which deals with the ways that cells can alter the function of their genes without altering their DNA sequence. Often the histone

Immunology Graduate Program

modifications, which are thought to switch underlying genes off and on, appear to function independently of the underlying DNA, the *Cell* paper reports.

Nominations Sought for Leadership in Women's Advancement

"It really hammers the point home," said Tanita Casci, senior editor of *Nature Reviews Genetics*, who wrote a perspective on the study for the March issue. "Here is hard evidence that histone modifications are quite distinct from the genome. It reinforces the importance of looking at epigenetic marks."

Nominations Invited for Biostatistics Award

The Genetic Gateway

Genomes may carry the blueprint to make proteins, but histones control access to those genes. Their power over gene activity comes from the structure of chromosomes. Methyl and acetyl groups turn genes on or off by grabbing onto different spots on the histone tails and altering their chromatin structure. In fact, chromatin biologist David Allis at Rockefeller University has proposed that a "histone code" outside of the DNA is a fundamental regulatory mechanism.

Grants Available for Collaborative Research in Women's Health

Honors and Advances

Baldwin Named New President of CBR

"One of the great challenges in genome research is to understand the complex regulatory network that controls gene expression," said Bradley Bernstein, co-first author of the paper and HMS instructor in pathology at Brigham and Women's Hospital, who works in the Harvard University lab of Howard Hughes investigator Stuart Schreiber. "Chromatin is a key component of this regulatory network."

Forum

Lines Drawn Over Recommended Cuts in Medicare Hospital Reimbursement

For their study, Bernstein and his colleagues analyzed the chromatin of the two shortest human chromosomes, numbers 21 and 22, containing about two percent of the human genome, and sampled other regions of the human and mouse genomes.

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Bernstein and Schreiber adapted techniques they developed several years earlier while studying the chromatin structure of the smaller yeast genome.

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First, Bernstein isolated the regions of genome wrapped around histones carrying certain major methyl and acetyl tags. He purified the DNA bits and made multiple copies for analysis on new DNA microarrays containing entire human chromosomes, rather than a subset of known genes. The new microarray technology, developed by co-author Tom Gingeras and his colleagues at Affymetrix in California, identified the underlying genetic sequence of the tagged chromatin.

To confirm the results of the new technology, Bernstein used traditional molecular biology techniques to verify about 100 of the genomic regions that were found to be associated with the histone marks.

Next, Michael Kamal, co-first author of the paper, Eric Lander, and their colleagues at the Broad Institute of MIT and Harvard began the daunting computational analysis. Kamal correlated the extensive maps of the chromatin structure with the underlying genetic sequence and compared the results between mouse and human.

"We certainly noticed something special about some regions," Kamal said.

Most of the histone tags hovered over the transcription starts of active individual genes. Unexpectedly, some tags idled in the vicinity of genes, but apparently they were not related to the underlying DNA sequence. The researchers think these sites have important, if unknown, regulatory functions, because the methylation patterns were similar in comparable portions of the mouse genome.

Hox Hits

Strikingly, in both mouse and human, the cluster of genes that control the body plan of the developing embryo had extensive regions of chromatin marks covering entire genes and the regions between them.

“In most of the genome, we see short regions associated with activated histones, such as the starts of individual genes,” Bernstein said. “In the Hox clusters, we see huge regions tens of thousands of base pairs in length completely covered by tags.”

These huge regions may correspond to active chromatin domains that lock in the characteristic gene expression patterns of Hox genes, Bernstein said. Additional experiments showed markedly different chromatin structures in the Hox regions of lung, gum, toe, and foreskin cells. Because Hox gene-expression patterns help determine the destiny of a cell, these diverse chromatin structures may help explain how cells with the same genome can be programmed to assume vastly different roles in the body, such as a macrophage guarding against invading pathogens or a pancreatic beta cell secreting insulin.

Bernstein is particularly interested in the implications of the Hox chromatin structure for cancer. Many of the methyl tags are known to be ferried to the histone tails by MLL, a protein made by the mixed-lineage leukemia gene. A translocated form of the protein causes about 10 percent of all leukemias. Bernstein hopes to apply the new technology to characterizing chromatin structure in leukemic cells and gaining insight into the molecular basis of disease.

“It’s a safe bet that the chromatin structure of Hox regions is going to be involved in the aberrant Hox gene-expression patterns implicated in certain cancers,” said Bernstein, who is following up this research angle.

Kamal is more interested in the way that histone mapping helps reveal new areas of the genome that deserve further study. “We have a lot to learn about the information in the genome,” Kamal said. “Comparative epigenomics can help guide our search for the important signals.”

—Carol Cruzan Morton

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