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Man and Mouse Share Genome Structure

In the most detailed large-scale study to date of the proteins that package DNA, researchers have mapped a family of switches that turn genes on and off. Their findings may help scientists understand regulatory mechanisms underlying cancer and human development.

The research team includes first author Bradley Bernstein, recipient of a Howard Hughes Medical Institute (HHMI) physician postdoctoral fellowship who works in the Harvard University laboratory of HHMI investigator Stuart L. Schreiber. Other co-authors are from the Broad Institute of MIT and Harvard, and Affymetrix. Their findings are published in the January 28, 2005 issue of *Cell*.

“Now that the human genome has been sequenced, it is vital to learn how the genome is translated to make living cells and organisms, and how we can use that information to improve human health,” said Bernstein, who is an instructor of pathology at Brigham & Women's Hospital and Harvard Medical School. “Every one of our cells has the same genome, yet is completely different. Muscle cells are different from neurons. They are different because different genes are on.”

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Many scientists believe changes in the regulatory scaffolding surrounding the genome may be as important as changes in the genome itself in causing diseases such as cancer.

This regulatory structure, called chromatin, is a key regulator of gene expression in healthy and diseased cells, Bernstein said. Chromatin is

composed of DNA spooled around bundles of histone proteins, and resembles a chain of beads which is then compressed into a working chromosome. Chemical tags placed on the histones alter the way chromatin is organized, thus allowing the right combination of genes to be turned on.

In their study, the researchers analyzed the chromatin structure of the two shortest human chromosomes, numbers 21 and 22, containing about two percent of the human genome. They also sampled additional regions in both the human and mouse genomes, finding similar patterns along equivalent chromosomal regions, even where the underlying DNA sequences are different.

Bernstein and Schreiber began to develop the analytical techniques several years earlier, working with the smaller yeast genome. To investigate the much larger human genome, they collaborated with Affymetrix. They isolated the DNA regions with certain major methyl and acetyl tags, and used new microarray technology to identify the underlying genetic sequences associated with the tagged chromatin. Next, they teamed up with Michael Kamal, the co-first author of the paper, Eric Lander, and their Broad Institute colleagues, for the daunting computational analysis required to interpret the resulting data.

In most cases, the mapped tags coincided with the transcription starting points of active genes, as they and others had seen earlier in the yeast. Unexpectedly, they also found tags idling over regions near genes. The researchers think these sites have important regulatory functions, because the methylation patterns are similar in comparable portions of the mouse genome. Until now, they'd been missed by more standard genome analysis tools.

Most exciting to Bernstein is the unusual density of histone tags spread over the regions of genome containing the *HOX* genes, which are key regulators of development.

“In most of the genome, we see short stretches associated with activated histones,” Bernstein said. “However, in the *HOX* regions, we see huge stretches of genome, many thousands of base pairs in length, that are completely covered by tags.” The researchers speculate that these unique chromatin structures could be activating sets of *HOX* genes for specific developmental programs.

This global activation may have implications for understanding mechanisms behind certain cancers, Bernstein believes. For example, proteins that place methyl groups on histones can, when mutated, cause leukemia. Bernstein hopes to apply the new technology to characterize chromatin structure in leukemic cells and gain insight into the molecular basis of disease.

“The human genome still has many surprises lurking within it,” said Lander, director of the Broad Institute and senior author on the study. “One of the most important is the mystery of how genes are turned on. The ability to take global views of chromatin in human cells holds tremendous promise for unraveling this mystery.”