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By Melissa Lee Phillips

Epigenetics mark regulatory elements

Unique histone modifications distinguish transcriptional promoters and enhancers

[Published 5th February 2007 03:21 PM GMT]

Distinct chromatin modifications identify human transcriptional promoters and enhancers, and these marks can be used to predict novel regulatory elements, according to a new paper in *Nature Genetics*. The study reports that trimethylation of a particular amino acid residue in histone H3 consistently identifies promoters, while monomethylation of the same residue marks enhancers.

"This is the first time that we've discovered a histone modification mark that is different between enhancers and promoters," said senior author Bing Ren of the University of Californria, San Diego (UCSD). The promoter signature is "consistent with previous findings in other organisms," Ren said, but "the enhancer-specific marks are novel."

Previous work identified histone modifications, such as acetylation and methylation, that are associated with regulatory elements involved in gene transcription. Work in yeast, flies, and mice showed that active promoters are often marked by trimethylation of a lysine residue in histone H3, but this is the first study to use high resolution technology to look for this mark systematically in the human genome, said study first author Nathaniel Heintzman, a student in UCSD's Biomedical Sciences Graduate Program. Additionally, scientists know little about potential marks of enhancers, he said. "People have been striving for a long time to find a way to computationally predict these distal regulatory elements."

Heintzman and his co-workers used chromatin immunoprecipitation and microarray (ChIP-chip) experiments to analyze the chromatin architecture of approximately 1% of the human genome. They first examined epigenetic modifications of well-annotated promoters and found that transcriptional start sites of active promoters were strongly marked by trimethylation of histone H3 lysine 4, just as in other species.

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"That's actually quite interesting that you end up having the same type of chromatin structure at promoters in all sorts of different organisms," said Oliver Rando of the University of Massachusetts in Worcester, who was not involved in the study.

The researchers then analyzed histone modifications in regions likely to be enhancers and found that they displayed monomethylation of the same lysine residue.

"This paper makes it clear that these histone modifications... really do associate with specific elements such as promoters and enhancers," said Richard Young of the Massachusetts Institute of Technology in Cambridge, also not a co-author.

Heintzman and his colleagues next used these characteristic marks to develop a computational algorithm to predict novel promoters and enhancers. Of about 200 predicted promoters in the 20 Mb they analyzed, more than 90% corresponded to known 5' ends of genes. Of nearly 400 predicted enhancers in this region, the researchers found that most displayed known qualities of enhancers.

To validate their results, the authors examined more closely one putative enhancer, located upstream of a gene that encodes a carnitine transporter. Mutations in this gene prevent the body from using fats for energy. The researchers found that deleting the predicted enhancer of this gene caused a 2.5-fold reduction in transporter gene expression.

Based on these results,"monomethylation may be a really good way to just go into the genome and pick out all the enhancers," Rando told *The Scientist*, adding that it will be important for the researchers to figure out what the false-positive rate is with this method.

It will also be interesting to study "the mechanism by which those histone marks are created at those sites" and how that relates to the control of gene expression, Young said.

The study also revealed that active human promoters contain nucleosome-free regions at transcriptional start sites. These regions are established in yeast and fly but experiments suggested they did not exist in the human genome. The high resolution of array technology enabled the researchers to find these regions, according to Heintzman. "Because we were actually looking at 38-base pair resolution, we were able to identify these very distinct nucleosome-free regions at active promoters," he said.

Clarification (posted February 7): When originally posted, the article implied that no researchers had looked for epigenetic marks in active human promoters. In fact, scientists have conducted these experiments, but the study described here is the first to use high resolution microarray technology.

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Links within this article

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 ISSN 1759-796X