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Where the expressed genes are

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Despite widely held beliefs that open and condensed regions of chromatin correlate with active and silent regions of expression, respectively, there is no strict correlation between open chromatin and the activity of a gene, according to a paper in Cell this week(*Cell* 2004, **118:**555-566). Instead, genes that need to be rapidly activated or switched off are held in regions of open chromatin structure - possibly constraining certain genes to lie within the same genomic region throughout evolution, according to lead author Wendy A. Bickmore of the MRC Human Genetics Unit in Edinburgh.

"Previously, chromatin structures have really only been studied as individual genes, one by one, so we wanted to take a more global approach to ask questions about how chromatin is organized across the whole human genome," Bickmore told us.

Bickmore's team labelled the DNA from open or closed chromatin by fluorescence in situ hybridization (FISH) so they appeared either green or red, respectively, and hybridized them to metaphase chromosomes. At a subchromosome level, gene-rich T-bands - for example at the distal end of 1p (1p34-p36), and at 11q13 and q23 - were enriched in open chromatin. Their microarray analysis confirmed the gross picture derived from the FISH data.

"We already knew that human genes are not uniformly spread across the whole genome, they tend to be clustered together in fairly tight clusters, and these are the genes that corresponded with the open chromatin," Bickmore said.

The study marries biochemistry with morphology, according to Tom Misteli who heads the Cell Biology of Gene Expression Group at the US National Cancer Institute. "A biochemical definition of chromatin is taken and then applied to chromosomes and to the linear sequence of the genome," said Misteli, who was not involved in the study. The result is a fairly low-resolution map of the chromatin fiber. "So this is the next level from the genome sequence - that's the significance. It's the first study to map the chromatin fiber genome-wide," said Misteli.

"I think that what this suggests is that a lot of the regulation is really done by transcription factors rather than simply by accessibility. That really changes the simple view," said Misteli.

Bickmore suggested these open chromatin structures represent readable regions of the human genome. "But it doesn't mean to say that every gene in there is being read - it just means it can be if it needs to be," she said, and neither do these genes have to be of a particular type, such as only developmental genes.

Open chromatin regions may also represent easy targets for retrotransposon insertion, and even retroviral infection, according to already published data Bickmore said. "We would speculate that these regions are rather vulnerable to physical and chemical damage, as well as to genetic damage from invading sequences - but presumably that's a price that's worth paying for the cells," she said.

"What we are also suggesting is that it may have been important in evolution to keep certain genes in open chromatin structure regions, ready to be activated or shut down," Bickmore said.

"This idea is consistent with our own results," said Linheng Li, an assistant professor in the Department of Pathology & Laboratory Medicine, University of Kansas School of Medicine. "We had the hypothesis that stem cells have an open chromatin structure and this may be the basis for stem cells' multipotentiality," said Li, who was not involved in the study. Li said it would be interesting to compare a chromatin map in stem cells with a similar map in differentiated somatic cells to see if their hypothesis is borne out.

"At the DNA sequence level, comparative studies between different species has been extremely valuable for understanding what are the important elements in the genome, and I think the same sort of thing is going to be true of chromatin structure," Bickmore said.

References

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