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New findings challenge established views about human genome

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A team of researchers led by University of Virginia Health System geneticists has uncovered a major secret in the mystery of how the DNA helix replicates itself time after time. It turns out that it is not just the sequence of the bases (building blocks) in the DNA, but also how loosely or tightly the chromatin (the material that makes up chromosomes) is packed at different points of the chromosome that is critical.

Where chromatin is packed more loosely, the genes are replicated earlier than other genes and are expressed at high levels. Where chromatin is dense, these genes are replicated later and are not expressed.

“Our work showed that by looking at time of replication, we could predict which genes are in an environment that could be expressed and the potential that cell has of going down different paths of differentiation,” says Anindya Dutta, M.D., UVa professor of biochemistry and molecular genetics, who headed the replication portion of the major ENCODE project published in *Nature* journal (June 14). “The time of replication of different parts of our genome is very nicely correlated with the chromatin packaging.”

This finding held true for both cell lines studied, the HeLa cervical cancer cell line and a normal cell line (lymphocytic cells). “To our surprise, what the HeLa cells were predicting in terms of chromatin packaging held true in the lymphocytes, even though the HeLa cells are cancer cells with scrambled genes,” Dutta said. “The chromatin packaging predictions were approximately comparable.”

Chromosomes, then, are not just a framework of DNA but also are influenced by the proteins that pack the DNA, particularly histones. This packaging determines how the cell's enzymes get access to the DNA to read off the DNA and replicate, ultimately to create all of the proteins needed by a given cell.

Several other researchers around the country were part of this larger project, the Encyclopedia of DNA Elements (ENCODE) project, using two preset cell lines. Overall, the consortium looked at just 1 percent of the human genome, using HeLa and lymphocytic cells for the study. Groups that were performing other experiments found that their data about genetic expression perfectly correlated with what the Dutta lab would have predicted, in terms of gene expression timing. In the ENCODE study, the next project is to examine the remaining 99 percent of the genome, using at least 10 more cell lines, Dutta says.

One of the very intriguing questions that comes from the findings is: what determines the boundaries between the actively expressing domains of a chromosome and the inactive portions"

“The length that is active in each chromosome is likely to be different between different types of cells because different genes are expressing,” Dutta said. “How does that boundary shift so that something that was inactive in one cell is now active in another cell line""

Future research will help to tell this story, but one possibility is that special proteins come and bind with the chromosome elements. Their job may be to grab on to a site on the chromosome and define the boundary element.

“There is nothing in the DNA sequence of bases that sets up the boundary areas between active and inactive portions, but clearly the chromosome is set up to have these domains,” Dutta explains.

Another interesting finding shows that a different longtime idea about genetics is apparently false. Humans get copies of a gene from both mother and father. The expectation was that each copy would behave the same way. The researchers thought that both copies would either be expressed and replicated early or repressed and replicated late. Instead, they discovered that 20 percent of the pairs of genes have different (asynchronous) replication due to the two copies in the pair being in different chromatin environments.

“One copy is replicating early and the other is replicating,” Dutta said. “Even though we get two copies of the genes, not all of the genes are expressed from both copies. There are a significant number of gene pairs where the chromatin is packed differently between the copies.”

What this means, unfortunately, is that one of the copies of a gene X might be inactive because of chromatin packaging, losing the redundancy that comes from both copies being active. If tumor suppressor genes, the ones that turn off cancer cells, reside in areas of the genome with asynchronous replication, the cancer cell can turn such genes off merely by mutating the one active copy instead of going through the trouble of separately mutating both copies.

Dutta and colleagues are now gearing up for their next project, looking at the remainder of the genome, grateful for significant findings they uncovered in just one percent of the genome, through the ENCODE project. “This study could not have been done without NIH funding,” Dutta stressed. “This type of basic research is not funded by the pharmaceutical firms or the biotech firms. We are all anxious because later this summer we will find out if we will receive the money to study the remaining the 99 percent of the human genome.”

If the next portion goes unfunded, “it would be one the biggest missed opportunities in biology,” Dutta says. “We used the one percent of the

genome as a trial area, and it would be a tragedy if we couldn't expand this to the remaining 99 percent of the genome and to different cell lines. The difference between cell lines is where biology lies."

Source: University of Virginia Health System