

Access to DNA secrets yields better understanding of genes, possible tool for disease diagnosis

DALLAS – July 8, 2004 – A new technique for examining DNA is giving scientists a more detailed picture of which genes have the propensity for activation, offering a new tool for understanding how genes function and possibly for diagnosing disease.

The technology, called a chromatin array, was developed by researchers at UT Southwestern Medical Center at Dallas and is described in the July issue of the journal *Genome Research*.

DNA, which contains the genetic instructions needed to make a human or any other life form, is a long molecule that is tightly compacted in a cell's nucleus. Various pieces of DNA are constantly being compressed and expanded like the folds of an accordion as a cell responds to its changing needs.

When the DNA relaxes, or expands, proteins called transcription factors gain access to the genetic code to “read” its instructions for making a molecule called RNA, which in turn makes other proteins that carry out life's essential functions, from immune response and muscle contraction to cholesterol and hormone regulation.

When DNA is highly compacted, like a closed accordion, it's not as accessible to transcription proteins, and cannot make RNA, said [Dr. Harold “Skip” Garner](#), professor of biochemistry and internal medicine at UT Southwestern and senior author of the study.

Using the chromatin array, UT Southwestern researchers can detect the relative compactness of several stretches of DNA at a time with very high resolution, allowing them to determine which genes have the propensity for making RNA. They found that for many genes, but not all, the more open the DNA is, the more RNA is produced.

“The interesting genes are the ones that don't behave this way,” Dr. Garner said.

Exactly what controls compaction and expansion of DNA is still under scientific debate. In their next set of experiments, Dr. Garner and his team will apply various drugs – such as those used in cancer therapy – to cells in order to understand if and how these drugs affect DNA compaction. Such studies might lead to therapies aimed at activating beneficial genes, or turning off faulty ones.

The researchers also will investigate whether certain compaction and expansion states might be indicative of cancer or other diseases.

“Our current study describes the platform technology necessary to try to understand larger questions,” Dr. Garner said. “The next step will involve using the technique to look at different types of cancer cells to see whether this type of assay could be a diagnostic tool.”

Other techniques have been used to examine the compactness of DNA, but only a small piece of DNA at a time, said Ryan Weil, a UT Southwestern biophysics graduate student and the study’s lead author. “One of the advantages of our array is that it sorts through lots of pieces of DNA and gives us information about each segment all at once.”

Currently, scientists determine which genes are turned on, or expressed, in a cell by extracting RNA and measuring how much of it is being produced for each gene. An RNA microarray, or “gene chip,” is the standard equipment used to measure RNA expression levels.

“Only a small fraction of genes are making sufficient RNA to be detected with RNA microarrays,” said Dr. Garner. “Many of the genes that make very small quantities of RNA are nonetheless very important, but they fall below the threshold of detection for current techniques.”

The UT Southwestern technique allows researchers to study genes that previously weren’t accessible because there was not enough RNA to make a measurement of their activity.

“We can get information on a much larger number of genes, and whether or not they are in a state in which they can make RNA, using this technique than by using traditional RNA microarrays,” Dr.

Garner said. “This technology can tell us not only whether the DNA for a given gene is present or not, but also whether it is compacted or expanded and therefore ready to make RNA.”

Mr. Weil said, “We can tell not just what cells are doing now, but what they could do in the future.”

Other UT Southwestern researchers who contributed to the study were [Dr. John Minna](#), director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. “Tex” and Deborah Moncrief Center for Cancer Genetics, and Dr. Piotr Widlak, a postdoctoral researcher in molecular biology. The research was supported by the National Institutes of Health and the National Cancer Institute.

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