MedicalXpress

Scientists map out regulatory regions of genome, hot spots for diabetes genes

February 2 2010

Together with colleagues in Barcelona, researchers at the University of North Carolina at Chapel Hill have generated a complete map of the areas of the genome that control which genes are "turned on" or "off." The discovery, made in pancreatic islet cells, opens new avenues for understanding the genetic basis of type 2 diabetes and other common illnesses.

"Most of the human genome is uncharted territory - entire stretches of sequence with no clear function or purpose," said Jason Lieb, Ph.D., associate professor of biology at UNC, a member of the UNC Lineberger Comprehensive Cancer Center and one of the senior authors of the study. "In fact, the majority of the DNA sequences associated with disease found thus far reside in the middle of nowhere. Here we have developed a map that can guide scientists to regions of the genome that do appear to be functionally relevant, instead of a dead end."

The research, published online Jan. 31, 2010, in the journal *Nature Genetics*, presents the first high-resolution atlas of these regulatory elements in the most studied cell type for treatment and prevention of type II diabetes.

The completion of the human genome project has spurred a flurry of research into the exact genetic changes underlying disease. But while these studies have discovered thousands of sequences associated with human illness, pinpointing which sequence variations are the true culprits has proven difficult. That is because the underlying genetic

sequence - the A, C, T, and G that code for your entire being - is only part of the story. It is not just the message, but the packaging - whether those four letters are laid out like an open book or tightly packaged like a message in a bottle - that determine which genes are active and which are not.

Using a new method developed in the Lieb laboratory called FAIRE-seq, Lieb and his colleagues isolated and sequenced a total of 80,000 open chromatin sites within pancreatic islet cells. They then compared these sites to those in non-islet cells to narrow the number down to 3,300 clusters of sites specific to this cell type. Each cluster typically encompassed single genes that are active specifically in islet cells. Twenty of these genes are known to harbor gene variants associated with type II diabetes.

The researchers decided to continue their studies on the variant most strongly associated with the disease, a single nucleotide polymorphism - or SNP - occurring in the TCF7L2 gene. They found that the chromatin is more open in the presence of the high risk version of the gene (a T) than in the presence of the non-risk version (an A). Further analysis demonstrated that the risk variant enhanced the activity of the gene, indicating that it may possess functional characteristics that could contribute to disease.

Lieb says his map is likely to help others within the diabetes research community identify new targets for understanding - and ultimately treating - the disease more effectively. But the approach is not limited to diabetes, or even pancreatic islet cells. He plans to use FAIRE-seq to chart the open chromatin regions present within other cells, such as the immune system's lymphocytes.

Provided by University of North Carolina School of Medicine