DNA mapping tool helps scientists better understand how genes are regulated

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Scientists have devised a powerful new tool for understanding how DNA controls gene activity in cells. The tool allows researchers to map at high resolution, across large swaths of a cell's genome, which DNA nucleotides work to regulate gene activity.

"This is the first method that enables us to simultaneously test thousands of human DNA regulatory regions for their ability to turn genes on and off, and to map in high resolution the elements that activate and repress genes within them," said Jason Ernst, the study's lead author and an assistant professor of biological chemistry at the David Geffen School of Medicine at UCLA.

Ernst, who is also a computer science professor at the Henry Samueli School of Engineering and Applied Science, and colleagues applied the new tool to more than 15,000 sections of DNA predicted to contain regulatory control elements in two human cell types. Their resulting map of activating and repressive elements in these regions contains several surprises. For example, the scientists found that a repeated short pattern within the DNA sequences with the greatest average activity was one that has not yet been well described. Also included among the most active regulatory elements are segments of DNA that are widely believed to be remnants of ancient retroviruses.

"We still have a lot to understand about human DNA, and how strings of A, C, G, T nucleotides assume meaning inside our cells," said coauthor Manolis Kellis, a professor of computer science at the Massachusetts Institute of Technology. "Our technique reveals important nucleotides within regulatory regions, bringing us a step closer to understanding the complex language of our genome."

Learning how DNA regulates genes enables scientists to understand how cells and organs work when people are ill and healthy. Many diseases that are poorly understood and have no cure could be treated successfully if scientists knew more about regions of DNA that regulate genes.

With the help of experimental automation and advanced algorithms, the researchers took thousands of small pieces of DNA from suspected gene-regulating regions in the human genome and tested each one for its ability to boost or repress the activity of a special "reporter" gene in cultured cells. Unlike previous methods, the researchers tested densely overlapping pieces of DNA, enabling them to recognize subtle differences between neighboring pieces and to map the activating or repressive contributions of regulatory nucleotides at high resolution in two distinct types of human cells.

The new tool will help speed the scientific effort to map and characterize regulatory DNA elements, leading to a better understanding of how genes are regulated, and potentially how mutations or nucleotide variations in regulatory DNA contribute to illnesses.

The study was published online before print in *Nature Biotechnology*.

More information: Jason Ernst et al. Genome-scale high-resolution mapping of activating and repressive nucleotides in regulatory regions, *Nature Biotechnology* (2016). DOI: 10.1038/nbt.3678

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