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UC San Diego Biologists Unlock Code Regulating Most Human Genes



Molecular biologists at UC San Diego have unlocked the code that initiates transcription and regulates the activity of more than half of all human genes, an achievement that should provide scientists with a better understanding of how human genes are turned on and off.

The discovery of this critical DNA sequence code—what molecular biologists term the “human Initiator”—is detailed in a paper in the February 10 print issue of the journal *Genes & Development*. An advance copy of the paper is now online.

“There are many sequence signals that control gene activity in human cells and the Initiator is the most commonly occurring sequence at the start sites of genes,” says James T. Kadonaga, a molecular biology professor at UC San Diego who headed the team of researchers. “The solution of the human Initiator code will enable us to explore new frontiers in gene regulation. In the future, it will be possible to use the code to identify other regulatory signals and, in this way, gain a more complete understanding of how human genes are turned on and off.”

Each tiny human cell contains about six feet of DNA, a double-helical molecular chain containing several billion chemical nucleotides—adenine (A), cytosine (C), guanine (G) and thymine (T)—arranged in a specific sequence, or code, that when transcribed guide the cell into producing specific proteins.

“In these six feet of DNA, there are tens of thousands of genes, which are segments of DNA that direct specific functions, such as the production of a hormone or an enzyme,” explains Kadonaga. “It is essential for the cell to control the activity of each of its tens of thousands of genes, because the improper control of gene activity can lead to adverse outcomes such as cell death or the formation of a cancer cell.”

That’s where the human Initiator comes in.

First observed by Pierre Chambon and his colleagues in Strasbourg, France in 1980, the human Initiator and its role in gene activation were articulated in 1989 by two MIT biologists, Stephen Smale and David Baltimore at MIT, who revealed in the 1990s, the approximate sequence code of the Initiator.

Since then, however, other scientists had proposed a number of different sequences for the human Initiator, but none of them were found to be consistently associated with the start sites of human genes. As a result, the true Initiator sequence code remained a mystery until now.

Kadonaga and his team employed emerging genomic techniques and devised novel computational strategies to unlock the DNA sequence code for the human Initiator. They also discovered that this sequence is located precisely at the start site of more than half of all human genes, underlining the importance of the human Initiator in the human genome.

Other coauthors of the paper are Long Vo ngoc, California Jack Cassidy, Cassidy Yunjing Huang and Sascha Duttke. The research was support by grants from the National Institutes of Health (R01 GM041249, R21 HG008781, and R35 GM118060).

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