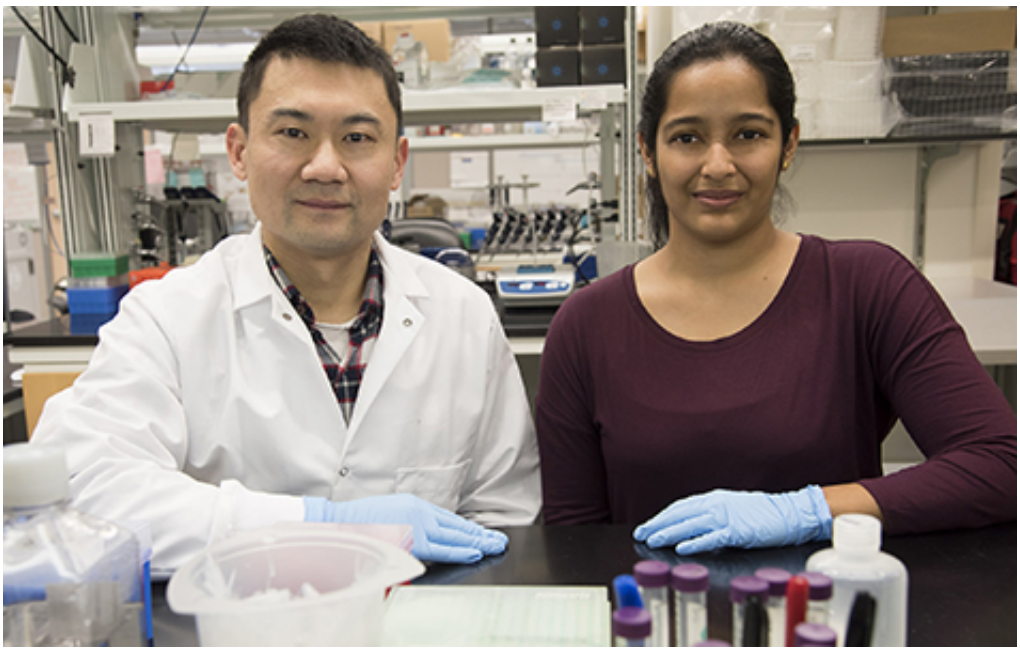
New insight can help determine when mouse models are good stand-ins for studying humans

November 20 2014, by Caroline Arbanas



New research by Ting Wang, PhD, (left) and graduate student Vasavi Sundaram looked closely at the DNA of the mouse and human to uncover some striking differences in the way their genes are controlled. Credit: Robert Boston

For decades, the mouse has been a mainstay for researchers studying human diseases because the two species share many of the same genes. But now, a comprehensive analysis of the inner workings of the DNA in humans and mice has uncovered some striking differences in the way

their genes are controlled.
While the research also shows many similarities in gene regulation in humans and mice, the differences provide new information to help scientists determine when the mouse is a good stand-in to study human biology and disease and when it may have limitations.

The research, by an international team of scientists, is reported online Nov. 19 in studies in the journals *Nature*, *Genome Research* and the *Proceedings of the National Academy of Sciences*. The work is part of the mouse ENCODE project, which stands for ENCyclopedia Of DNA Elements, and is funded by the National Institutes of Health (NIH) through the American Recovery and Reinvestment Act.

As part of the project, scientists at Washington University School of Medicine in St. Louis and elsewhere have compiled a catalog that details critical elements in human and mouse genomes that control gene activity.

"Understanding what controls the activity of genes and the way they are expressed is important because genes that are expressed in error or not at all can contribute to numerous diseases," said Ting Wang, PhD, an assistant professor of genetics and a corresponding author of a study in Genome Research.

The researchers delved into an expansive area of the genome once commonly referred to as junk but now recognized for playing an essential role in regulating genes. Of the 3 billion chemical building blocks that make up human and mouse DNA, only about 2 percent is made up of genes, which code for proteins and enzymes that keep the body running.

Until about 20 years ago, the rest of the genome was not thought to do much of anything. But research since then lends credence to the idea that

what was once considered trash actually contains treasure. In fact, the new findings confirm that so-called noncoding regions of DNA are rich in regulatory elements that maintain exquisite control over gene expression.

Wang and his colleagues in the Department of Genetics looked at small fragments of DNA, called transposable elements, which move from place to place in the genome to control the expression of genes. They make up 50 percent of the mouse and human genomes, but little has been known about the extent to which they control gene expression and whether that control is similar across both species.

These stretches of DNA harbor binding sites where master switches called transcription factors engage to turn genes on or off. The researchers, including Washington University graduate student Vasavi Sundaram, the study's first author, studied 26 transcription factors in two cell types in the mouse and the human to see how often they bind to the moving DNA elements.

They found that such binding varies by transcription factor, but that on average, 20 percent of binding sites were embedded in transposable elements. Moreover, they showed that these binding sites are vastly different in the mouse and human, suggesting that the control of gene expression varies dramatically between the species.

"This was a complete surprise," Wang said. "These differences can play a role in gene expression that, over time, enhance innovation within the genome and contribute to the evolution of a species.

"Our findings also highlight the importance of transposable elements in the regulation of gene expression and suggest that they should not be ignored in studies of disease or human biology."

The new discoveries by Wang and other researchers will provide a valuable resource to scientists across the globe.

"These results provide a wealth of information about how the mouse genome works, and a foundation on which scientists can build to further understand both mouse and human biology," said Eric Green, MD, PhD, director of the National Human Genome Research Institute, which funded much of the work. "The collection of mouse ENCODE data is a tremendously useful resource for the research community."

More information: Sundaram V, Cheng Y, Ma Z, Li D, Xing X, Edge P, Snyder MP and Wang T. "Widespread contribution of transposable elements to the innovation of gene regulatory networks." *Genome Research*. Oct. 15, 2014.

Provided by Washington University School of Medicine in St. Louis

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