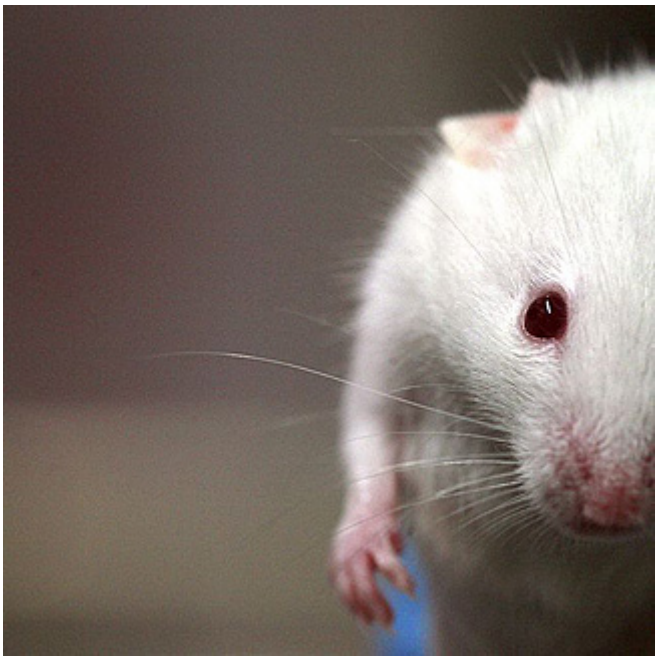
Of Mice, Not Men

Catalog of mouse functional genome pinpoints similarities and some significant differences

November 19, 2014 | Scott LaFee

For more than a century, the laboratory mouse (Mus musculus) has stood in for humans in experiments ranging from deciphering disease and brain function to explaining social behaviors and the nature of obesity. The small rodent has proven to be an indispensable biological tool, the basis for decades of profound scientific discovery and medical progress.



Laboratory mouse.

But in new findings published online Nov. 19 in the journal *Nature*, researchers at the University of California, San Diego School of Medicine and Ludwig Cancer Research, with colleagues across the country and world, have discovered that a significant number of mouse genes do not in fact behave like their human counterparts, suggesting science will need to rethink at least some roles of the lab mouse as a model organism.

"The assumption has long been that whatever was discovered in the mouse would likely be true in humans too, but the idea has never been systematically evaluated and assessed," said Bing Ren, PhD, professor in the Department of Cellular and Molecular Medicine, head of the Laboratory of Gene Regulation at the Ludwig Institute for Cancer Research at UC San Diego and one of the paper's senior authors.

"We know now that this assumption is not entirely true. There are a substantial number of mouse genes that are regulated in ways different from similar genes in humans. The differences are not random. They are clustered along certain pathways, such as in genes regulating the immune system."

The findings, part of a series of related papers being published together in *Nature*, *Science*, and *Genome Research*, derive from the ongoing mouse ENCODE (Encyclopedia of DNA Elements) project, a multi-institution effort launched in 2007 to build a comprehensive parts list of functional elements of the mouse genome. It complements the earlier human ENCODE project, which published its functional catalogue in 2012.

"Both the original human and mouse genome projects gave us the sequence of genetic letters (adenine, thymine, guanine and cytosine) that comprise each organism, but no idea how they worked or worked together to create and sustain life," said Ren. "The human ENCODE project was designed to answer some of those questions. The mouse ENCODE project is its complement. It's intended to provide scientists with comprehensive annotation of what mouse genes do; information that may ultimately be used for human therapeutic purposes."

The mouse is not our closest genetic cousin, of course. Only half of human genomic DNA aligns to mouse genomic DNA. Chimpanzees, by comparison, match 96 percent. But protein-coding genes, which provide the actionable instructions to build a living organism, are more strongly conserved across the two species. Mice and humans share approximately 70 percent of the same protein-coding gene sequences, though these genes constitute just 1.5 percent of their respective genomes.

Ren said scientists had assumed that significant conservation would occur at the deeper level of gene regulation as well, that similar genes in humans and mice would be expressed in similar ways. Using the same high throughput technologies applied in the human ENCODE project, they analyzed 100 different mouse cell types and tissues. To their surprise, they found that while much conservation did exist, the expression profiles of some distinct biological pathways in mouse samples diverged considerably from human samples.

Put another way, core genomic programs were largely conserved between the species, but genes and their underlying regulatory programs had changed significantly over time. Each species had evolved to find different ways to do some of the same things.

The findings are not entirely unexpected. Ren said previous studies had documented rapidly evolving transcription factors in a handful of cell types and model organisms, but the ability to more systematically discern how humans and mice differ in genomic function marks an important milestone.

"One benefit is that while mice have proved to be substantially different than humans in some ways, we now have a better idea of where exactly they are different, where we will need to take into account those differences, perhaps finding or developing a better model, and where the mouse continues to be a very good model indeed."

There are 136 cited co-authors of this paper. The seven listed corresponding authors are Bing Ren, UC San Diego; Michael A. Beer, Johns Hopkins University; Ross C. Hardison, Pennsylvania State University; David M. Gilbert, Florida State University; Thomas R. Gingeras, Cold Spring Harbor Laboratory, New York; Roderic Guigo, Center for Genomic Regulation, Catalonia, Spain; Michael P. Snyder, Stanford University; and John Stamatoyannopoulos, University of Washington.

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