

Strains of laboratory mice more varied than previously thought

A collaborative study by scientists at the University of North Carolina at Chapel Hill and The Jackson Laboratory in Bar Harbor, Maine, has found that the genetic variation in the most widely used strains of laboratory mice is vastly greater than previously thought.

Where previously there were only 140,000 variations in DNA sequence described, it turns out there are 8.3 million.

Moreover, the study found that the pedigrees of the 15 mouse strains studied are not what they were previously assumed to be. It appears they differ from each other to a far greater degree than do the pedigrees between humans and chimpanzees.

The research, published online July 29 in the journal *Nature Genetics* and slated for the September print issue, could have major implications for the interpretation and design of studies past and future.

“Our article reports the first comprehensive analysis of such variation with an emphasis in evolutionary origin of the variation and its implications for biomedical research. We have rejected many long-held assumptions about the origin and relationships among mouse strains. In the light of our results, the conclusions of previous studies and the design of future studies need to be reevaluated,” said study co-author Fernando Pardo-Manuel de Villena, Ph.D., associate professor of genetics at UNC’s School of Medicine.

Animal models are essential tools in medical research because they allow researchers the opportunity to systematically probe questions within a defined biological system. The mouse is the most popular mammalian model for the study of human disease and normative biology, partly because their genomes are highly conserved. And, since 99 percent of genes in humans have counterparts in the mouse, cloning of a gene in one species often leads to cloning of the corresponding gene in the other.

The genome of the laboratory mouse has been thought to be a mosaic of DNA regions with origins in distinct subspecies. But the new study found that the majority of the mouse genome has unexpected levels of variation within their subspecies origin.

“The common laboratory mouse is not what we thought it was,” said coauthor Gary Churchill, Ph.D., a Jackson Laboratory senior staff scientist. “We’ve established that laboratory mice are derived almost entirely from a single subspecies, not three as previously believed.”

The Jackson Laboratory is a world-wide source for more than 3,000 genetically defined mice.

With support from the National Institute of General Medical Sciences, part of the National Institutes of Health, the researchers analyzed lineage and sequence variation based on the most extensive genetic data sets of inbred mouse strains. This information came from the National Institute of Environmental Health Sciences (NIEHS).

In testing the Y chromosomes and mitochondria for ancestry, the researchers found that the mouse strains were not offspring of their putative fathers and mothers.

The researchers concluded that the NIEHS data set, “despite its exceptional size, density and quality...captures only a fraction of the variation present in the laboratory mouse.”

Said Pardo-Manuel, “if one is studying mouse strains for responses to particular drugs, you make assumptions that the strains have certain pedigrees. If they don’t, what you are doing may not mean anything.”

He pointed out that the new knowledge of increased variation will enable scientists to conduct studies of genetic variation across the entire mouse genome.

“We plan to examine how many of the 8.3 million variants are actually knocking out genes, making them nonfunctional. If we already have that information from nature, we can actually go and ask about the function of these genes and what their implications are for disease,” he said.

“When the genome was completed, people were saying now that we have a genome sequence we should be able to find the underlying genes and find the causes of disease. This is naïve,” said Pardo-Manuel.

“Genetics works by comparing people with and without disease in the hope of finding genetic variants that are shared within these two groups of people but not between them. At the genetic level both conservation and variation are important.”

Source: University of North Carolina School of Medicine

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