Mouse can do without man's most treasured genes

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The mouse is a stalwart stand-in for humans in medical research, thanks to genomes that are 85 percent identical. But identical genes may behave differently in mouse and man, a study by University of Michigan evolutionary biologists Ben-Yang Liao and Jianzhi Zhang reveals.

Their results, which have implications for the use of mouse models in studying human disease, appear in the current issue of the journal *Proceedings of the National Academy of Sciences (PNAS).*

"Everyone assumes that deletion of the same gene in the mouse and in humans produces the same phenotype (an observable trait such as presence or absence of a particular disease). That's the basis of using the mouse to study human disease," said Zhang, an associate professor of ecology and evolutionary biology. "Our results show that may not always be the case."

Zhang and his graduate student Liao focused their study on so-called essential genes—genes which, through their effects on survival or fertility, are necessary for organisms to reach sexual maturity and reproduce. They then homed in on 120 essential human genes for which the mouse has an identical counterpart that also has been studied. Next they consulted a database that catalogs the results of experiments in which the mouse equivalents of human genes are deleted, or "knocked out."

If those 120 essential human genes are also essential in the mouse,

deleting any of them should result in infertility or death before reproductive age. But the database showed an unexpected discrepancy.

"To our surprise, 22 percent of the 120 human essential genes are nonessential in the mouse," Zhang said. "I expected there would be some, but I never expected the percentage to be so high."

Intrigued, the researchers wanted to understand why the "essentiality" of some genes has changed in the time since human and mouse last shared a common ancestor. Looking more closely at the protein products of the individual genes that are essential in humans but nonessential in the mouse, they discovered that a much higher than expected percentage are located in the vacuole, a sac-like cellular structure that functions as a garbage dump—but a highly important garbage dump.

"The main function of the vacuole is to contain and degrade cellular wastes and toxins," Zhang said. "In humans, the absence of vacuole proteins causes those wastes and toxins to accumulate, often leading to fatal neurological diseases."

The same thing happens in the mouse, but at a much later stage of life, often past reproductive age. As a result, "many of these vacuole proteins are not so 'essential' to the mouse," Zhang said. "Even without the proteins, the mouse can survive long enough to reproduce."

The researchers speculated that in the course of primate evolution, as life span increased and reproductive age was delayed, efficient waste management became increasingly important.

Additional results of their analysis support the idea. By developing an index that incorporated metabolic rate (a measure of how fast cellular waste products are generated) and reproductive age, and then using that index to compare human and mouse, the researchers determined that the

total amount of waste produced per gram of body mass from birth to reproductive age is about 18 times higher for humans than for the mouse.

"Hence, waste management is much more important in humans than in the mouse for maintaining proper cellular functions until the time of reproduction," Zhang said. "And when a biological process becomes more important to a species, the genes involved in that process tend to become essential."

Zhang acknowledges that the study involved a relatively small number of genes, and he hopes that other researchers will be able to confirm the results as more information on human and mouse genes becomes available.

"If our sample is unbiased, our results will have some important implications," he said. "First, in many genome projects, people draw inferences about gene function by using information from other model organisms. We need to be careful doing this because we now know that a large fraction of the genes may have different functions or different importance in different species."

In addition, the results raise concerns about the widespread use of mouse models for studying human disease.

"Our study does not say that mouse models are useless," Zhang said. "Even for those genes that have changed essentiality, the mouse model may provide useful information. For example, it may tell us the molecular function of the gene, even if the gene's importance differs between species. But for some diseases, such as neurological diseases related to vacuole proteins, the phenotype is so different that it may be necessary to establish a primate model."

Source: University of Michigan