Researchers use Ranger supercomputer to identify genetic differences related to social lives of mammals

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The California mouse (*Peromyscus californicus*) is a species of rodent in the family Cricetidae found in northwestern Mexico and central to southern California. Most rodents are polygamous, but the California mouse pair bonds, making it a model organism for researchers studying the genetics and implications of partner fidelity. Credit: The University of California, Berkeley

In the foothills of the Santa Cruz Mountains two closely related species of mice share a habitat and a genetic lineage, but have very different social lives. The California mouse (*Peromyscus californicus*) is characterized by a lifetime of monogamy; the deer mouse (*Peromyscus maniculatus*) is sexually promiscuous.

Researchers at the University of California Berkeley recently showed

how these differences in sexual behavior impact the bacteria hosted by each species as well as the diversity of the genes that control immunity. The results were published in the May 2012 edition of [PLoS One](#).

Monogamy is a fairly rare trait in mammals, possessed by only five percent of species. Rarely do two related, but socially distinguishable, species live side-by-side. This makes these two species of mice interesting subjects for Matthew MacManes, a National Institutes of Health-sponsored post-doctoral fellow at UC Berkeley.

Through a series of analyses, MacManes and researchers from the Lacey Lab examined the differences between these two species on the microscopic and molecular levels. They discovered that the lifestyles of the two mice had a direct impact on the [bacterial communities](#) that reside within the [female reproductive tract](#). Furthermore, these differences correlate with enhanced diversifying selection on genes related to immunity against [bacterial diseases](#).

Bacteria live on every part of our bodies and have distinctive ecologies. The first step of MacManes project involved testing the bacterial communities that resided in the vaginas of both species of mice—the most relevant area for a study about monogamous and promiscuous mating systems.

Next, MacManes performed a genetic analysis on the variety of DNA present, revealing hundreds of different types of bacteria present in each species. He found that the promiscuous [deer mouse](#) had twice the [bacterial diversity](#) as the monogamous California mouse. Since many bacteria cause sexually transmitted infections (like chlamydia or gonorrhea), he used the diversity of bacteria as a proxy for risk of disease. Results of the study were published in *Naturwissenschaften* in October 2011.

But this wasn't the end of the exploration.

"The obvious next question was, does the bacterial diversity in the promiscuous mice translate into something about the immune system, or how the immune system functions?" MacManes asked.

MacManes hypothesized that selective pressures caused by generation after generation of bacterial warfare had fortified the genomes of the promiscuous deer mouse against the array of bacteria it hosts.

To find out, he sequenced genes related to immune function of the two mice species and compared each species' versions of one important immunity gene, MHC-DQa. Some forms of genes (alleles) are better at recognizing different pathogens than others. If an individual has only a single common allele, it may only recognize a limited set of bacterial pathogens. In contrast, if an individual has two different alleles it may recognize a more diverse set of bacterial pathogens, and thus be more protected against infection.

Peromyscus maniculatus is a rodent native to North America. It is most commonly called the Deer mouse. Like other *Peromyscus* species, it is a vector and carrier of emerging infectious diseases such as hantaviruses and Lyme disease. Credit: The University of California, Berkeley

Based on a comparison of the two species' genotypes he confirmed that the promiscuous mice had much more diversity in the genes related to their immune system.

"The promiscuous mice, by virtue of their sexual system, are in contact with more individuals and are exposed to a lot more bacteria," MacManes said. "They need a more robust immune system to fend off all of the bugs that they're exposed to."

The results, published in *PLoS One*, match findings in humans and other species with differential mating habits. They show that differences in social behavior can lead to changes in the selection pressures and gene-level evolutionary changes in a species.

Motivated by this result, MacManes began work on a project that looked to understand the genetics of a far more complex behavior—whether to stay at home with relatives, or to disperse to a new burrow.

Scientists have been sequencing and exploring the genome for more than a decade. For much of this time, studies have been limited to the most common and well-known species: humans, lab-mice, and fruit flies. But in recent years, as the cost of sequencing has dropped and the methods of exploring genomic information have improved, researchers have begun to analyze other less traditional organisms.

MacManes project was one of the first studies to use next-generation gene sequencing and high performance computers to assess the influence of behavior on genes in a non-model species.

"This is a field that people have always been interested in, but the tools hadn't existed yet for people to really understand how complex the

mechanisms were," MacManes said.

Next-generation sequencing determines the order of the nucleotide bases in a molecule of DNA by breaking the double helix into short fragments and rapidly analyzing thousands of chunks at a time. Once hundreds of millions of genetic snippets have been read out by a DNA sequencer, they must be assembled into a single genome, or mapped to a reference genome, and compared to other genetic sequences to be useful.

"The sequencing is something that you can do in any molecular biology lab—that's easy," MacManes said. "But when you try to do an analysis of the data, you get back something like several billion base pairs of data. How to actually analyze the data is the real issue."

As a National Science Foundation (NSF) graduate research fellow, MacManes learned that researchers could access NSF supercomputers through the Extreme Science and Engineering Discovery Environment (XSEDE) to analyze datasets too big for their university laboratory clusters. Once he had his sequences, MacManes turned to the Texas Advanced Computing Center (TACC) at The University of Texas at Austin, a lead partner in XSEDE and home to the Ranger supercomputer.

"When we first started using Ranger, it was a breakthrough moment for us," he said. "We had the data set, but we didn't have any way to do anything with it. Ranger was really our first real chance at analyzing this data. "

The alignment and analysis that MacManes accomplished on Ranger in a few weeks would have taken years with his local resources. It organized the data so MacManes could find insights about the relationship between genes and behavior.

"The ability to isolate and compare genetic differences related to social behavior using advanced computing is a fascinating application of emerging technologies," said Jennifer Verodolin, a researcher specializing in social rodents at the National Evolutionary Synthesis Center in Durham, North Carolina. "We often see individual and population-level social and mating differences within the same species. While ecological factors are linked to this variation, these sophisticated new tools will now allow us to see the genetic signature of how natural selection has shaped behavior."

Mating systems, and social systems more broadly, are important to basic evolutionary biology, MacManes asserted. "The things an animal does, the way it behaves, and who it interacts with, are important to natural selection. These factors can cause immunogenes to evolve at a much faster rate, or slower in the case of monogamous mice. That connection is important and probably under-recognized."

[Monogamy] and promiscuity are only one of a variety of social behaviors that are thought to influence gene expression. MacManes' current research involves analyzing gene expression in the hippocampus brain region of tuco tucos (a sort of South American gopher) who live together in social groups and others who live independently. He is hoping to find what differentiates the social animals from the loners and what impact this change in their behavior has on their genetic profile.

"Now that we have these new sequencing technologies, people are going to be really interested in looking at the mechanisms that underlie these behaviors," MacManes said. "How might genes control what we do, and how we behave? We're going to see an explosion in these studies where people start to understand the very basic genetic mechanism for all sorts of behaviors that we know are out there."

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