New technique helps link complex mouse behaviors to the genes that influence them

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Mice are one of the most commonly used laboratory organisms, widely used to study everything from autism to infectious diseases. Yet genomic studies in mice have lagged behind those in humans.

"Genome-wide association studies—matching genes to diseases and other traits—have been a big deal in human genetics for the past

decade," said Abraham Palmer, PhD, professor of psychiatry at University of California San Diego School of Medicine. "But progress hasn't been so great in animal genetics. That's because researchers have mostly been using crosses between inbred strains, making it impossible to pinpoint specific genomic regions or individual genes associated with a trait. In addition, we didn't previously have good ways of genotyping animals in a cost-efficient way."

Now, in a study published July 4, 2016 in *Nature Genetics*, Palmer's team used 1,200 outbred mice, which are more similar to a natural population, to test a new cost-effective technique to search for specific genes linked with 66 different physical and behavioral traits.

"This is a system that could be used to discover genes associated with any complex trait a researcher is interested in, in any animal model," Palmer said. "We can look at any trait and rapidly develop hypotheses about specific genes. It's like genome-wide association studies in humans, but less expensive. And we can look at certain traits that we can't in humans."

Previously, only large regions of a chromosome could be associated with a particular mouse trait or behavior. Palmer's method takes advantage of the superior mixing that is present in an outbred population to help drill down to specific genes using two steps: genotype-by-sequencing, which sequences about one percent of the mouse genome; and RNA sequencing, which identifies only genes turned "on" in a particular tissue, such as the brain.

With this approach, the researchers found numerous associations between genes and the traits they are associated with. For example, they report that the mouse gene *Azi2* is associated with the effects methamphetamines have on body movements, and that mouse gene *Zmynd11* is associated with anxiety-like behavior. The findings may be

clinically relevant, as humans have analogous genes, Palmer said.

Next, the team will engineer mice that specifically lack these genes to determine if the associations are truly causal and to better understand the underlying mechanisms.

"This study has been extremely gratifying since this is the first time these two genes have been identified as playing roles in psychological conditions," Palmer said. "And now we can think about targeting these genes or the proteins they encode with novel therapeutics."

More information: Genome-wide association study of behavioral, physiological and gene expression traits in commercially available outbred CFW mice, *Nature Genetics*, DOI: 10.1038/ng.3609

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