Cocaine, meth response differ between two substrains of 'Black 6' laboratory mouse

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Separated by more than six decades, the C57BL/6N substrain (left) of laboratory mouse has undergone multiple genetic changes due to spontaneous mutations and is now visibly different from the founder strain, the C57BL/6J of The Jackson Laboratory. Credit: The Jackson Laboratory

Researchers including Jackson Laboratory Professor Gary Churchill, Ph.D., have found a single nucleotide polymorphism (SNP) difference in cocaine and methamphetamine response between two substrains of the C57BL/6 or "Black 6" inbred laboratory mouse, pointing to Cyfip2 as a regulator of cocaine response with a possible role in addiction.

The research team, led by Joseph Takahashi, Ph.D., of University of Texas Southwestern Medical Center and the Howard Hughes Medical Institute, compared the sensitivities to cocaine and methamphetamine in C57BL/6J mice from The Jackson Laboratory and C57BL/6N mice from colonies raised at the National Institutes of Health, finding that 6N mice have lower response than the 6J ones.

Mapping the difference to a single quantitative trail locus (QTL) on chromosome 11, followed by whole-genome sequencing, led to the researchers' identification of a SNP in a gene known as Cyfip2, a highly conserved protein associated with fragile X-mental retardation protein (FMRP), part of a complex that is the most common cause of mental retardation in humans.

The researchers' methods demonstrate that the variations among some 20 C57BL/6 substrains can be used as a rich gene-finding resource. But these variations also highlight the issue of genetic quality control in mouse populations.

Jackson Laboratory founder Clarence Cook Little first developed the C57BL/6 mouse in 1921, and it is now the world's most widely used laboratory mouse strain. In 2002 an international consortium published the first genome of a laboratory mouse: that of a 6J mouse from The Jackson Laboratory.

Because of genetic drift over nearly a century, populations of 6J mice originally obtained from The Jackson Laboratory have developed into at least 20 substrains. Notable among them is the C57BL/6N substrain based on 6J mice that the National Institutes of Health first obtained in 1951. In the intervening decades, the genomes of the substrains have diverged.

"This means that researchers should be very cautious when comparing behavioral data from studies using 6J and 6N strains," Churchill says. "They are clearly not interchangeable."

To address the issue of genetic drift, The Jackson Laboratory uses a genetic quality control program for its most widely used inbred strains, including C57BL/6J. Every five generations, the Laboratory "refreshes" its production colonies by raising mice from cryopreserved 6J embryos,

preventing spontaneous mutations from altering the 6J line.

More information: Kumar et al.: C57BL/6N Mutation in Cytoplasmic FMR interacting protein 2 Regulates Cocaine Response. *Science*, Dec. 20, 2013.

Provided by Jackson Laboratory