Drink-seeking rats provide sobering look into genetics of alcoholism

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A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Alcohol-craving rats have provided researchers with a detailed look into the complicated genetic underpinnings of alcoholism.

By comparing the genomes of rats that drank compulsively with those that abstained, Purdue and Indiana University researchers identified 930 genes associated with alcoholism, indicating that it is a highly complex trait - on par with human height - influenced by many genes and the environment.

The study confirmed genes previously identified as being linked to alcoholism and uncovered new genes and neurological pathways, some of which could be promising targets for treatment. But the sheer number of genes that contribute to the trait suggests pharmaceutical treatments for alcoholism could be difficult to develop, said William Muir, professor of genetics.

"It's not one gene, one problem," he said. "This trait is controlled by vast numbers of genes and networks. This probably dashes water on the idea of treating alcoholism with a single pill."

One of the best predictors of alcoholism in humans is the drinking behavior of their families. But to what extent this link can be chalked up to inherited genetics - versus a shared environment - has been poorly understood and a challenge to study: Parsing out the influence of genetics on drinking habits from other factors such as stress, boredom or peers who drink is not possible in humans.

"It's very difficult to tease out the difference between what your genes are telling you to do and what you choose to do," Muir said.

To gain insights into genes that contribute to alcoholism, Muir and Feng Zhou, a professor of neuroscience at Indiana University School of Medicine, used a model based on rats, mammals with which we share a

majority of genes. Beginning with a population of genetically diverse rats, researchers at the Indiana Alcohol Research Center bred two lines: one group that displayed classic clinical signs of alcoholism and another that completely abstained from alcohol.

Breeding rats to drink was no small challenge and required several decades, Muir said. Like most animals, rats tend to have a natural aversion to drinking a high concentration of alcohol.

"But typical of any genetic study, there's always an outlier - in this case, a rat that will drink large amounts," he said.

Choosing and breeding the rare rats that would take a tipple of pure grain alcohol eventually yielded a line of rats that compulsively drank to excess, preferred alcohol to water, drank to maintain intoxication, performed tasks to receive alcohol and showed signs of withdrawal if alcohol was absent.

Still, rats responded to intoxication in individualized ways, Zhou said.

"Under the influence of alcohol, some rats became docile and fell asleep in a corner while others became aggressive," he said.

The researchers sequenced and compared entire genomes from 10 rats in each line to determine genetic characteristics of drinking and abstaining. They also repeated the experiment with two additional lines of alcohol-seeking and teetotaler rats to discern which gene alterations were the result of natural selection and which were random genetic crosses.

The results highlighted 930 genes associated with excessive drinking behavior, the vast majority of which are in genetic regulatory regions, not coding regions, as many researchers previously expected. Muir compared coding regions to a car and regulatory regions to the gas and

brake pedals that determine the car's speed.

"We all have the genes for alcoholism, but our genetic abilities to control it differ," he said.

While the researchers stressed that the genetic complexity of alcoholism complicates potential treatments, they pinpointed the glutamate receptor signaling pathway - which can control a sense of reward in the brain - might be a possible target for treatments due to the number of alcoholism-associated genes it contains.

One of the next steps in the research is to verify that the genes identified in alcoholic rats are relevant to human alcoholism.

Though the study shows there is a large genetic component to alcoholism, environment still plays a crucial role in shaping people's drinking habits, the researchers said.

"Even with the same genetics, one person might be prone to getting drunk while another doesn't drink at all," Zhou said. "Your environment can trigger the expression of genetic tendencies toward alcoholism."

Or, as Muir put it, "You can't just blame your drinking on your parents."

More information: High Resolution Genomic Scans Reveal Genetic Architecture Controlling Alcohol Preference in Bidirectionally Selected Rat Model, *PLOS Genetics*, DOI: 10.1371/journal.pgen.1006178

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