Genetic predisposition to liking amphetamine reduces risk of schizophrenia and ADHD

April 7 2014

Children with ADHD find it more difficult to focus and to complete their schoolwork. Credit: public domain image

Genetic variants associated with enjoying the effects of d-amphetamine—the active ingredient in Adderall—are also associated with a reduced risk for developing schizophrenia and attention deficit hyperactivity disorder (ADHD), report scientists from the University of

Chicago in the *Proceedings of the National Academy of Sciences* on April 7. The results support a long-standing hypothesis that dopamine, the neurotransmitter connected with the euphoric effects of amphetamine, is related to schizophrenia and ADHD.

"Some of the variants that make you like amphetamine also appear to make you less likely to develop schizophrenia and ADHD," said study leader Abraham Palmer, PhD, associate professor of human genetics at the University of Chicago. "Our study provides new insights into the biology of amphetamine and how it relates to the biology of risk for these psychiatric diseases."

Palmer and his team previously conducted a genome-wide association study (GWAS) to identify genetic variants associated with experiencing the euphoric effects of amphetamine, which is thought to affect risk for drug abuse. Almost 400 volunteers were given d-amphetamine in a double-blind, placebo-controlled experiment. They were then asked to report how the drug made them feel using carefully designed questionnaires. The researchers measured genetic differences between these subjects at approximately a million sites throughout the genome to identify variations in the DNA code known as single nucleotide polymorphisms, or SNPs. They assessed the relationships between each of these SNPs and sensitivity to amphetamine.

Using data from other large-scale GWAS studies, the team examined these same SNPs for possible overlapping associations with psychiatric disorders. Through rigorous statistical testing they found that an unexpectedly large number of SNPs were associated with both sensitivity to amphetamine and risk of developing schizophrenia or ADHD. This suggested that these traits are influenced by a common set of genetic variants.

Moreover, a significant proportion of this observed overlap appeared to

be caused by variants that increased enjoyment of the effects of amphetamine but decreased the risk for both psychiatric diseases.

The researchers performed similar analyses for traits that were not expected to be related to amphetamine sensitivity, such as height, irritable bowel disease and Parkinson's disease. In all of these cases they observed no more overlapping SNPs than would have been expected by chance alone.

"While this approach would not be a useful diagnostic test, we expect that people who like the effects of amphetamine would be slightly less likely to develop schizophrenia and ADHD," Palmer said. "And people who did not like amphetamine, we would predict, are slightly more likely to develop these diseases."

"What is particularly striking is that by examining people's responses for just a few hours after taking a drug, we can identify an underlying genetic propensity that can manifest as a psychiatric disease over the course of a lifetime," he adds.

These results provide unique genetic evidence for the role of dopamine in schizophrenia and ADHD. Schizophrenia is commonly treated using drugs that block dopamine signaling, while ADHD is treated using drugs, including d-amphetamine itself, that enhance dopamine signaling. Despite opposite treatments, amphetamine-liking SNPs reduced the risk for developing both diseases, suggesting that dopamine's role is more complex than hypothesized.

The study also offers a new direction for the analysis of a wide range of similar genetic studies, particularly ones with smaller sample sizes. By analyzing the results of those studies for overlap with data from much larger genetic studies, promising genetic variants that would otherwise never stand out among the noise of hundreds of thousands of other

random variants can be identified.

"Our approach offers a promising new direction for studying complex psychiatric behaviors using the whole-genome approach," said co-author Harriet de Wit, PhD, professor of psychiatry and behavioral neuroscience at the University of Chicago.

The team plans to further study the SNPs identified in this study for their functional roles in amphetamine liking, schizophrenia and ADHD. In addition, Palmer hopes to explore genetic predispositions toward liking or disliking other therapeutic drugs and whether sensitivity to those drugs might also overlap with the diseases for which these drugs are used.

"When we use a drug treatment, we know exactly what systems have been perturbed," Palmer said. "So when we see overlap for alleles that affect how you respond to drugs and a disease, we can hone in on what those alleles are doing biologically. This is instrumental for translating those results into new treatments and cures, which is the ultimate reason for performing genetic studies of disease."

More information: Genetic variation associated with euphorigenic effects of d-amphetamine is associated with diminished risk for schizophrenia and attention deficit hyperactivity disorder, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1318810111

Provided by University of Chicago Medical Center