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# Researchers discover gene variant associated with cocaine dependence, cocaine induced paranoia

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Researchers from Boston University School of Medicine (BUSM) and Yale University School of Medicine and the University of Connecticut School of Medicine, have discovered that variants in the α-endomannosidase (MANEA) gene are associated with cocaine addiction and cocaine-induced paranoia in European American and African American populations. These findings appear in the March issue of the *Archives of General Psychiatry*.

Cocaine is widely abused in the United States. The 2002 National Survey on Drug Use and Health revealed that nearly six million Americans age 12 or older used the drug during the preceding year. Compulsive use of cocaine is also common with more than one million individuals considered dependent on the drug. Several studies have suggested a substantial genetic contribution to cocaine dependence and related behaviors.

The researchers took a total of 3,992 individuals from two family-based samples (European American and African American) and two case-control samples (European American and African American) enrolled in studies of drug addiction and classified them as either cocaine dependent, suffering from cocaine-induced paranoia or controls. They were then genotyped for 11 markers spanning the MANEA gene. MANEA encodes an enzyme (a-endomannosidase) that metabolizes complex carbohydrates. MANEA was chosen for further study based on

evidence from a low-resolution scan of the entire genome the researchers performed previously to search for genes associated with substance dependence.

The researchers found cocaine induced paranoia was associated with six of the 11 markers in the European American family sample. They also found these six markers and three other markers were significant in the African American sample. The strongest evidence for association in either population and in the total sample was observed for marker rs9387522, which is located in the 3' untranslated region of the gene. The A allele for this marker was associated with increased risk of cocaine induced paranoia in all four data sets.

"Our findings suggest that cocaine dependence and associated behaviors may involve biological pathways not typically thought to be associated with brain metabolism and now opens a new pathway to understanding these highly prevalent disorders and their psychopathological manifestations," said lead author Lindsay A. Farrer, PhD, chief of the Genetics Program and professor of medicine, neurology, genetics & genomics epidemiology and biostatistics at BUSM.

According to the researchers, given MANEA's role in carbohydrate metabolism and relatively minor expression in brain, it would not appear initially to be a good biological candidate to modulate susceptibility to cocaine dependence or its associated psychotic complications. "However, insight into the relationship between MANEA, paranoia, and cocaine dependence can be gleaned from studies of mannosidase and other glycoproteins," notes Farrer.

MANEA is one of several glycosidic enzymes that remove oligosaccharide chains of dopamine β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. Low levels of DBH in plasma or cerebrospinal fluid and genetic variants in DBH have been associated

with greater vulnerability to psychotic symptoms in several psychiatric disorders including cocaine dependence, schizophrenia, and major depression. MANEA may also influence susceptibility to cocaine dependence by modifying the function of liver carboxylesterase, a glycoprotein of the high mannose type, two forms of which hydrolyze cocaine and other drugs.

"This finding suggests that drug dependence and associated behaviors may involve biological pathways not typically associated with brain metabolism, and opens a new pathway to understanding these highly prevalent disorders and their psychopathological manifestations," added Farrer.

Source: Boston University

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