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Specific DNA variations of the serotonin transporter gene can influence drinking intensity

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The brain's serotonergic system plays an important role in alcohol preference and consumption. The serotonin transporter gene (SLC6A4), in particular, may regulate a person's propensity for severe drinking. A study of six different single nucleotide polymorphisms – DNA sequence variations – of SLC6A4 has found that they influence drinking intensity among alcohol-dependent (AD) individuals in treatment.

Results will be published in the February 2009 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Serotonin is a neurochemical that carries information between nerve cells in the brain, mediating the rewarding effects of alcohol," explained Ming D. Li, Jean and Ronald Butcher Professor at the University of Virginia and corresponding author for the study. "Acute drinking increases serotonin release and signaling in brain regions involved in controlling consumption of alcohol, while chronic drinking reduces serotonergic function, leading to a serotonin-deficient state. One hypothesis is that alcoholics drink to alleviate this serotonin-deficient state."

Given that the serotonin transporter is a well-known pharmacological target, added Robert A. Philibert, professor of psychiatry and director of the Laboratory of Psychiatric Genetics at the University of Iowa,

researchers are using relatively larger study samples and more in-depth measurements and analyses to try to develop more personalized approaches to alcohol treatment.

"An implicit assumption of the Human Genome Project was that deciphering of the human genome would lead to better treatment," said Philibert. "By and large, that promise has not yet been realized,-particularly for those with psychiatric illnesses."

Li agreed. "Alcoholics are a heterogeneous group in terms of their drinking patterns, etiology of the disorder, and social background," he said. "All these factors may affect treatment outcomes, as well as the development of other general medical complications because of heavy drinking. One of the main goals of treatment is to reduce the intensity of drinking. Therefore, finding a functional genetic marker could be used for sub-typing alcoholics and better determining which treatment methods can target specific underlying molecular mechanisms."

Li and his colleagues analyzed associations between drinking intensity among 275 (216 males, 59 females) AD individuals seeking treatment and six SLC6A4 polymorphisms. Of the six polymorphisms examined, rs1042173 in the 3' untranslated region of SLC6A4 showed a significant association with drinking intensity. The G allele carriers for rs1042173 were associated with significantly lower drinking intensity compared to T allele homozygotes.

"In other words," said Li, "we detected a genetic variant caused by a single-nucleotide difference in the DNA sequence of serotonin transporter gene that could predict drinking intensity in alcoholics. In this population of heavy drinking adult alcoholics of European descent, those who carried two alleles of T drank more intensely than those who carried one or two alleles of G."

The researchers also investigated the possible mechanisms by which these two alleles contributed to the change in drinking behavior.

"Given the location of the genetic variation within the gene, we hypothesized that T and G alleles may have differences in serotonin transporter expression levels affecting the function of serotonergic system," said Li. "We transfected cells with plasmid carrying either T or G alleles of the gene, and measured the levels of serotonin transporter mRNA and proteins in these transfected cells. We found that cells carrying T allele, the variant associated with more intense drinking, had lower serotonin transporter expression levels than cells carrying G allele."

All in all, said Philibert, this paper establishes linkages between a genetic marker and quantitative clinical measures. "It further connects the laboratory benchtop with the patient," he said.

"Some individuals may possess inherent risk factors for more intense drinking than others," said Li, "making them more vulnerable to complications arising from heavy drinking. In future studies, we hope to investigate whether this genetic variant can be used as a marker to predict treatment outcomes of different serotonergic agents."

Source: Alcoholism: Clinical & Experimental Research