Examining alcohol use disorders through gene networks instead of individual genes

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Alcohol use disorders (AUDs) are influenced by multiple genetic, environmental and behavioral factors, which makes it difficult to find individual genetic markers to help identify those at risk of developing AUDs. This study examined how a person's level of response (LR) to alcohol, which is closely linked to the development of AUDs, is related to "gene sets" rather than individual genes. Findings show that glutamate receptor signaling genes that enable brain cells to respond to chemicals, and then to communicate that response, are involved in a person's LR.

Results will be published in the May 2010 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Alcohol dependence (AD) is a very complex disorder," said Geoff Joslyn, senior scientist at the Ernest Gallo Clinic and Research Center and corresponding author for the study. "We know that inherited genes account for about half of a person's risk of becoming AD but this genetic risk is spread across many genes. To simplify the genetic risk, we took advantage of clinical and epidemiological studies that have shown that a person's innate response to alcohol is related to their risk of becoming AD. Individuals that have a low response to alcohol, that is people who must drink more than the average person to become drunk, are at a greater risk of becoming AD. We studied this alcohol response because we think it is a sub-component of AD and is much less genetically complex."

"With complex diseases such as alcoholism, diabetes or cancer, which

are caused by many genes working together, there has been a great deal of difficulty identifying "a gene" that represents a good target for developing new medical therapies," said Michael F. Miles, a professor in the departments of pharmacology/toxicology and neurology at Virginia Commonwealth University. "The approach described in this manuscript sidesteps the entire issue of the "gene" and focuses on the functional unit of genes, or biological pathways. So, to paraphrase a mantra from another field, "it's the network, stupid." By focusing on networks rather than single genes, genetic studies such as genome-wide association studies can have increased power for detecting biological factors affecting complex diseases."

Miles added that, while gene networks have been widely used to analyze data related to different diseases, this study combined several different approaches to improve the yield of significant gene networks associated with AD.

Joslyn and his colleagues analyzed data on subjects selected from a larger, long-term study called the San Diego Sibling Pair investigation: 367 (233 females, 134 males) Caucasian participants 18-25 years old with a positive family history of AD, from 186 independent families. All subjects were tested for their LR to alcohol, and Gene Set Enrichment Analysis (GSEA) was performed to determine if a gene set - genes that participate in a common biological function - demonstrate a greater genetic association than would be randomly found.

"We characterized 367 people whose LR to alcohol had been measured in the laboratory," said Joslyn. "We were looking for variation in genes that correlated with variation in alcohol response. No single gene was correlated well enough with alcohol response to be confident that the observation was not just due to statistical fluctuation. The results suggest that variation in sets of genes that encode the components that enable neuronal communication contribute to individual differences in alcohol

LR. The neuronal signaling pathways identified were the same pathways that had been implicated in alcohol response in experimental animal and tissue culture models. Glutamate neurotransmitter signaling systems were most strongly implicated."

"Identifying neuronal signaling genes, including glutamate receptor signaling, in a genetic study of human variation in responses to alcohol is hugely important because it reinforces the years of work that has pointed to single genes in such systems," said Miles. "However, the GSEA largely focuses on previously defined ontology gene sets or known biological pathways. Alternative approaches, such as using novel gene-gene correlation structures derived from protein-protein interaction or microarray expression correlation datasets, might illuminate results from the genome-wide association studies analysis that fall far away from "under the streetlight." Despite this, the recapitulation of glutamate signaling … will more than likely further encourage the search for pharmacological agents targeting glutamate signaling as therapies in alcoholism or alcohol toxicity."

"The results of this study do not suggest any new mechanisms," noted Joslyn, "but rather add corroborative evidence to established ideas. The study does suggest that natural, inherited variability in glutamate signaling may contribute to variability in alcohol response. We thus hypothesize that it is possible to alter alcohol response through therapies that target altering glutamate signaling. It will take many years of further study to determine the validity of the hypothesis and if such therapies can be useful in treating AD."

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