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Childhood adversity hinders genetic protection against problem drinking in white men

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While the influence of heritable factors on the development of alcohol use disorders (AUDs) has been documented in family pedigree and twin studies for decades, identification of specific genetic variants that influence AUDs continues to be challenging. The ADH1B gene has consistently been implicated in problem drinking, but rarely incorporated into gene/environment investigations of alcohol phenotypes. A study examining the joint effects of variation in ADH1B and childhood adversity on heaviness of alcohol consumption and AUD symptoms has found that, under conditions of childhood adversity, the genetic variant on the ADH1B allele that typically protects against problem drinking does not exert its protective effects in European-American men.

Results will be published in the December 2014 online-only issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"We have only scratched the surface in terms of identifying gene variants that influence the development of AUDs," said Carolyn E. Sartor, assistant professor in the department of psychiatry at Yale University School of Medicine as well as corresponding author for the study. "In view of the complex nature of the disorder and the likelihood that there are dozens of risk variants, we have a long way to go to account for substantial variance in risk for AUD. However, there are

numerous variants that have substantial support at this point, implicating several systems, most notably, alcohol metabolism."

"While we still don't understand everything, we have come far over the past 20 years in our understanding of the genetic vulnerability of alcoholism." added Victor Hesselbrock, professor of psychiatry at the University of Connecticut School of Medicine. "Rather than hypothesizing about 'genetic susceptibility,' we now have identified over 30 different genes that are associated with alcohol dependence and its clinical features. Some of the findings were expected and relate to ethanol metabolism or central nervous system functioning. Other findings were less expected and relate to other biological systems such as the perception of taste. Many of these findings have contributed to our better understanding of the etiology and the sequela of chronic heavy drinking, including AUDs."

Sartor and her colleagues analyzed data drawn from a multi-site study of the genetics of alcohol, cocaine, and opioid dependence. The sample for this study comprised 2,617 African-American (AA) and 1,436 European-American (EA) participants. In both AA and EA subsamples, women accounted for just less than half of the subjects, the average age was about 40, and approximately one-third of subjects had completed fewer than 12 years of education. The authors tested the most significant ADH1B single nucleotide polymorphisms (SNPs or DNA sequence variations) for alcohol dependence pulled from a larger genome-wide association study with this sample, ADH1B-rs1229984 (Arg48His) in the EA subsample and ADH1B-rs2066702 (Arg369Cys) in the AA subsample.

"AA women, AA men, and EA women who reported experiencing adverse events in childhood were at elevated risk for heavy and problem drinking, regardless of which genetic variant they carried," said Sartor. "In EA men, an interaction between ADH1B and childhood adversity

was observed. EA men carrying the protective His allele at ADHD1B-rs1229984 who had no history of childhood adversity showed significantly fewer AUD symptoms than Arg-allele carriers, however, this protective effect was not evident in His-allele carriers who reported experiencing adverse events in childhood. In fact, His-allele carriers with a history of childhood adversity reported nearly the same number of symptoms as Arg-allele carriers."

"These findings highlight the importance of considering the possible effects of both gender and ethnicity," said Hesselbrock. "As is likely the case with other identified vulnerability genes, certain environmental factors, in this case adverse childhood experiences, affect the vulnerability conferred by the risk allele. It is also important to note that a 'protective' allele can also be overwhelmed by adverse environmental factors, emphasizing the importance of gene/environment studies."

Neither Sartor nor Hesselbrock were surprised by the effects of childhood adversity on alcohol outcomes, even in those persons with the 'protective' allele.

"A number of studies over the past 40-50 years have demonstrated the role of stress as a vulnerability factor for many psychiatric illness, including addictions," said Hesselbrock. "In the 1970s, epidemiological studies showed that early parental loss was associated with poor adult outcomes and more recently several studies have associated childhood adversity, variously defined, with alcohol problems, depression and other psychiatric outcomes in adolescence and adulthood. We often forget that the susceptibility to developing an addiction problem, as well as many other medical and psychiatric problems, is a combination of both genetic and environmental factors. Sometimes a strong deleterious genetic component can overcome a positive environment, and an extremely poor environment can sometimes overcome protective effects offered by genes."

"Our findings highlight the breadth of the effects of adverse childhood experiences on the biological processes involved in alcohol use and misuse, including alcohol metabolism," added Sartor. "More generally, they underscore the importance of considering environmental risk and protective factors in genetically informed alcohol studies."

"While we know that alcoholism runs in families and is highly heritable, we sometimes forget that 'heritability' contains genetic as well as environmental components," observed Hesselbrock. "This interplay between genes and environment is not well understood and will be a primary area of research for both basic scientists and for clinical researchers. Such studies will have important implications for both prevention and for treatment once 'environments' are better characterized and the function of the associated genes are better understood."

"We hope the results of our study further increase clinicians' awareness of the importance of assessing for adverse events in childhood, both with respect to prevention for children and adolescents, and treatment recommendations for individuals who have already developed AUDs," said Sartor. "The specificity of the gene/environment effects to EA men should not be interpreted as a lack of need to ask about childhood adversity when working with other populations. Rather, our findings should be a reminder that men are no more resilient - and in some cases, more vulnerable - than women to the effects of childhood adversity on problem drinking, even in the absence of an AUD family history."

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