

Genome-wide study of alcohol dependence points to chromosome 11

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Alcohol dependence (AD) is a complex disease for which both genetic and environmental factors affect susceptibility. Previous research had identified several genes associated with AD through linkage analysis or candidate-gene approaches. Findings from a genome-wide association study (GWAS) support an association between AD and a cluster of genes on chromosome 11.

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

"Previous studies have looked at one or a few genes at a time, choosing the genes based upon hypotheses about possible mechanisms underlying differences in risk for alcoholism," explained Howard J. Edenberg, Distinguished Professor at the Indiana University School of Medicine and corresponding author for the study. "We chose to examine the entire genome, all the genes at once, as an unbiased approach that has the potential of uncovering previously unsuspected genes."

"Geneticists use many strategies to find gene locations, and genes," said David Goldman, section chief of Human Neurogenetics at the National Institute on [Alcohol](#) Abuse and Alcoholism. "Here, approximately one million genetic polymorphisms or variants were analyzed in a population framework of approximately 1400 unrelated individuals. Then the most significant variants were followed up in several ways: 'Were they also associated in families?' 'Were they expressed in brain?' 'Were their patterns of expression altered by alcohol?' Several were. [These results]

illustrate the power of new genetic technology to perform a genome-wide sieving, something that was impossible only a few years ago."

Researchers used data drawn from the ongoing, seven-center Collaborative Study on the Genetics of Alcoholism (COGA). The primary analyses were in 1399 unrelated European Americans (847 cases, 552 controls); a smaller group of African Americans was also studied (345 cases, 140 controls). Researchers then genotyped most of the top 199 single nucleotide polymorphisms (SNPs) - DNA sequence variations that occur when a single nucleotide in the genome sequence is altered - and examined whether the genes harboring these SNPs were expressed in human brain or were differentially expressed in the presence of alcohol in lymphoblastoid cells.

"Although we did not find definitive evidence for the role of any one gene, we found suggestive evidence that a gene or genes in one region of [chromosome 11](#) might be involved," said Edenberg. "We also provided support for several genes that had been found by others. Identifying additional genes that might be related to the risk for alcoholism is an important starting point. Future studies will need to confirm their importance in other populations, to determine which aspect of the disease process they might impact, and to examine the mechanisms through which they work."

Goldman agreed. "The alcoholism risk [genes](#) that have been identified so far are not strong in their effects and, as the authors explain, the new gene locations found here did not meet the required criterion for 'genome-wide significance,'" he said. "Has the result been a complete understanding of the genetic basis of those disorders? No, and generally GWA has failed to explain more than 10 percent of the genetic vulnerability. However, as difficult as the progress sometimes seems, each piece of the genetic puzzle that can be identified is bringing us closer to the goals of understanding why some individuals are more

vulnerable, and individualizing their treatment."

"This is one stage in a large ongoing study," said Edenberg. "We will be working with other groups to replicate our findings and test their findings. We will be examining the aspects of alcoholism risk that are related to variations in each gene we identify, and starting functional studies of how the genetic variations affect cells and tissues. We have also embarked on a large prospective study of adolescents and young adults, to examine the effects of genetic variations on the development of alcoholism and related disorders. These studies, funded by NIAAA, are critical to increase our understanding of alcoholism, a widespread and devastating disease."

Provided by Alcoholism: Clinical & Experimental Research

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