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Researchers find a strong association between alcohol dependence and chromosome 5q13.2

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Excessive drinking is not only the third leading cause of preventable death in the United States, there is also a very strong genetic influence on the risk of developing alcohol dependence (AD). Given its serious public-health impact, as well as strong evidence for genetic influence, a new study has examined links between AD and genetic variations called common copy number variations (CNVs), finding a significant association between AD and CNVs on chromosome 5q13.2.

Results will be published in the September 2012 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Twin and adoption studies have estimated the heritability of AD – the proportion of variability in risk that is due to genetic factors – to be to be about 50 percent," said John P. Rice, a professor of mathematics in psychiatry at Washington University and corresponding author for the study.

Rice explained that CNVs are a form of structural variation in which relatively large regions of the genome have been deleted, meaning fewer than a normal number, or duplicated, meaning more than a normal number. "For two unrelated individuals, they can differ by about .5 percent with respect to copy number," he said. "They can be inherited or be a genetic mutation that neither parent possessed nor transmitted.

CNVs are in contrast to single nucleotide polymorphisms, which differ by one base pair. In addition, CNVs have been reported to influence diseases such as autism and schizophrenia."

"Alcoholism's pervasive impact on public health and its heritability make searches for genes influencing vulnerability a priority," said David Goldman, chief of the lab of neurogenetics at the National Institute on Alcohol Abuse and Alcoholism. "Although only a few genes influencing alcoholism risk have been discovered so far, we can expect this picture to change rapidly as more powerful genomic tools, including genotyping arrays and next-generation sequencing, are applied, and as geneticists become ever more ambitious in the size and phenotypic depth of the populations they study."

As part of the larger Study of Addiction: Genetics and Environment (SAGE), Rice and his colleagues interviewed 3,829 adult participants (1,761 males, 2,068 females) using the Semi-Structured Assessment for the Genetics of Alcoholism; subsequently, 2,610 non-Hispanic, European-American individuals (1,144 males, 1,466 females) were genotyped using the Illumina Human 1M array, and CNV analysis was conducted.

"We found two CNVs – on chromosomes 5q13.2 and 6q14.1 – that were associated with AD," said Rice. "For both CNVs, AD cases tended to have more duplications than controls without AD. These two CNVs are statistically significant but the effect on risk is modest. The region identified on chromosome 5 contains several genes that have been implicated is rare neurological disorders and play a role in the nervous system. It will be a challenge to understand what gene(s) are causing this association and how they work to increase one's risk for AD."

"This is a carefully done study and results are conservatively interpreted," noted Goldman. "The association to the 5q13.2 region is

highly significant statistically, but further it is compelling that the region they have found is one that plays a role in other neurologic disorders. The chromosome 6 findings are statistically more highly significant but more difficult to pursue because the region involved is a gene desert. It will be fascinating to see the outcome of efforts to replicate these findings in other populations and validate through other means, for example, by studies of the individual genes in the regions involved in the CNVs."

Rice agreed. "Our results need to be replicated in independent samples," he said. "If they hold, then researchers who study the basic biology of how changes in the genome lead to increased or decreased risk for illness can add to our understanding. It is important to note that the associations are modest, so these findings cannot be used to predict who will become an alcoholic. The results open up a new line of investigation, but it can take many years before we have a true understanding."

"These findings are indicative of the increasing pace of genetic and genomic research on alcoholism," added Goldman. "However, the findings are at least several years removed from clinical impact, except in the sense of showing that alcoholism is a biomedical disease whose genetic influences are beginning to be understood."

Provided by Alcoholism: Clinical & Experimental Research

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