Genome Scan Reveals Areas Linked to Alcoholism

BY JEFF EVANS
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The most extensive analysis of genetic variations more common in people with alcohol dependence than in healthy controls has identified 51 small chromosomal regions spread across the genome that hold genes with various important functions, reported Catherine Johnson of the National Institute on Drug Abuse and her associates.

"This identification provides the first genome-wide, association-based assessment for genomic loci likely to contain variants that contribute to dependence on alcohol," wrote Ms. Johnson of the intramural research program in the molecular neurobiology branch at the institute in Baltimore, and her associates.

Previous research has shown that a substantial portion of the regions where these genes are located have been associated with alcoholic and other addictive phenotypes, according to Ms. Johnson and her colleagues.

The researchers identified and pooled together samples from 120 unrelated alcohol-dependent individuals and then pooled a separate group of samples from 160 unrelated, unaffected controls who self-reported European American ethnicities. Most of the healthy control participants had married into the pedigrees, which were collected as part of the Collaborative Study on the Genetics of Alcoholism (Am. J. Med. Genet. B Neuropsychiatr. Genet. Epub ahead of print 2006;DOI:10.1002/ajmg.b.30346).

Instead of conducting association and linkage studies with whole family pedigrees, the investigators performed association genome scanning to assess the location and significance of the relationships among many more single nucleotide polymorphisms (SNPs) than would be possible with these other techniques, the investigators said.

Using a new kind of SNP microarray chip, the investigators assessed a set of 104,268 SNPs that were localized to the autosomal chromosomes. In each of the sample pools, alleles with frequencies of 2% or higher could be identified, allowing the study of many more SNP markers for more unrelated individuals than were previously available.

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From these 104,268 SNPs, the investigators narrowed their analysis down to 188 SNPs that lay in 51 clusters in people with alcohol dependency. These clusters had to contain at least 3 SNPs that were close to one another and have an allele frequency that was significantly different from that of the controls.

Of the 26 candidate genes that were identified within these clusters, 10 also had been identified in the results of other association and linkage studies of addictions in European American, African American, and Japanese individuals who were dependent on at least one substance. "This level of replication is especially remarkable, since these convergences were sought for samples from different ethnic backgrounds and different addictions," Ms. Johnson and her associates said.

The candidate genes that were identified in the study involve a potassium channel, intra- and intercell–signaling molecules, enzymes that convert propeptides to biologically active peptides, phospholipid-signaling pathways, regulatory and developmental genes that could alter brain development and/or adult form and function, cell adhesion molecules and their possible ligands, as well as those that encode proteins with unknown function, they noted.

"While these data nominate interesting genes, it is only confirmation in multiple data sets in ongoing and future studies that will link each of them securely to addiction vulnerability," the researchers cautioned.

However, this investigation represents a step forward in the area of identifying genetic pathways to addiction. "As we identify more and more of the allelic variants that contribute to vulnerability to abuse of alcohol and other substances, we will be better able to understand addictions themselves," they said. ■