ALCOHOL ALERT

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The Genetics of Alcoholism

Research has shown conclusively that familial transmission of alcoholism risk is at least in part genetic and not just the result of family environment (1). The task of current science is to identify what a person inherits that increases vulnerability to alcoholism and how inherited factors interact with the environment to cause disease. This information will provide the basis for identifying people at risk and for developing behavioral and pharmacologic approaches to prevent and treat alcohol problems. The advances being made now are built on the discovery 50 years ago of the role in inheritance of DNA, the genetic material in cells that serves as a blueprint for the proteins that direct life processes. Alcoholism research, like other fields, is capitalizing on the scientific spinoffs of this milestone, among them the Human Genome Project and related efforts to sequence the genomes, the complete DNA sequences, of selected animals.

Alcohol Alert, *a publication of the National Institute on Alcohol Abuse and Alcoholism, provides timely information on alcohol research and treatment to health professionals and other interested people. This issue is the sixtieth in the series.*

A Complex Genetic Disease

Studies in recent years have confirmed that identical twins, who share the same genes, are about twice as likely as fraternal twins, who share on average 50 percent of their genes, to resemble each other in terms of the presence of alcoholism. Recent research also reports that 50 to 60 percent of the risk for alcoholism is genetically determined, for both men and women (2–5). Genes alone do not preordain that someone will be alcoholic; features in the environment along with gene-environment interactions account for the remainder of the risk.

Research suggests that many genes play a role in shaping alcoholism risk. Like diabetes and heart disease, alcoholism is considered genetically complex, distinguishing it from genetic diseases, such as cystic fibrosis, that result primarily from the action of one or two copies of a single gene and in which the environment plays a much smaller role, if any. The methods used to search for genes in complex diseases have to account for the fact that the effects of any one gene may be subtle and a different array of genes underlies risk in different people.

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Scientists have bred lines of mice and rats that manifest specific and separate alcohol-related traits or phenotypes, such as sensitivity to alcohol's intoxicating and sedative effects, the development of tolerance, the susceptibility to withdrawal symptoms, and alcohol-related organ damage (6,7). Risk for alcoholism in humans reflects the mix and magnitude of these and other phenotypes, shaped by underlying genes, in interaction with an environment in which alcohol is available. Genetic research on alcoholism seeks to tease apart the genetic underpinnings of these phenotypes and how they contribute to risk.

One well-characterized relationship between genes and alcoholism is the result of variation in the liver enzymes that metabolize (break down) alcohol. By speeding up the metabolism of alcohol to a toxic intermediate, acetaldehyde, or slowing down the conversion of acetaldehyde to acetate, genetic variants in the enzymes alcohol dehydrogenase (ADH) or aldehyde dehydrogenase (ALDH) raise the level of acetaldehyde after drinking, causing symptoms that include flushing, nausea, and rapid heartbeat. The genes for these enzymes and the alleles, or gene variants, that alter alcohol metabolism have been identified. Genes associated with flushing are more common among Asian populations than other ethnic groups, and the rates of drinking and alcoholism are correspondingly lower among Asian populations (8,9).

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Genes, Behavior, and the Brain

Addiction is based in the brain. It involves memory, motivation, and emotional state. The processes involved in these aspects of brain function have thus been logical targets for the search for genes that underlie risk for alcoholism. Much of the information on potential alcohol-related genes has come from research on animals. Research has demonstrated a similarity in the mechanisms of many brain functions across species as well as an overlap between the genomes of animals—even invertebrates—and humans.

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One approach to identifying alcohol-related genes is to start with an aspect of brain chemistry on which alcohol is thought to have an impact, and work forward, identifying and manipulating the underlying genes and ultimately determining whether the presence or absence of different forms, or alleles, of a gene influence alcoholism risk. For example, genetic technology now permits scientists to delete or inactivate specific genes, or alternatively, to increase the expression of specific genes, and watch the effects in living animals. Because genes act in the context of many other genes, interpretation of these studies can be difficult. If one gene is disabled, for example, others may compensate for the loss of function. Alternatively, the loss of a single gene throughout development may be harmful or lethal. Nonetheless, these techniques can provide important clues to function. These approaches have been used to study how altering the expression of genes encoding the receptors (or their subunits) for neurotransmitters and intracellular messenger molecules alters the response to alcohol (10).

Scientists also have an increasing array of methods for locating alcohol-related genes and gene locations and only then determining how the genes function, an approach known as reverse genetics. Quantitative trait loci (QTL) analysis seeks to identify stretches of DNA along chromosomes that influence traits, like alcohol sensitivity, that vary along a spectrum (height is another quantitative trait). QTLs have been identified for alcohol sensitivity, alcohol preference, and withdrawal severity (11). Ultimately, the goal is to identify and determine which candidate genes within the QTLs are responsible for the observed trait. Among the candidate genes already known to lie near alcohol-related QTLs are several that encode neurotransmitter receptors and neurotransmitters themselves. One of these, neuropeptide Y (NPY), lies within a QTL for alcohol preference in rats. NPY is a small protein molecule that is abundant in the brain and has been shown to influence the response to alcohol (12).

Scientists also can scan the genome to identify genes whose activity differs among animals that respond differently to alcohol. The methods used are designed to measure the amount of messenger RNA which, as the first intermediary in the process by which DNA is translated into protein, is a reflection of gene expression. The advantage of this approach is its power to survey the activities of thousands of genes, some of which might not otherwise have been identified as candidates for involvement in alcohol-related behavior. Recent work in rats identified a gene that is differentially expressed in brain regions of alcohol-preferring rats and nonpreferring rats. The gene is within an already identified QTL for alcohol preference and codes for alpha-synuclein, a protein that has been shown to regulate dopamine transmission (13).

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Genetic Studies in Humans

Knowledge gained from animal studies has assisted scientists in identifying the genes underlying brain chemistry in humans. Much research suggests that genes affecting the activity of the neurotransmitters serotonin and GABA (gamma-aminobutyric acid) are likely candidates for involvement in alcoholism risk. A recent preliminary study looked at five genes related to these two neurotransmitters in a group of men who had been followed over a 15-year period (14). The men who had particular variants of genes for a serotonin transporter and for one type of GABA receptor showed lower response to alcohol at age 20 and were more likely to have met the criteria for alcoholism. Another study found that college students with a particular variant of the serotonin transporter gene consumed more alcohol per occasion, more often drank expressly to become inebriated, and engaged more frequently in binge drinking than students with another variant of the gene (15). The relationships between neurotransmitter genes and alcoholism are complex, however; not all studies have shown a connection between alcoholism risk and these genes.

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Individual variation in response to stressors such as pain is genetically influenced and helps shape susceptibility to psychiatric diseases, including alcoholism. Scientists recently found that a common genetic variation in an enzyme (catechol-0-methyltransferase) that metabolizes the neurotransmitters dopamine and norepinephrine results in a less efficient

form of the enzyme and increased pain susceptibility (16). Scientists in another study found that the same genetic variant influences anxiety in women. In this study, women who had the enzyme variant scored higher on measures of anxiety and exhibited an electroencephalogram (EEG) pattern associated with anxiety disorders and alcoholism (17).

The drug naltrexone has been shown to help some, but not all, alcohol-dependent patients reduce their drinking. Preliminary results from a recent study showed that alcoholic patients with different variations in the gene for a receptor on which naltrexone is known to act (the mu-opioid receptor) responded differently to treatment with the drug (18). This work demonstrates how genetic typing may in the future be helpful in tailoring treatment for alcoholism to each individual.

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NIAAA's Collaborative Study on the Genetics of Alcoholism (COGA) is searching for alcohol-related genes through studies of families with multiple generations of alcoholism. Using existing markers—known variations in the DNA sequence that serve as signposts along the length of a chromosome—and observing to what extent specific markers are inherited along with alcoholism risk, they have found "hotspots" for alcoholism risk on five chromosomes and a protective area on one chromosome near the location of genes for alcohol dehydrogenase (19). They have also examined patterns of brain waves measured by electroencephalogram. EEGs measure differences in electrical potential across the brain caused by synchronized firing of many neurons. Brain wave patterns are characteristic to individuals and are shaped genetically—they are quantitative genetic traits, varying along a spectrum among individuals. COGA researchers have found that reduced amplitude of one wave that characteristically occurs after a stimulus correlates with alcohol dependence, and they have identified chromosomal regions that appear to affect this P300 wave amplitude (20). Recently, COGA researchers found that the shape of a characteristic brain wave measured in the frequency stretch between 13 and 25 cycles per second (the "beta" wave) reflected gene variations at a specific chromosomal site containing genes for one type of GABA receptor (21). They suggest that this site is in or near a previously identified QTL for alcoholism risk. Thus, brain wave patterns reflect underlying genetic variation in a receptor for a neurotransmitter known to be involved in the brain's response to alcohol. Findings of this type promise to help researchers identify markers of alcoholism risk and ultimately, suggest ways to reduce the risk or to treat the disease pharmacologically.

Brain wave patterns reflect underlying genetic variation in a receptor for a neurotransmitter known to be involved in the brain's response to alcohol.

Genetics Research—A Commentary by NIAAA Director, Ting-Kai Li, M.D.

Even from the first drink, individuals differ substantially in their response to alcohol. Genetics research is helping us understand how genes shape the metabolic and behavioral response to alcohol and what makes one person more vulnerable to addiction than another. An understanding of the genetic underpinnings of alcoholism can help us identify those at risk and, in the long term, provide the foundation for tailoring prevention and treatment according to the particular physiology of each individual.

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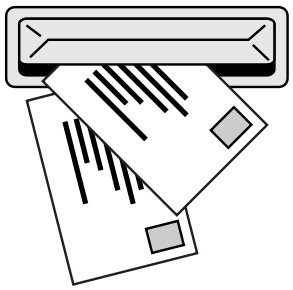

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