

The Genetics of Alcoholism

Why can some people have a glass of wine or beer with their meal without feeling compelled to drink more, whereas others can't seem to stop drinking? Can some people "hold" their liquor better than others? Does alcoholism tend to run in families? Does genetics hold the key to developing medications to treat alcoholism and its effects on the body? Researchers have been trying to find answers to questions such as these for several decades, seeking to identify the factors that influence a person's risk of becoming alcohol dependent.

Research, to date, indicates that both your genetic makeup (i.e., the information stored in the DNA that you inherited from your parents) and your environment (i.e., how you live) influence your risk for alcohol abuse and alcoholism.¹ Your genes certainly play an important role, influencing how your body responds to alcohol, how sensitive you are to its effects, and how likely you are to have a problem with alcohol. However, environmental factors—such as being surrounded by people who are heavy drinkers and who encourage you to drink—also can raise your risk for drinking too much.

The next question then becomes just how much of this risk is determined by our genes—that is, how much can be attributed to factors beyond our control. By studying large families with alcoholic and nonalcoholic members, comparing identical and fraternal twins, and studying adopted children and their biological and adoptive families, researchers found that about half of our risk for alcoholism is influenced by genetics.^{2,3} The remaining risk is related to the influence of environment—where and how we live. The two factors also work together in complex ways.

Understanding how genetics influences alcoholism also is important for another reason. Knowing the genes involved in this disease could help researchers and clinicians identify those who are most at risk of becoming alcoholic and understand how alcohol affects the body. These individuals then could be targeted more effectively for prevention and treatment efforts.¹

This *Alcohol Alert* describes how research is helping to identify the genes involved in alcoholism. In examining this research, one thing becomes clear: Unlike for some other diseases, there is no single gene that determines whether you will develop a problem with alcohol; instead, many genes influence your risk for developing alcoholism, each of which only has a small impact. Further, environmental influences may override or blunt the effects of the genes that increase risk. This overview describes how researchers are trying to tease apart which of the thousands of genes and millions of gene



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variants that make up your DNA play a role in alcoholism, how some of these genes act, and how these genes interact with your environment to determine how you and your body respond to alcohol.

Identifying Genes That Play a Role in Alcoholism

Genetic research has made tremendous advances in the past decade. Researchers have determined the order of the billions of DNA building blocks that make up human genetic material (the genome) and now are working to unravel how all the genes hidden in this genome work together to form each of us. These investigations have shown that some simple traits, such as eye color, are determined by only one or a few genes. Other traits or diseases, however—such as an increased risk for alcoholism—are highly complex. These traits are determined by numerous genes that can be found in different variants, some of which increase the risk of developing the disease, whereas others may decrease risk.

So how do researchers go about finding these genes and gene variants that influence the risk for alcoholism? One way is to look specifically at genes that are likely candidates role, such as the genes involved in the breakdown of alcohol in the body.^{1,4} This approach looks at only a small number of genes and gene variants at a time, however, and additional genes may go undetected simply because they were not suspected as candidates in the first place.

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Another strategy is to cast the net more broadly, looking at larger stretches of DNA throughout the entire genome to see if any DNA regions are found more commonly in alcoholic than in nonalcoholic people. Researchers then can analyze these regions more closely to identify the genes located there and determine their potential roles in alcoholism.^{1,4}

Using minute DNA samples applied to microchips that can be tested with numerous molecular probes, researchers now are capable of analyzing the presence of millions of small DNA variations across a person's genome. Using such so-called genome-wide association studies, researchers can find those variants that occur more often in people with alcoholism than in those without the disease.⁵ Such studies have identified numerous such DNA variants and have mapped their locations in the genome.⁴ Researchers now face the significant challenge of determining how those DNA variants actually affect a gene's function and how those genes, in turn, influence the risk for alcoholism.

To better understand how gene function translates to alcoholism risk, scientists have used animals bred specifically for certain alcohol-related traits.^{6,7} For example, mice and rats have been used to assess how genes influence withdrawal symptoms when alcohol use is discontinued.^{8,9} To this end, investigators either breed animals specifically so that they show a desired trait (e.g., severe withdrawal symptoms) or they use genetic engineering to manipulate specific genes.^{6,7} Using such techniques, researchers have identified a gene that influences alcohol withdrawal seizure severity in mice, enabling them to study this very human behavior more closely.^{10,11}

Specific Genes Influencing Alcoholism Risk

Although the task of isolating the genes involved in alcoholism is daunting, researchers have had some success. For a number of these genes, their roles seem relatively straightforward, such as those that participate in breaking down alcohol or help cells in the brain to communicate with one another. For other genes, however, their involvement is more unexpected, such as genes that help control the body's daily "clock" rhythms or aid in the body's immune defense system.

Genes Encoding Enzymes Involved in Alcohol Breakdown

Some of the first genes linked to the risk of alcoholism were those that help break down alcohol in the body.¹² This breakdown occurs in two steps: first, alcohol is converted into acetaldehyde, and then

acetaldehyde is converted into acetic acid, before being eliminated from the body. This breakdown is caused by two enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). A number of genes contain the genetic codes that produce these enzymes, and each of those has several variants.¹² The rate at which a given person breaks down alcohol depends on the combination of gene variants he or she inherited. For example, some people may metabolize alcohol quickly but have a problem breaking down the in-between by-product acetaldehyde, leaving it to accumulate in the body.¹³ Acetaldehyde is a toxic substance, and if its levels in the body get too high, the person experiences unpleasant effects, such as flushing and nausea after drinking alcohol. As a result, people carrying this gene variant may be less likely to drink and therefore may have a lower risk of alcoholism.^{14,15}

Genes Encoding Brain-Signaling Molecules

The basis for alcohol's intoxicating effects can be found in the brain-cell networks that signal the body's responses. Not surprisingly, these brain-signaling networks also affect a person's risk of alcoholism.¹⁶ Nerve signals in the brain are relayed by numerous types of signaling molecules that are released from one brain cell and then bind to "docking molecules" on other brain cells, thereby increasing or decreasing the likelihood that the signal-receiving brain cell fires a new nerve signal. Alcohol modifies the functions of some of these signaling systems, including one called γ -aminobutyric acid (GABA) and its receptors. It seems to be one of the main targets of alcohol in the brain.¹⁷ Alcohol's effects on the GABA system influence how pleasant or rewarding you perceive alcohol to be.¹⁸

One gene associated with the GABA system, called *GABRA2*, is considered a major genetic player in alcohol dependence.¹⁹ People with certain variants of this gene may be particularly sensitive to alcohol's effects. One study found even simply smelling alcohol was able to elicit a greater response in the brain regions of people with these gene variants compared with those who did not have these variants.¹⁸ This may make them more likely to drink alcohol to keep experiencing its pleasant effects and therefore place them at higher risk for alcoholism.¹⁸

Immune Function Genes

In contrast to the examples given above, the relationship between the risk of alcoholism and genes involved in the body's defense system (i.e., the immune system) is less obvious.²⁰ Certain cells of the immune system are activated by a variety of factors, including stress and alcohol. This triggers genes that help initiate immune responses, such as inflammation. When these immune-activated signals fire through certain brain regions, they may interfere with other important functions, such as decision making. So genes involved in the immune response may then put a person at risk for alcoholism.²¹

Immune responses and inflammatory reactions are highly complex, involving a variety of cells and molecules that need to interact in a coordinated manner. One key molecule that helps regulate all these processes is called nuclear factor (NF)- κ B; its activity seems to be affected by alcohol and may play a role in alcoholism risk.²² People carrying certain variants of the NF- κ B genes are at increased risk for alcohol dependence.^{23,24} Currently also under investigation are a number of other immune-system genes that are more active in the brains of alcoholics than in nonalcoholics.²⁰

If you inherit a certain combination of genes from your parents, are you destined to become an alcoholic unless you never drink alcohol? The answer to this is a clear "no" because how you live also plays an important role.

Genes Regulating the Body's Daily Rhythm

Your body naturally maintains a daily rhythm for various functions (e.g., body temperature or blood pressure) that is controlled by certain "clock" genes.²⁵ This internal system and its genes (i.e., the circadian system) both influences and is influenced by alcohol use. For example, disrupting the

body's normal daily rhythm seems to increase alcohol use. Stress (or the body's response to stress) also may play a role in this process because it activates certain clock genes, which can result in increased drinking.²⁶ At the same time, alcohol consumption can alter the activities of several clock genes.^{27,28} Because of the interactions between stress and the circadian system, alcohol-related changes in clock-gene activity may affect your response to stress so that you are more likely to drink after stressful events, which may contribute to an increased risk of alcoholism.

The bottom line is that genes alone do not determine our destiny—lifestyle choices and other environmental factors have a substantial impact.

Cutting-Edge Genetic Research in Alcoholism

Although researchers already have made much progress in identifying genes that contribute to the risk of alcoholism, even more sophisticated approaches are needed to further discover how our genes influence our drinking behavior.

New techniques using animal models allow researchers to control more specifically when and where a specific gene or gene variant can be activated or inactivated to study the resulting effects.²⁹ Researchers also can modify genes of interest to change how they are expressed and, in turn, what function they have. This strategy has been used, for example, with the gene encoding a component of the GABA signaling system. The animals with the modified gene showed distinct changes in alcohol-related behaviors, such as a preference for alcohol over water.³⁰

Other approaches focus on the fact that many of the genes identified to date are part of larger networks of genes that interact with one another rather than act independently.³¹ Researchers looking at such networks are using novel techniques to simultaneously study thousands of DNA probes spread over the entire genome. Such studies found that numerous alcohol-related gene networks participate in important brain-signaling pathways.³² However, many important questions remain about how such networks interact and are affected by alcohol or how they may increase the risk of alcoholism.

Another new line of research was triggered when scientists observed that gene activity may be altered by proteins (called histones) that help to package and organize DNA in the cells. These so-called epigenetic changes alter the way the DNA is expressed over time, either increasing or decreasing gene activity.³³ Both short-term and long-term alcohol drinking can cause such epigenetic changes in certain brain circuits and may modify GABA signaling.³⁴ Through these mechanisms alcohol may influence behavior—for example, how sensitive a person is to alcohol's effects³⁵ or whether a person is likely to develop feelings of anxiety or become dependent on alcohol.^{36,37} Although scientists are only just beginning to tap the potential of these new lines of research, they are likely to result in important discoveries that may help identify new targets for the prevention and treatment of alcoholism.

Genes Versus Environment

As described above, researchers are learning more and more about how your genetic makeup can influence your drinking behavior and its consequences and which genes may put you at increased risk of alcoholism. But does this mean that if you inherit a certain combination of genes from your parents, you are destined to become an alcoholic? The answer to this is a clear “no” because how you live also plays an important role. People with the same genetic makeup may be more or less likely to develop alcoholism depending on their environment and life circumstances.

Researchers can study the interactions between genes and the environment and the relative impact of each through a variety of direct and indirect approaches.³⁸ These approaches have helped identify several environmental factors that either protect us from or place us at increased risk for alcoholism; for example, marital status and religiosity have been found to be protective factors, lessening the impact of genetic risk factors on drinking in women.^{39,40}

For adolescents in particular, drinking seems to be influenced strongly by environmental factors in addition to genetic makeup. Adolescents who carry high-risk genes and whose parents do not monitor their activities and/or who have friends that use alcohol and other drugs are more likely to develop alcohol problems than those with a similar genetic makeup whose behavior is monitored more closely.^{41,42} Modifying the environment also can help adolescents avoid risky drinking behavior. Participants in one prevention program designed for youth were less likely to engage in high-risk behavior, such as drinking, even though they had a high-risk genetic background.⁴³

The bottom line is that genes alone do not determine our destiny—lifestyle choices and other environmental factors have a substantial impact.³⁸ In addition, many other individual and psychosocial variables influence when and how much we drink, both in the short and long term, and how this influences our risk of alcoholism.

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Resources

Source material for this *Alcohol Alert* originally appeared in *Alcohol Research: Current Reviews*, 2012, Volume 34, Number 3.

Alcohol Research: Current Reviews, 2012, 34(3) (formerly titled *Alcohol Research & Health*) presents the latest research on the genetics of alcoholism. Articles in this issue explore why some people may be at greater risk for developing an alcohol use disorder and how genes and the environment dovetail to influence that risk. Other articles examine the latest technologies being used to identify genetic variations and the complex interactions between genes and gene networks. A special section delves more deeply into specific classes of genes and their relationship to alcoholism. The issue rounds out with a listing of Web resources for researchers.

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