

# SEEKING THE CONNECTIONS: ALCOHOLISM

BY JOHN I. NURNBERGER, JR., AND LAURA JEAN BIERUT

## AND OUR GENES

Identifying genetic influences on vulnerability to alcohol addiction can lead to more targeted treatments and help those at risk to make informed choices about their own lives

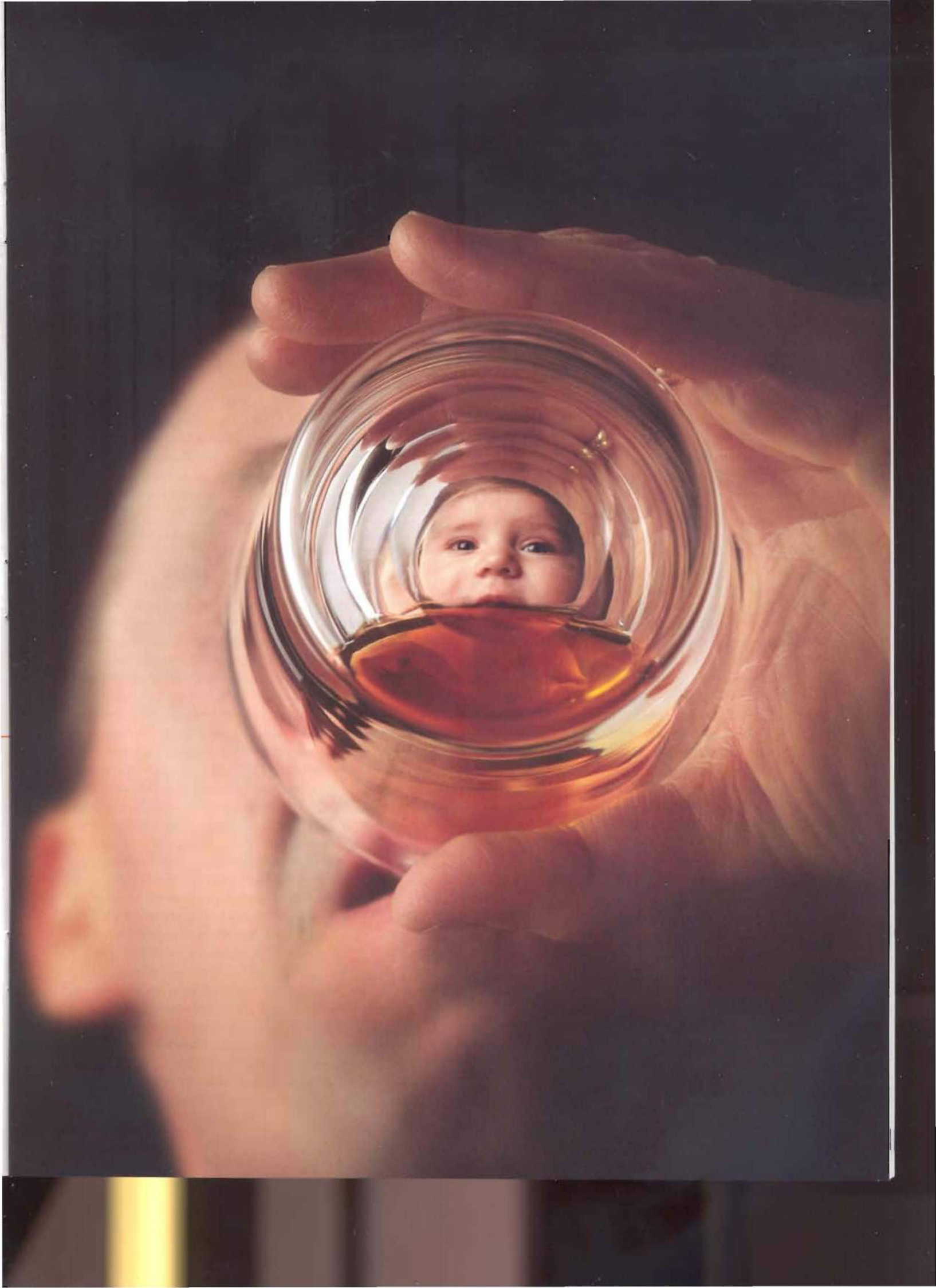
**The tendency** to become dependent on alcohol has long been known to run in families, which for some only added to the social stigma attached to this complicated condition. But to scientists, that apparent heritability suggested that some genetic component underlying vulnerability to alcohol problems was being transmitted from generation to generation.

With rapid advances over the past 10 years in technologies for discovering and analyzing the functions of genes, researchers are now increasingly able to get at the biological roots of complex disorders such as substance abuse and addiction. The power to examine patterns of inheritance in large populations, and to survey hundreds of thousands of tiny variations in the genomes of each of those individuals, enables investigators to pinpoint specific genes that exert strong or subtle influences on a person's physiology and his or her resulting risk for disease.

As is true of many other human disorders, alcoholism does not have a single cause, nor is its origin entirely genetic. Genes can play an important role, however, by affecting processes in the body and brain that interact with one another and with an individual's life experiences to produce protection or susceptibility. Teasing these effects apart is challenging, and to date fewer than a dozen genes that influence one's risk for alcoholism have been identified, although more surely exist.

Variants of each of the known genes only modestly alter an individual's vulnerability to alcohol, but many are common in the general population and may have wider effects on drinking habits, on other addictions or problematic behaviors, and on disorders such as depression and anxiety. Finding the genes involved in our responses to alcohol and understanding their effects may thus illuminate a broader array of conditions, too. Revealing the biological processes that can

IAN MCKINELL/Photonic/Getty Images (man with glass);  
BRIAN BERMAN/Toxi/Getty Images (baby face);  
EMILY HARRISON (photoillustration)





build and reinforce alcohol addiction will most certainly help to better target existing treatments and devise new ones to break alcohol's hold.

### Clues in Human Variations

GENES POWERFULLY INFLUENCE a person's physiology by giving rise to some 100,000 different types of protein, each of which has a direct role in the daily functioning of the body and brain or in regulating the activity of other genes. The strong connection between variations in basic physiology and an individual's susceptibility to alcohol problems is well illustrated by the very first gene to be identified as affecting the risk of developing alcohol dependence.

Decades ago researchers began investigating the widely observed tendency of persons from Chinese, Japanese or other East Asian backgrounds to become "flushed" when they drank an alcoholic beverage. Blood tests on subjects displaying this effect showed increased levels of acetaldehyde, a breakdown product of alcohol, which resulted in an uncomfortable sensation of warmth in the skin, palpitations and weakness. By the 1980s investigators traced the reaction to an enzyme involved in alcohol metabolism, aldehyde dehydrogenase, and eventually to the gene that encodes it, *ALDH1*. The enzyme breaks down acetaldehyde, but slight variations in the gene's DNA code in these subjects caused the enzyme to work more slowly. When these individuals ingested alcohol, the acetaldehyde—which may be toxic in high doses—was building up in their bodies.

This *ALDH1* gene variant has since been found to be common in Asian populations—seen in 44 percent of Japanese, 53 percent of Vietnamese, 27 percent of Koreans and 30 percent of Chinese (including 45 percent of Han Chinese)—yet it is rare in people of European descent. As might be expected, people with this slow-metabolizing gene variant also have a decreased risk, by up to sixfold, for alcoholism, so it is an example of a genetic variation that can protect against developing the disorder.

People who meet criteria for dependence often have multiple cases of alcoholism in their families.

Other enzymes that break down alcohol have also been studied for their genetic contribution to alcohol dependence. Alcohol dehydrogenase (ADH), the enzyme responsible for the first step in the conversion of alcohol to acetaldehyde, for example, is actually produced by a family of genes, each of which affects different properties of the enzyme. The genes most important to alcohol metabolism are the *ADH1* group and *ADH4*. Our own studies of a U.S. population of European descent have recently provided strong evidence that variants in the *ADH4* genes in particular enhance the risk of alcoholism in members of that population, although exactly how these *ADH4* variants affect alcohol metabolism remains to be discovered.

Alcoholism is genetically complex, meaning that multiple genes are likely to be involved, and their interactions with one another and with an individual's environment also have to be examined before a complete picture of the processes that can lead to the disorder is assembled. People are also complex

and manifest problems with alcohol in diverse ways, especially in the early stages of disease, although cases come to resemble one another clinically in the later stages of illness. Thus, when investigating the biology of alcoholism, researchers must carefully define the problem—for example, distinguishing between true dependence on alcohol and alcohol abuse, which is a less medically severe syndrome.

A widely used psychiatric standard for diagnosing dependence, be it on alcohol or another substance, requires that a person have experienced at least three of the following symptoms within the preceding 12 months: tolerance for large doses, withdrawal reactions, loss of control over use of the substance, efforts to stop or cut down, a great deal of time spent on the activity, giving up other activities, and continued use despite resulting physical or psychological problems. People who meet these criteria often have multiple cases of alcoholism in their families. With the willing participation of these subjects, we and other researchers have begun connecting individual symptoms with their physiological origins and ultimately with the responsible genes.

Indeed, an important strategy in the search for genes that affect a person's risk for alcohol dependence has been the examination of endophenotypes, which are physical traits—phenotypes—that are not externally visible but are measurable, and can therefore be studied to see whether certain patterns are more common in people with a complex disorder and may be linked to risk for that condition. The idea is grounded in an assumption that endophenotypes can reveal the biological bases for a disorder better

## Overview/Seeking Alcoholism Genes

- Dependence on alcohol is a complex and controversial disorder, but susceptibility to it shows clear patterns of inheritance, which indicates that genes transmit some biological basis for greater vulnerability.
- Physiological traits, such as distinctive brain activity patterns in alcoholics and their children, help scientists pinpoint variant genes that affect a person's responses to alcohol.
- Finding the genes that influence alcoholism and related disorders provides insight into how the conditions develop, opens the way for better treatments, and allows individuals at high risk to make informed choices about their own health and behavior.

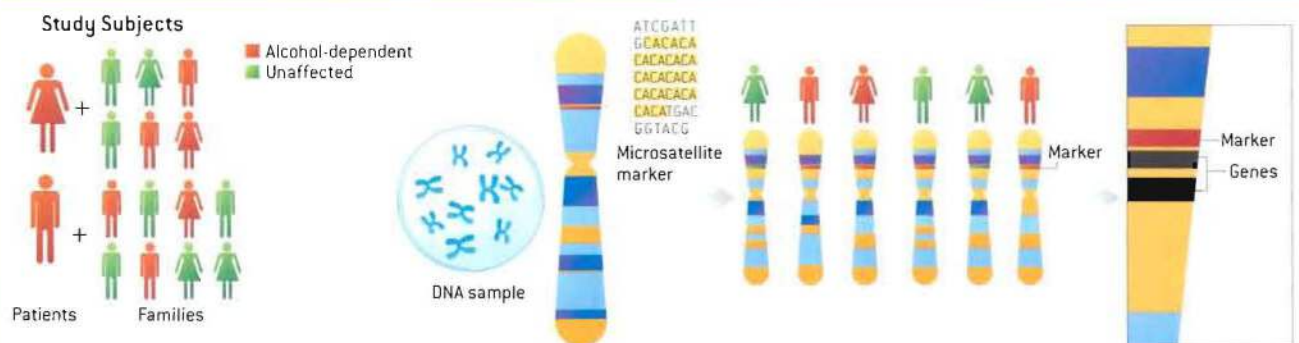




## FINDING LINKS THROUGH FAMILIES

Identifying genes that influence a disorder as complex as alcoholism first involves linking the condition's traits to specific regions on chromosomes. This "linkage analysis" is easiest in genetically similar groups, such as families, with multiple members affected to some degree by the disorder.

Chromosomal features known as markers that appear more frequently in the affected relatives can flag potentially significant stretches of DNA. Detailed investigation of those regions can then reveal a gene whose function affects responses to alcohol.



### RECRUITMENT

Alcoholics seeking treatment and their willing relatives are interviewed and diagnosed according to psychiatric criteria for alcohol dependence. All subjects provide DNA samples.

### CHROMOSOME SURVEY

Researchers scan every person's chromosomes for patterns of repeated DNA known as microsatellite markers. In one individual, an alternating sequence of the bases cytosine and adenine might repeat 17 times, for example, whereas at the same location another relative has only 12 repeats of the sequence.

### LINKAGE ANALYSIS

Markers frequently found in people with a specific trait of the disorder, but less often in unaffected kin, flag a chromosomal region linked to that trait.

### GENE ASSOCIATION

Closer mapping of the DNA region near a marker reveals specific genes whose role in the disorder can be investigated.

than behavioral symptoms because they represent a fundamental physical trait that is more closely tied to its source in a gene variant. Although this approach to studying complex behaviors was first proposed in the 1970s by psychiatric researchers investigating schizophrenia, it has recently proved even more valuable with modern tools for assessing biologic processes and analyzing genetic data.

The brain's electrical activity patterns, for example, are a form of endophenotype. Using electroencephalography (EEG) to detect such activity through electrodes on the scalp, researchers can record patterns of neural firing. Sophisticated computer algorithms can analyze the data to identify the brain regions where the signals are likely to have originated, offering additional clues to the type of cognitive processing taking place. The overall brain waveforms and spikes in neural activity in response to specific stimuli seen in such EEG readings are distinctive in different individuals and serve as a kind of neurological fingerprint. These patterns can also reflect the general balance between excitatory processes within the brain, which render neurons more responsive to signaling from other neurons, and those that are inhibitory, making neurons less responsive.

Such electrophysiological patterns are highly heritable and they differ in characteristic ways in alcoholics and non-alcoholics, with excitation exceeding and overpowering inhibition in the alcoholic subjects' brains. This imbalance, or "disinhibition," can also be seen in the children of alcoholics and strongly predicts their own subsequent development of

heavy drinking and alcohol dependence, which suggests that these patterns are a marker for a biologically inherited predisposition to alcoholism. Moreover, the signature patterns may point to the heritable vulnerability itself: disinhibition is believed to stem from a generalized lack of functioning inhibitory neurons in the brain areas responsible for judgment and decision making, and people lacking these inhibitory circuits may be more prone to acting on impulses originating in lower brain regions, such as the amygdala.

In the 1980s evidence from several laboratories showing that electrical activity in the brain could reveal a person's risk of alcohol dependence helped to stimulate the idea that an intensive search for the genes underpinning alcoholism-associated phenotypes was feasible and worthwhile. With support from the National Institute on Alcohol Abuse and Alcoholism, the Collaborative Study on the Genetics of Alcoholism (COGA), in which we are both participants, started in 1989. The study currently involves eight research centers across the U.S. and thousands of alcoholics and their family members who have agreed to help in this ongoing investigation.

### Family Ties

AT COGA'S OUTSET, researchers at sites around the country sought to identify families severely affected by alcoholism. Previous twin, adoption and family studies had indicated that alcohol problems are strongly heritable—indeed, more than 50 percent of the overall risk for alcoholism is attributable to inherited factors, which makes family groups a powerful re-



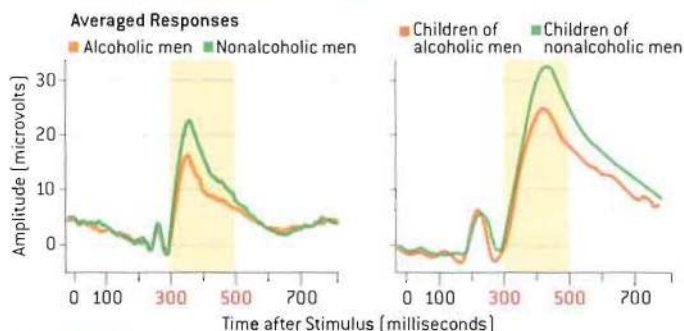
## SIGNATURES IN THE BRAIN

Certain patterns of brain electrical activity serve as measurable traits, known as endophenotypes, which reveal distinctive physiological characteristics of alcoholics and others at high

risk for the disorder. Investigators have used these signature differences in brain function to uncover genes linked to alcoholism and related conditions.

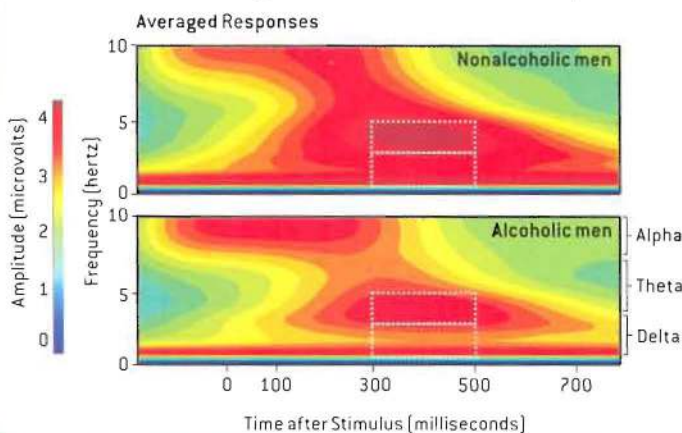
### The P300 Response

Measuring brain activity through electrodes on the scalp reveals a spike in signal strength [amplitude] between 300 and 500 milliseconds after a stimulus, such as a flash of light. Known as P300, this distinctive evoked response is significantly weaker in alcoholics, even when abstinent, than in nonalcoholics. A muted P300 is also typical in the children of alcoholic parents, indicating that this functional brain difference predates the onset of heavy drinking and is itself a risk factor for becoming alcoholic.



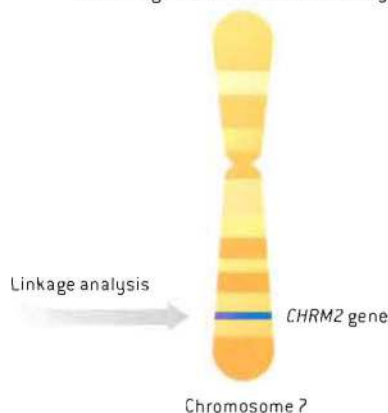
### Dissecting the Response

P300 consists largely of neural signaling in low-frequency ranges known as delta and theta, which are associated with awareness and decision making. Mapping the EEG readings of nonalcoholic (*below*) and alcoholic (*bottom*) subjects by frequency reveals weaker signal strength in those bands among the alcoholics after 300 milliseconds. This trait was linked in family studies to both alcoholism and depression.



### Linkage to a Gene

Reduced delta- and theta-frequency signal strength in alcoholic subjects was also traced to variants of *CHRM2*, a gene encoding a cellular receptor for the neurotransmitter acetylcholine, which regulates neural excitability.



source for tracking specific traits and linking them to the relevant genes [see box on preceding page].

Some 1,200 subjects seeking treatment for alcohol dependence and their relatives—more than 11,000 people in all—were extensively interviewed. Among these, 262 families were found to be “deeply affected,” which means that they included two or more first-degree relatives of the patient—such as parents or siblings—who were also diagnosed as alcohol-dependent. The electrophysiological brain endophenotypes of both affected and unaffected members of those families were assessed, and the subjects underwent further interviews to evaluate additional characteristics that are associated with alcoholism risk and believed to be genetically influenced. These traits include “low response,” meaning that the person must consume larger-than-average amounts of alcohol before feeling its effects; previous experience of major depression; and certain drinking history patterns, such as a high maxi-

num number of drinks ever consumed in a 24-hour period.

The participants also provided DNA samples, which allowed COGA scientists to examine the chromosomes of each individual and take note of distinctive molecular features, which can serve as markers for a potentially significant region of a chromosome. Markers appearing most frequently in family members exhibiting alcoholism-associated phenotypes would suggest a causal link between that region of a chromosome and the trait. Significant linkages were identified in this manner on chromosomes 1, 2, 4 and 7, and many years of genetic mapping subsequently pinpointed several specific genes in those regions, including *ADH4* and *GABRA2* on chromosome 4, as well as *CHRM2* on chromosome 7. Other research groups studying separate populations have also documented associations between a risk for alcoholism and these chromosomal regions and genes, confirming their likely role in the disorder.

LUCY READING-IRKANDA; FROM “EVENT-RELATED POTENTIALS IN COGS.” BY BERNICE FORJESZ AND HENRI BEGLEITER, IN ALCOHOL HEALTH & RESEARCH WORLD, VOL. 21, NO. 3, 1997 (top right graph); FROM “THE UTILITY OF NEUROPHYSIOLOGICAL MARKERS IN THE STUDY OF ALCOHOLISM.” BY BERNICE FORJESZ ET AL., IN CLINICAL NEUROPHYSIOLOGY, VOL. 116, NO. 5, MAY 2005; USED WITH PERMISSION FROM ELSEVIER (top left graph and bottom left graph)



For instance, a growing body of research has revealed that some variants of genes that encode cell-surface docking sites for the protein GABA (gamma-aminobutyric acid), which carries signals between certain nerve cells, increase vulnerability to alcoholism. GABA is the most common inhibitory neurotransmitter in the mammalian nervous system. It modulates the activity of neurons by binding to GABA-specific receptors in their cell membranes and literally inhibiting their responsiveness to signaling. One class of these receptors, known as GABA<sub>A</sub>, is made of protein subunits arrayed around a channel that admits chloride ions into the cell. Variations in the *GABRA2* gene, which encodes one of the GABA<sub>A</sub> receptor subunits, have been found to strongly influence an EEG endophenotype, known as the beta frequency, that appears to play a role in mediating neuronal disinhibition.

Neurons that bear GABA receptors are especially abundant in the brain's frontal cortex, where a generalized loss of inhibition can cause seizures, and seizure disorders are commonly treated with medications that boost GABA activity, promoting inhibition. A less generalized loss of GABA-induced inhibition, however, is thought to be involved in behavioral undercontrol or impulsivity, which is a feature of a number of psychiatric disorders, including bipolar affective disorder, substance abuse and chronic conduct problems. Studies by COGA consortium members have demonstrated that variants of the *GABRA2* gene are linked to alcoholism, a finding that has since been confirmed by at least four groups. Interestingly, these variations in *GABRA2* do not change the protein structure of the GABA<sub>A</sub> receptor; instead they seem to modify production of the affected protein subunit, perhaps reducing the total number of functioning receptors.

Studies are under way to identify exactly how this GABA receptor gene variant affects disinhibition in the brain, but a connection between GABA activity and alcohol dependence certainly makes sense, because impulsivity is a feature of many cases of alcohol dependence. That trait is particularly

associated with an early-onset form of addiction seen primarily in males. People with this kind of addiction are generally prone to "externalizing" disorders that involve problematic behavior, as opposed to "internalizing" disorders such as anxiety and depression. Thus, even without a genetic screen of such a patient, understanding the likely involvement of GABA in that addiction profile can help target therapeutic approaches.

Another neurotransmitter highlighted in the development of alcoholism by the study of endophenotypes is acetylcholine, which, like GABA, affects neurons widely distributed through the central nervous system. Neurons that respond to acetylcholine—described as cholinergic neurons—also have an important role in modulating the overall balance between excitation and inhibition in the brain. Our measures of brain responses in COGA subjects uncovered a connection to the chromosomal region containing the *CHRM2* gene, which encodes a particular type of cholinergic receptor known as the

M2 muscarinic acetylcholine receptor (*CHRM2*).

Activation of the *CHRM2* receptor alters neural signaling in the slow delta and theta frequencies, which are associated with cognitive functions such as decision making and attention [see box on opposite page]. We were also able to link variants of the *CHRM2* gene to the clinical conditions of alcohol dependence and major depression. As with *GABRA2*, the *CHRM2* variants that appear to influence the brain's electrical activity, alcoholism and depression do not seem to alter the structure of the receptor protein but rather its manufacture.

This particular association is exciting because it confirms part of a hypothesis articulated in 1976 by psychiatrist David Janowsky and his colleagues at Vanderbilt University regarding the brain's need to maintain a fine balance between different signal-regulating processes to function normally. Janowsky's group proposed that muscarinic supersensitivity—that is, an enhanced effect of acetylcholine on the muscarinic cholinergic receptors—in persons prone to depression and related conditions was an underlying source of imbalance in the brain.

The recently discovered links between *CHRM2*, alcoholism and depression are the first to show a direct connection between a specific gene and such hypersensitivity, and these findings about the cholinergic system provide new targets for the development of more specific pharmacological treatments for alcoholism and depression. They also underscore the need to understand how subtle differences in physiology can contribute to a disorder as complex as addiction.

There are different paths to alcoholism and different pathways underlying them.

#### THE AUTHORS

**JOHN I. NURNBERGER, JR., and LAURA JEAN BIERUT** are psychiatric geneticists who often collaborate to study the genetic influences on many forms of substance addiction as well as on mental illnesses such as depression and bipolar disorder. Nurnberger is professor of psychiatry at Indiana University School of Medicine, where he is also director of the Institute of Psychiatric Research. Bierut is associate professor of psychiatry at Washington University in St. Louis and, like Nurnberger, an investigator in the Collaborative Study on the Genetics of Alcoholism (COGA). Both authors wish to acknowledge the late Henri Begleiter and Theodore Reich, principal and co-principal investigators of COGA since its inception: "We are indebted to their leadership in the establishment and nurturing of COGA and acknowledge with great admiration their seminal scientific contributions to the field."



## Insight, Not Destiny

THE COGA PROJECT has been structured around families, but this type of research has also strengthened understanding of the relative importance of specific gene variants as risk factors in different ethnic groups. This is not to say that certain ethnicities are more prone to alcoholism; instead, like the *ALDH1* gene version that makes many East Asians intolerant of alcohol, certain of the genetic variants that contribute to risk are much more prevalent in some ethnic groups than in others. The knowledge that such genes are likely to be influencing dependence in patients belonging to one of these populations is another tool that can be used to assess the nature of an individual's problem and to tailor treatment accordingly.

Our research group recently discovered, for example, that variation in a gene encoding a receptor involved in taste perception, known as *hTAS2R16*, is significantly linked to alcoholism in the COGA subjects. The risk variant, which causes decreased sensitivity to many bitter taste compounds, is uncommon in European Americans, whereas 45 percent of African-Americans carry this version, making it a much more significant risk factor in that population.

The genetic contributions to dependence identified so far affect many different aspects of human physiology, from alcohol metabolism to brain activity and taste perception just in

the examples we have described. The effect of each of these genes by itself is modest, probably increasing average risk by 20 to 40 percent, and other as yet unidentified genes undoubtedly also contribute to vulnerability to alcohol problems.

An important test to confirm and refine these genetic findings is to see how they influence people early in life, even before the onset of heavy drinking, and whether the variants can predict the later development of alcoholism. COGA added such a prospective arm to the study to follow young members of the high-risk families. Initial results have shown that in adolescents, the *ADH* gene risk variants are indeed associated with early drinking and subsequent development of alcohol problems. Carriers of the *CHRM2* risk variants, however, are more likely to have early symptoms of depression than drinking problems when they are adolescents. Youngsters with the *GABRA2* risk variant more frequently display conduct problems, such as trouble with the police, fighting and expulsion from school, rather than early drinking. In young adults, on the other hand, the GABA receptor gene risk variants do become associated with alcohol dependence.

These findings reinforce the notion that there are different paths to alcohol dependence and different physiological pathways underlying them. The *ADH* risk variants may contribute to the development of alcoholism directly by promoting heavy

## RISKY GENES

The genes found so far to influence a person's risk of becoming alcohol-dependent represent a wide variety of physiological processes, including breakdown of alcohol itself, balanced brain function, taste and reward reinforcement. Variations in the genes controlling these traits can protect people from,

or predispose them to, responding to alcohol in ways that enhance addiction. Some of the same gene variants have also been linked to other traits or disorders, which suggests that certain problems involving behavior, mood and dependence may have overlapping origins.

GENE; LOCATION	ENCODED PROTEIN; FUNCTION	GENE VARIANT EFFECT	LINKED TO OTHER TRAITS OR DISORDERS
<i>ADH4</i> ; chromosome 4	Alcohol dehydrogenase; alcohol-metabolizing enzyme	Increased risk (certain variants)	None
<i>ALDH1</i> ; chromosome 4	Aldehyde dehydrogenase; alcohol-metabolizing enzyme	Protective	None
<i>CHRM2</i> ; chromosome 7	Muscarinic acetylcholine receptor M2; regulates neural signaling	Increased risk	Major depression; delta- and theta-frequency EEG variations
* <i>DRD2</i> ; chromosome 11	Dopamine D2 receptor; regulates reward reinforcement	Increased risk	Habitual smoking
<i>GABRG3</i> ; chromosome 15	GABA <sub>A</sub> receptor g3 subunit; regulates neural signaling	Increased risk	None
<i>GABRA2</i> ; chromosome 4	GABA <sub>A</sub> receptor α2 subunit; regulates neural signaling	Increased risk	Drug dependence; conduct disorders; beta-frequency EEG variations
<i>HTAS2R16</i> ; chromosome 7	<i>hTAS2R16</i> receptor; contributes to bitter taste sensitivity	Increased risk	None
<i>OPRK1</i> ; chromosome 8 <i>PDYN</i> ; chromosome 20	Kappa opioid receptor and prodynorphin, the peptide to which the receptor binds; both participate in regulating aversion and reward	Increased risk	Stress response; may play a role in heroin and cocaine habituation

\* To date, evidence for *DRD2* is contradictory. Further investigation is needed to confirm this gene's role in alcohol or nicotine dependence.



drinking, whereas the *GABRA2* variants predispose a person to conduct problems, which are themselves a risk factor for alcoholism. Meanwhile *CHRM2* may act through depression and other internalizing symptoms to foster drinking.

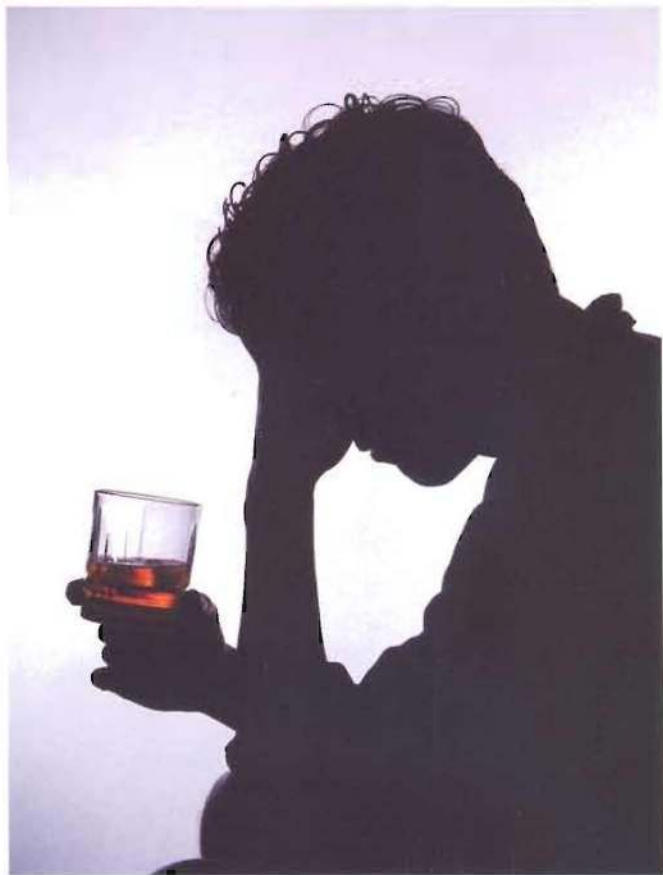
As more genes are linked to the development of alcohol dependence, these insights will be used to improve tools for gauging an individual's risk for developing alcoholism and identifying those with alcohol problems who may respond better to specific treatments. Doctors commonly consider a person's genetic profile and other family and environmental risk factors when combining medications and behavioral prescriptions for complex conditions such as hypertension, cancer and bipolar affective disorder. Clinicians are in the earliest stages of using genetic variants to shape treatment decisions for alcoholism, and in the future we expect to have molecular guidelines to help develop such individualized strategies.

The recent genetic findings related to alcoholism may also suggest ways to improve the prevention and treatment of smoking and other forms of substance dependence that are frequently seen in people with alcohol problems and tend to cluster in the same families. Mood and anxiety disorders fall into this category as well, and the association between *CHRM2* variations, alcoholism and depression illustrates how these problems may stem in part from a common source. Improved understanding of alcohol dependence should therefore help dissect factors involved in the development of related conditions.

Genetics is never destiny, however. Genes may interact with specific toxic environments, such as abuse or neglect, to result in problems for some gene carriers but not for others. And if half of alcoholism risk is heritable, the other half must derive from other sources. Nobody gets to be alcohol-dependent without making some poor choices, but clearly some people are more sensitive to alcohol than others in the same set of circumstances, and scientists are working to identify the sources of that vulnerability.

Critics have argued that genetic research into alcohol dependence and other forms of addiction, including smoking, is not cost-effective from a public health perspective. For instance, some claim that it would make more sense to direct resources toward reducing the use of potentially addictive substances across the board than to identify—and potentially stigmatize—the individuals who would be most affected by such reductions. Undoubtedly, there is value in limiting the use of alcohol, nicotine and other mood-altering drugs in general. There is also value, however, in supporting individual self-knowledge as it pertains to susceptibility so that people can make informed choices for themselves and in shaping a culture that regards this as a positive goal.

Genetic testing is already providing opportunities for self-assessment that were impossible in the past, and the demand for genetic profiling will increase in the coming years. Microarrays, often called gene chips, can be used to detect a person's gene variants as well as variations in gene activity and to produce a series of medical, psychiatric and behavioral recommendations that the individual may take or leave as he or she wish-



es. This use of scientific knowledge is surely inevitable, especially in free nations with capitalist economies, where it will be market-driven and competitive. The scientific and academic communities must therefore help guide this process by distinguishing true physiological relations from false claims and by encouraging socially responsible uses for these discoveries.

The risks of smoking were first widely publicized by the Surgeon General's Report of 1964, and the combination of that medical information and social pressure has reduced the prevalence of smoking over the subsequent decades. An individual's awareness of personal genetic medical risks may similarly change his or her choices. The broader health and social effects of this new type of information may not be seen quickly, but they could be quite profound over time. SA

#### MORE TO EXPLORE

**The Collaborative Study on the Genetics of Alcoholism: An Update.** Howard J. Edenberg in *Alcohol Research & Health*, Vol. 26, No. 3, pages 214–218; 2002.

Available at [www.niaaa.nih.gov/Publications/AlcoholResearch](http://www.niaaa.nih.gov/Publications/AlcoholResearch)

**Evidence of Common and Specific Genetic Effects: Association of the Muscarinic Acetylcholine Receptor M2 (*CHRM2*) Gene with Alcohol Dependence and Major Depressive Syndrome.** Jen C. Wang et al. in *Human Molecular Genetics*, Vol. 13, No. 17, pages 1903–1911; June 30, 2004.

**Endophenotypes Successfully Lead to Gene Identification: Results from the Collaborative Study on the Genetics of Alcoholism.** Danielle M. Dick et al. in *Behavior Genetics*, Vol. 36, No. 1, pages 112–126; January 2006.





# Questions for Review

## TEST YOUR COMPREHENSION

- Gene variants that increase the risk of alcoholism generally do so by
  - 0.1–0.5%.
  - 1–2%.
  - 3–5%.
  - 20–40%.
  - 300–400%.
- A genetically complex disease is one in which
  - none of the associated genes has yet been identified.
  - there is one gene with many different, complex variants that causes the disease.
  - environmental agents cause complex alterations of disease-associated genes.
  - multiple genes interact with environmental factors to produce the disease.
  - multiple environmental factors alone cause the disease.
- A psychiatric standard for diagnosing alcohol dependence is
  - consuming alcoholic beverages at least twice a day.
  - any form of alcohol abuse.
  - alcohol abuse that disrupts family relations or job performance.
  - a craving for alcohol.
  - meeting at least three of a set of defined symptoms over a 12-month period.
- Individuals carrying an aldehyde dehydrogenase (ALDH1) gene variant that reduces the rate of acetaldehyde breakdown
  - die at an early age.
  - suffer neurodegenerative conditions late in life.
  - are less likely to become alcohol dependent.
  - are more likely to become alcohol dependent.
  - are more likely to abuse alcohol, but not to become alcohol dependent.
- An example of an endophenotype is
  - depression.
  - anxiety.
  - brain electrical activity patterns.
  - heavy drinking.
  - alcohol dependence.
- Genetic factors account for roughly \_\_\_\_\_ of the risk for alcoholism.
  - 1%
  - 5%
  - 15%
  - 50%
  - 90%
- Compared to the brains of nonalcoholics, the brains of most alcoholics
  - respond more slowly to a stimulus.
  - respond more rapidly to a stimulus.
  - show an excess of inhibitory processes.
  - show an excess of excitatory processes.
  - show identical electrophysiological properties.
- For alcoholism,
  - genetics is destiny.
  - genetics is immaterial.
  - genes and environment interact.
  - genetic studies are the only route to effective treatment of the disease.
  - genetic studies are fascinating but unlikely to be cost-effective for preventing or treating the disease.
- Genetic findings related to alcoholism are envisioned to help
  - prevent early-onset Alzheimer's disease.
  - prevent and treat other substance dependencies.
  - in the treatment of other complex genetic diseases such as hypertension.
  - insurance companies minimize risk.
  - create a federal registry of potential alcoholics.
- Regarding genetic profiling for alcoholism risk, scientists have an obligation to
  - distinguish false claims from sound science.
  - block use of this dangerous technology.
  - prevent market forces from driving the use of these genetic technologies.
  - prevent competition between groups working to improve genetic testing.
  - speak out against this and other cost-ineffective technologies.



# Seeking the Connections: Alcoholism and our Genes

by John I. Nurnberger, Jr., and Laura Jean Bierut



## BIOLOGY IN SOCIETY

1. If genetic profiling advances enough to allow the prediction of the risk of alcohol dependence, what measures should be taken if a 12-year-old boy, living with both a father and older sister who are alcoholics, is found to be genetically at high risk of alcohol dependence? Before answering, you may want to consider what additional information would be helpful in coming to a decision. Ultimately, your answer needs to consider the balance between parental legal rights, best prevention practices for the child, and respect for the family.
2. A variant of the hTAS2R16 bitter taste receptor gene is linked to alcoholism. This gene variant is present in almost 45% of African-Americans and is uncommon in Americans of European descent. How can this information be misused in a racist way in drawing conclusions about alcoholism in blacks and whites? What is the correct interpretation of this finding in understanding the risk of alcoholism in these two groups?
3. Alcohol abuse places a huge burden on the nation. For example, in 2005, 40% of traffic fatalities involved alcohol. If effective genetic screens for susceptibility to alcohol abuse become available, should they be mandatory for all citizens over the age of 15? Should people who test positive for alcohol susceptibility be legally barred from alcohol consumption?

## THINKING ABOUT SCIENCE

1. Why are endophenotypes considered more helpful than behavioral phenotypes in searching for genes associated with alcoholism?
2. To what extent is an alcoholic responsible for his or her condition? Your answer should consider genetic and environmental factors in alcoholism and the idea that there are different paths to alcohol dependence.

3. The CHRM2 gene encodes a form of the acetylcholine receptor, and certain CHRM2 variants increase susceptibility to major depression and alcohol dependence. What are some possible relationships between major depression and alcoholism in individuals with the CHRM2 variant? Does the co-occurrence of major depression and alcoholism in some individuals with the variant CHRM2 gene prove that alcohol dependence and depression have the same underlying physiological cause?

## WRITING ABOUT SCIENCE

Imagine that Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA), knows that you are an unbiased expert on alcoholism. She has been receiving conflicting advice about the most effective way of spending limited funds to reduce alcoholism in the United States. Some experts tell her that the value of future genetic screens for potential alcohol susceptibility genes, each of weak effect, is questionable, particularly when current programs to limit alcohol consumption and to treat alcoholics give immediate returns. Dr. Volkow asks you to prepare a brief (2- to 3-page) position paper. She asks that you include a discussion of the current state of the field, when you believe a genetic screen will be available, and the effectiveness of genetic screening for prevention and customized treatment of alcoholism. Finally, she wants you to recommend whether substantial funds from NIDA should be committed to research into the genetics of alcoholism.

Answers: Testing Your Comprehension  
1 d; 2 d; 3 e; 4 c; 5 c; 6 d; 7 d; 8 c; 9 b; 10 a