

Millions of Americans know all too painfully that alcoholism runs in families.

Children of alcoholic parents are four times as likely to develop drinking problems as the general population. Sons of alcoholic fathers face up to nine times the usual risk. Even babies of alcoholics adopted into non-drinking homes have nearly the same risk of alcoholism as they would if they'd stayed with their biological parents, studies have shown.

Hidden Risks

HIDDEN RISKS | Variations in DNA, along with environmental factors, may play a role in drinking.



But untangling just which genes pass along the predisposition for problem drinking is devilishly difficult—largely because alcoholism itself is so complex. Genes that affect how fast the liver metabolizes alcohol and how the brain reacts to stress, reward and pleasure have all been implicated, as have genes for anxiety and depression. Some overlap with genes for nicotine, cocaine and other addictions.

About one in 10 Americans fit the criteria for alcohol dependence—mainly the inability to cut down—at some point in their lives. Environmental influences and social pressures also play complicated roles.

"All too often, you read that they've found a gene for this and a gene for that, and it's very rarely that simple. We don't expect to find a single gene in everyone," says Howard J. Edenberg, a professor of biochemistry and molecular biology at the Indiana University School of Medicine. Dr. Edenberg is one of four principal investigators in the government-funded Collaborative Study on the Genetics of Alcoholism (COGA), which has been tracking alcoholism in families since 1989. To date, COGA researchers have interviewed more than 14,000 people and sampled the DNA of 262 families. They've found evidence for several alcohol-related genes—and are increasingly convinced that different types of alcoholics reflect many genetic variations.

That idea is already showing promise in one area: identifying drugs that can help treat alcoholics based on their individual DNA profile. Most of the drugs currently on the market aim to cut alcohol cravings but don't work on everyone and compliance is a problem. That could change, experts say, if drugs could be targeted to patients with specific types of alcoholism.

Who Is an Alcoholic?

If you've done any three of these seven, you meet the criteria for alcohol-dependent:

- Drunk more or longer than you intended
- Been unable to stop or cut down
- Needed more alcohol to get the same effect
- Had withdrawal symptoms without it
- Spent an increasing amount of time drinking or recovering
- Neglected other activities due to drinking
- Continued to drink despite negative consequences
- About 5% of Americans currently meet the criteria, and more than 10% do at some time in their lives, according to the National Institute on Alcohol Abuse and Alcoholism.

Source: The Diagnostic and Statistical Manual of Mental Disorders

In one of the first such studies, reported in the American Journal of Psychiatry last month, alcoholics with two specific variations of a gene related to the neurotransmitter serotonin were able to cut their alcohol consumption significantly using the drug onadansetron. The anti-nausea drug often used with cancer treatments, also known as Zofran, blocks serotonin receptors and seems to diminish the buzz some alcoholics get from drinking. Subjects with different versions of the serotonin-receptor genes and those taking a placebo had less success cutting down.

"Imagine this scenario: You go to your doctor and say, 'I'm drinking and I need help,'" says Bankole Johnson, chairman of psychiatry and neurobehavioral sciences at the University of Virginia and the study's lead author. "The doctor can do a blood test and if you qualify, you can get tablets the next day and they're very likely to be effective. You don't even have to detox first. If you do not qualify, you don't waste your time with the medicine."

Since ondansetron has long been approved in larger doses, that scenario could be a reality in just a few years, predicts Dr. Johnson, who has a financial stake in a company that hopes to develop it as an alcohol treatment.

Several studies of alcohol-dependent patients treated with the drug naltrexone found that those with one variation of an opioid-receptor gene had a significantly lower rate of relapse than those with a different variation. Naltrexone, approved for alcoholism in 1995, seems to cut cravings by blocking the opioid release that addicts get from alcohol. Clinical trials are under way at the University of Pennsylvania that could also lead to more targeted uses of naltrexone.

Other studies of the opioid-receptor genes and alcoholism have been mixed. In fact, such associations are often found in one study and not in others. "With a disease like alcoholism, where dozens or hundreds of genes could have a small impact, to find any one of them in the size of the studies we are doing, you have to be sort of lucky enough to find the same gene," says Dr. Edenberg, "and the chance that the next group will be lucky is not that high."

The strongest gene associations found to date involve the so-called Asian flush. Roughly 40% of people of East Asian descent carry one or two gene variations that rapidly convert alcohol into the chemical acetaldehyde, which causes nausea, rapid heart beat and a severe flush. It's a strong deterrent to drinking, much like the drug disulfiram, or Antabuse. "You don't even need a genetic test to detect it," says David Goldman, chief of the Laboratory of Neurogenetics at the National Institute on Alcohol Abuse and Alcoholism. "If you have a dinner party and somebody has this variation, they'll turn red when they drink a glass of wine."

Researchers at the University of North Carolina-Chapel Hill have tentatively identified a similar "tipsy gene" that makes carriers feel inebriated after just one or two drinks. Between 10% and 20% of the population has this variation, which is also thought to protect against becoming alcohol-dependent.

Other people feel especially euphoric when they drink—probably due to variations in the neurotransmitter dopamine in the brain's reward circuits. A variation in the DRD2 dopamine receptor gene was identified in 1990 and found in a large number of alcoholics as well as drug addicts and smokers, although later studies have been mixed.

Last month, researchers at the University of California-San Diego reported that people with the DRD2 variation tend to have friends with the same genetic marker. That would give them both a biological compunction to drink and social reinforcement, the authors noted in the study published in the Proceedings of the National Academy of Sciences.

Like the Asian flush, some alcohol-related genes are particularly prevalent in certain ethnic or geographic groups. A recent study in Nature found that a rare variation in the HTR2b gene, linked to severe impulsiveness, is found almost exclusively in Finnish people. "Almost all these severely impulsive individuals are also alcoholic, and their worse impulsive problems occurred while they were drunk," says Dr. Goldman, the study's senior investigator.

Separately, variations in two genes for receptor to neurotransmitter neuropeptide Y, associated with stress and severe withdrawal symptoms from alcohol, are common to about one-quarter of the population. Clearly, not all those people are severe alcoholics.

So much is still unknown that most experts don't advise consumers to use genetic-testing services to try to understand their risk for complex conditions like alcoholism.

"Even if you learn you have a protective version of some gene, you could still be vulnerable due to a gene we haven't discovered yet," says Dr. Goldman, who adds that anyone with a family history of alcoholism should definitely approach alcohol with caution.

"Looking at your family history is simpler, cheaper and at the moment, gives you more information than a genetic test," says Dr. Edenberg. He also stresses that DNA is never destiny when human behavior is involved. "You can carry all kinds of genes, and if you manage to push away the glass or the bottle, you won't have an alcoholism problem."