One of the most important research questions in the field of addictionology is judging the influence of heredity versus the influence of the environment. Are there addiction genes? What is their actual influence? Is there more than one “addiction gene?”

Mark Schuckit, M.D., Professor of Psychiatry at the University of California Medical School and Veterans Affairs San Diego Healthcare System in San Diego, California is one of the world’s foremost researchers in the fields of alcoholism and addiction. He also has vast clinical experience with alcohol and drug-dependent patients.

Q: In your view, how many genes are associated with alcoholism and other addictions?

“If all of the genes that impact the risk of alcoholism are considered together, they explain about 60% or so of the risk. That means that environment explains 40% of the risk. Now, the picture is even a bit more complicated. Let me give you a parallel. Let’s say that you and I were talking about the genetic influences in heart attacks. I don’t know the specific data but it wouldn’t surprise me if 50–60% of the variance of risk for heart attacks might be explained by genes. But then we’d say how does it happen? And we would determine in some families what’s increasing the risk for heart attacks is high blood pressure, and the genes there really relate to high blood pressure, and the consequence for high blood pressure is an increased risk for heart disease. In other families they’re inheriting an increase in triglycerides, a bad blood fat, and it has nothing to do with what’s going on in the other families, it’s just in this group of families. Yet other families are carrying an increased risk for heart disease because they carry a heightened vulnerability toward the deterioration of the heart muscle called “cardiomyopathy.” So you could have asked me what proportion of the risk for heart attacks is genetically influenced. Well I don’t know, I’m going to guess 60% and then we would have to break the question down into what characteristics of each of these characteristics being genetically influenced are contributing to the risk?”

“So, let’s come back to alcoholism. I can think of about 5 different families of findings that probably contribute to that 60% genetic influence of alcoholism. First, there are the alcohol-metabolizing enzymes, those enzymes that break down alcohol. Real simple, substance alcohol; it’s broken down first into acetylaldehyde by one set of enzymes and then acetylaldehyde is broken down very quickly to carbon dioxide and water by a second set of enzymes. Well about one-half of Asian individuals, meaning Japanese, Chinese, Korean and related people, carry various forms of alcohol-metabolizing enzymes that either make them very very sick when they drink or enhance their sensitivity to alcohol. People carrying either of those types of genetic factors that impact on metabolism are at a relative decreased risk for alcoholism.”

“Totally unrelated to those genes that decrease the risk are genes that increase the alcoholism risk probably through disinhibition. Disinhibition here, behaviorally, is translated to being pretty impulsive and easily bored. But there’s also a component that you can see in the brain or other parts of the nervous system that relates to neuronal or electrical signs of disinhibition. In its extreme form, disinhibition is the antisocial
personality disorder in adulthood and conduct disorder in childhood. These are people representing the extreme form of disinhibition who basically act before they think. They don’t seem to care about the consequences of their problems and don’t seem to benefit from punishment. They also don’t tend to have a lot of empathy. If you have those characteristics (and those characteristics are genetically influenced) and you live in a heavy drinking society, it’s not surprising you’re going to have a great risk for problems with alcohol if you try to drink.”

“In fact this disinhibition mode, and there are probably a variety of genes that impact on disinhibition, this mode appears to increase your risk for alcohol and/or drug dependence whereas the alcohol-metabolizing enzyme pattern appears to only impact your risk for alcohol dependence.”

“A third category of findings that are genetically influenced are those people who inherit an increased risk (not predestination) for several major psychiatric disorders. The two that are easiest to talk about are schizophrenia and bipolar (manic depressive) disease. If you have those disorders, you are at increased risk for both alcohol and drug dependence.”

“There are a bunch of different theories about why you’re at an increased risk. My guess is that the poor judgment and other associated findings with those disorders, especially while manic or actively schizophrenic, make it very difficult for you to control your use of alcohol or other drugs.”

“There is a fourth factor and it’s the one that I study. It relates to the fact that if you live in a heavy drinking society and early in your drinking career when you expose yourself to alcohol, you discover that you need a fair amount of booze to have an effect. Other people are getting tipsy at two drinks and you’re not getting tipsy until four or five. That characteristic is first, genetically influenced and second, in a heavy drinking society, appears to be associated with drinking more often, using greater amounts when you drink, spending a lot more time drinking, and hanging out with a lot of other people who spend a lot of time drinking.”

“This fourth factor relates to an increased risk for alcohol dependence and there are probably a variety of genes that impact on whether somebody is a low responder to alcohol (meaning a lot of booze is needed to have an effect), fairly early in their career. We’re not going to go into the groups of findings.”

“So 60% of the risk for alcohol dependence appears to be genetically influenced. Some of that risk is related to a decrease in alcohol-metabolizing enzymes, some others appear to be related to high levels of disinhibition or impulsivity, others relate to psychiatric disorders, and yet others relate to something that is morally and psychologically neutral—it’s as if when you try to drink, you are going to have more trouble controlling your drinking because you’re not getting enough feedback concerning the effects of alcohol until the doses get pretty high. Our group and others are searching for these genes that are contributing to the low response to alcohol, which indirectly increases your risk for alcoholism in a heavy drinking society.”

Q: Can you talk more about the low response to alcohol as a factor?

“The low response to alcohol is something that if you carry that marker gene of alcoholism risk and you live in a society where nobody drinks, you’re not going to be any
different than anybody else. You won’t have an increased risk for psychiatric disorders, drug dependence, or anything. If you live in a society that drinks but you happen to be in a subgroup of people who say never, never, never get intoxicated (you drink for the taste, you only have two drinks, and you never go beyond that), well you’re not going to become alcoholic either. So it’s obvious that at least 40% of the picture for alcohol dependence, in the context of the low response to alcohol, is related to environment.”

“The specific neurochemical mechanisms that are responsible for the low response are difficult to pin down, as they are for almost any of the effects of alcohol, because alcohol goes almost everywhere in the brain and has a strong effect in many different brain areas. So from the standpoint of saying, ‘I’m going to figure out exactly what’s affected differently in these people and test it,’ you have to remember that these are very time-consuming expensive tests to do. We’re doing the reverse. We’re saying we know a low response to alcohol is genetically influenced; it’s seen before the alcoholism develops and on follow up, it predicts alcoholism later. What we are doing is saying, ‘Let us find the genes that appear to be related to the low response and from those genes we will gain clues and thus greater understanding of how the brains are responding differently because we’ll understand the mechanisms of the differences.’”

Q: In diagnosing alcoholism are there any short cuts?

“There is no short cut in diagnosing alcohol dependence. You’ve got to figure out what you’re trying to define. Are you studying the population and looking at the prevalence of drinking? You could also look for those factors that might contribute to the probability of developing some problems related to alcohol. About 40–60% of drinkers develop some problem, and most of them learn to modify their drinking and don’t go on to develop more severe problems. Or you can look at factors that contribute to the development of severe, pervasive, and persistent problems, which might be called “alcohol dependence.” That’s some of the work I’m doing.”