Genetic Predisposition to Addiction

A friend used to say “I don’t gamble because I have an addictive personality.” She felt that she was somehow predisposed to lose volitional control over her gambling. Indeed, curiosity about a putative genetic predisposition to addiction has not been restricted to a few would-be gambling addicts.

It is estimated that 40–60% of the “addiction” trait is controlled by gene products (Uhl, 2004). For example, the risk of becoming an alcoholic is elevated five- to eightfold if a primary relative is an alcoholic (Merikangas et al., 1998). For twins, genetically identical pairs show more sharing of alcoholism than fraternal twin pairs (Prescott & Kendler, 1999). But what are the genes implicated in addiction?

The thirst for understanding of, and potentially treatment for, addiction has pressured many to jump hastily to the conclusion that “THE” addiction gene has been identified. But it is clear that addiction, like any complex behavioral trait, is influenced by MANY genes and that these genes are only part of the story. An estimated 1500 (or more) genes influence addictive behaviors (Li et al., 2008). This complexity means that a prediction about an individual’s risk is impossibly hard to make. But it does not prevent us from trying to identify specific genes associated with addiction.

There are two main methods for identifying genes that predispose a person to addiction. The “candidate-gene” approach is hypothesis-driven but biased. It starts by hypothesizing that a specific gene (and therefore is biased to the genes one wants to investigate) involved in some drug-related process or pathway, if mutated, could influence the user’s experience with the drug. Many genes have been investigated in this candidate-gene approach (Goldman et al., 2005). For instance, alleles that manufacture nonoptimal versions of many drug-metabolizing enzymes result in a reduced frequency of drug use. The candidate-gene approach has also led to the analysis of genes that make receptors to which drugs or neurotransmitters bind. Because the reward pathway we previously discussed (Cunningham et al., 2012) is involved in addiction to many drugs, the dopamine-receptor encoding gene, D2DR, has been strongly implicated in a complex trait referred to as “reward deficiency syndrome” (Blum et al., 1996). In summary, the candidate-gene approach has led to many fruitful discoveries about genes that specifically influence drug response as well as those that might more generally predispose a person to use substances.

A “genome-surveillance” approach (Liu et al., 2005) is less biased because it makes no assumptions about the nature of the proteins encoded by addiction-influencing genes. However, this approach has been likened to finding the proverbial needle in the haystack. The human genome has some 25,000 genes. Nearly 1500 of them have been implicated in some way in addiction (Li et al., 2008). How do we find the ones correlated with a specific behavior? The answer involves years, an international collection of labs, and an extremely thorough bioinformatics analysis. In 2009, just such a bioinformatics approach investigated 30 years’ worth of research encompassing more than 2000 studies (Li & Burmeister, 2009, fig. 1). This analysis focused on five genetic pathways, including “old standards”
as well as new gene candidates that are implicated in addiction, generally. These pathways include the glutamate-reinforcing pathway, a pathway implicated in learning and memories related to addiction, and one that involves MAPK (mitogen-activated protein kinase), which may underlie synaptic changes that occur during use of addictive drugs. Again, they point to the importance of the reward pathway but also illuminate other important aspects of brain function, such as glutamate systems.

Although genetics can predispose a person to addiction, it is irresponsibly to imagine that a person can reasonably “blame” genes for addiction. Similarly, a person with predisposing alleles should not despair that addiction is inevitable. You have to participate in the use of an addictive substance to become an addict. Understanding one’s genetic predisposition can actually help an individual avoid behaviors that could lead to addiction. As with the woman who avoided gambling because she had an “addictive personality,” avoiding addictive habits is entirely possible. In addition, addictive patterns can also be turned around; this same courageous woman overcame a three-pack-a-day nicotine addiction that had plagued her for 46 years.

The next piece in this series will highlight the role of learning in addiction. Recent evidence suggests that this may be an important factor to consider. Join us to explore the evidence underlying this premise.

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References


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