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Genetics can influence addictive behaviour later in life, but linking genes to addiction is complicated.

GENETICS

No more addictive personality

The role of temperament, metabolism and development make the inheritance of addiction a complex affair.

BY MAIA SZALAVITZ

One drunkard begets another, wrote the Greek philosopher Plutarch nearly 2,000 years ago, demonstrating the age-old wisdom of the observation that alcoholism runs in families.

But determining exactly what it is that addicted parents pass down to their children has proved difficult. Scientists have searched for decades for an 'addictive personality' that leaves someone vulnerable to drug problems, but without success. Researchers have tried to identify the genes responsible for addiction, and they have examined the role of early exposure to trauma. Yet they have failed to isolate a single genetic factor that reliably distinguishes between the 10–20% of people who try alcohol or illegal drugs and get hooked and the majority who do not.

Now, however, research into genetics and epigenetics is finally starting to shed some light on the causes of addiction — and it turns out that the idea of an addictive personality is a myth. Instead, an enormous number of factors, ranging from early life trauma to genes that code for metabolic enzymes, have a role in how the genetics of addiction unfold. By understanding how these factors fit together, researchers hope to develop strategies for the prevention and treatment of addiction.

Plutarch was right to say that addiction is often a familial trait — and it seems that much of this risk is carried genetically. Joni Rutter, director of the Division of Basic Neuroscience and Behavioral Research at the US National Institute on Drug Abuse in Bethesda, Maryland, says that regardless of the drug involved, about 50% of the risk is genetic, within a range of about 40–60%.

Alcoholism is the most widely researched addiction because alcohol use has such a long history in many cultures. According to George Koob, director of the US National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, the children of people who are dependent on alcohol are 3–5 times more likely to develop the disorder than the rest of the population — and this risk is roughly the same regardless of whether they are raised by their alcohol-dependent parents or adopted by parents who are not dependent on alcohol. The condition is about 60% heritable, he says, adding that this is "reasonably high".

Researchers may have managed to demonstrate that genetic predispositions exist, but linking particular genes or traits with addictions has proved much more difficult. Initial genetic findings are often announced with great fanfare, only to fail in replication or be found to have extremely small effects. "Addiction is very heterogeneous," says Rutter, "There are many ways to get there."

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DRUGS AND DISORDERS

Some temperaments and disorders do raise the risk of addiction, however. About half of people with drug-use disorders have an additional psychiatric diagnosis, often a mood, anxiety or personality disorder. "What we're finding is that the addictive personality, if you will, is multifaceted," says Koob. "It doesn't really exist as an entity of its own." Some people with addictions have many personality traits, others have none, but only a few have all of them.

The personality disorder most commonly associated with addiction is antisocial personality disorder (ASPD), which involves dishonest, manipulative, insensitive and criminal behaviour. These characteristics make up the stereotype of someone with an addiction.

"Antisocial behaviour and alcoholism and drug abuse share a bunch of genetic risk factors," says Kenneth Kendler, professor of psychiatry and human genetics at Virginia Commonwealth University in Richmond, who has studied these links in twins. "That's replicated pretty robustly."

A large epidemiological study found that 18% of people with illegal-drug-use disorders have ASPD[1], as do 9% of people with alcohol-use disorders[2] — much higher than the 4% found in the general population. But although having high levels of antisocial traits is one of the best predictors of substance-use disorders, most people with addictions do not have fully fledged ASPD, and most people with ASPD do not have addictions.

Indeed, many people with substance dependency do not have abnormal levels of antisocial traits at all. However, because breaking the law is itself a diagnostic symptom for antisocial behaviour, this trait will automatically be associated with illegal drug addiction, even if the only laws that are violated are drug laws.

Moreover, being extremely sensitive and overly cautious — essentially the opposite of a callous, impulsive criminal — also raises the risk of addiction, although not by as much.

This suggests both that the stereotype of the addictive personality badly mischaracterizes many people who have a substance-use disorder, and that the genetic risk associated with ASPD does not account for most addictions.

Koob points out that addiction research, like the rest of psychiatry, is increasingly focusing on the genetics that underlie symptoms, such as poor impulse control, rather than on syndromes such as alcoholism or ASPD. "There are specific types of symptoms that have underlying neurobiological bases," he says.

These temperamental or physiological predispositions can potentially develop into many different disorders. For example, impulsivity could lead to a range of problems: it is a characteristic of addiction, ASPD, bipolar disorder, borderline personality disorder and many more. Impulsive behaviour also increases the risk that teenagers will try drugs — and make it harder for them to resist the urge when they want to stop.

By contrast, anxiety can drive addiction in a different way: people who feel anxious may take drugs to cope with social fears, and their difficulty stopping is not through a lack of control, but because of a lack of alternative ways to manage their emotions. This means that programmes must be tailored to individual needs, not based on the idea that all people with addictions are the same.

PHYSIOLOGICAL FACTORS

Personality is not the only way in which genes can influence addiction risk. The strongest and most replicated genetic risk factors for alcoholism involve genes linked to metabolism. These genes encode proteins that convert alcohol into acetaldehyde, and acetaldehyde into acetate. Acetaldehyde is particularly toxic, and genes that cause it to build up in the blood, such as a variant of *ALDH2*, make even light drinking unpleasant. "When it is floating in their system, people don't like it," says Rutter. "They get really hot or feel nauseous." Hangovers and the anti-alcohol drug disulfiram produce pretty much the same effect.

Genes that lead to slow alcohol metabolism are common in the Asian population. A 2006 meta-analysis of 15 studies included 4,500 Chinese, Japanese, Korean and Thai participants who were tested for genes related to the metabolism of acetaldehyde and acetate. The largest protective factor was the *ALDH2* variant, which makes people nine times less likely to develop alcoholism than those with other variants of the gene[3].

But even a gene that provides this much protection can be overridden by environmental pressures. Between 1979 and 1992, for example, the percentage of Japanese people who misused alcohol and who had this variant rose from 2.5% to 13%, as a heavy-drinking culture developed among businessmen that made it much harder to refuse to drink.

One gene that is strongly associated with cigarette addiction, *CHRNA5*, has essentially the opposite effect on smoking risk as *ALDH2* variant has for alcohol. Having just a single variant can double the risk of nicotine addiction[4]. This link is one of the best supported in any disease, not just in addiction, Rutter says.

Researchers initially thought that the *CHRNA5* variant, which codes for a subunit of the acetylcholine receptor that is affected by nicotine, would make nicotine more pleasurable. This would explain why people who smoke and who have the variant smoke more heavily than those without it. But instead, it softens nicotine's initial negative effects. Nearly everyone who has ever smoked reports that the first time is nauseating at best. "When I tried cigarettes when I was a kid, I turned green and hated it," says Rutter.

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But people with the *CHRNA5* variant have a less unpleasant experience, says Paul Kenny, a pharmacologist at New York's Mount Sinai Hospital. "Instead of the drug being more rewarding, what happened was that the aversive effects were diminished," he says.

Investigation of the *CHRNA5* gene in knockout mice showed that it is active in a brain region called the habenula, which is involved in avoidance and aversion, even though it had not previously been strongly linked with addiction. The evidence also suggests that heavy smoking may damage the habenula by harming the neurons that inhibit it. This would create strong negative feelings and distress in those who smoke, which they may try to fight with even more nicotine.

ADDICTION AND DEVELOPMENT

Epigenetic mechanisms, which control the activity of genes by switching them on and off, are also being seen as increasingly important in addictions. Kenny's lab studies these as well and found that one way that addiction can epigenetically 'rewire' the brain is by turning on genes that are normally activated only during brain development.

For instance, a mutation in the *MECP2* gene is known to cause Rett syndrome, a developmental disorder found mainly in girls that is associated with intellectual disability and autistic symptoms. During fetal and childhood development, *MECP2* regulates nerve-cell growth, and then it is silenced. However, when rats are allowed to binge on cocaine, *Mecp2* expression "goes through the roof", says Kenny. Bingeing on cocaine rewires the brain, turning on genes that are usually quiescent in adults.

Other animal experiments have shown that switching off the gene in the reward regions reduces cocaine intake[5]. This suggests that the aberrant learning, which resists the negative consequences of addiction, may be especially deeply engrained. But the actions of *MECP2* have not been studied in normal emotional learning processes in humans that activate similar circuitry, such as falling in love, so it is not clear whether this is unique to addiction. It is also not known whether these genes are normally reactivated during adolescent brain development, which might help to explain why adolescence and early adulthood is the highest-risk period for addictions. Because Rett syndrome is profoundly disabling, those affected are rarely exposed to drugs, so it is not known how the disorder affects addiction risk.

Kenny thinks that other genes linked to developmental disorders may also be important in addictions — and not just in people who have these conditions, whose brains are wired differently from the start. If addiction does reactivate brain-development genes, more common variants could be involved. "We should be looking for genes that cause developmental disorders," he says.

Another factor that affects both epigenetics and addiction risk is childhood trauma. Severe stress in early life is known to dramatically increase the risk of addiction, and the risk increases with greater trauma exposure. For example, a recent study of the entire Swedish population showed that people who as children either lost their parents, experienced a parent's diagnosis of cancer, or witnessed domestic violence had twice the risk of a substance-use disorder later in life compared with those who did not have such stressful experiences[6].

Indeed, some risk genes, such as those linked to the serotonin transporter, may not cause any problems unless there is a stressful early environment. Both chronic stress and addiction can induce some of the same epigenetic changes in stress systems and in those involved with pleasure, which may partly explain why addiction and trauma are so tightly linked. "Early life experience may dictate whether or not those genes or variations in those genes in those different circumstances tend to come into play," says Rutter.

Given the increasing evidence of how varied addiction is, treatment and prevention programmes will need to be significantly updated. Some researchers are trying to work out how to target prevention to particular temperaments, rather than attempt to reach both the anxious and the impulsive with the same message.

"That's the blessing and the curse," says Rutter. "There are many ways to get there, but that also means many ways to intervene." ■

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