Drugs that target ‘epigenetic scars’ may reverse drug addiction

Does drug addiction have a genetic basis?

That’s a question that has for years puzzled researchers, doctors, social workers, and leaders as they look for treatment solutions and possibly cures for drug addiction. The National Council on Alcohol and Drug Dependence (NCADD) states that about half of a person’s risk for drug dependency comes from genetics. But scientists have never been able to identify a single “drug addiction gene” and instead researchers are continuously adding to a long list of possible genes that may play a role in drug dependency. A few examples include variants of genes for receptors for the neurotransmitters acetylcholine, dopamine and serotonin, as well as genes that code for neuromodulators, molecules released in the brain that affect a large number of brain cells, like neuropeptide Y and tyramine.

Furthermore, while 50 percent may sound like a lot, it also means that 50 percent of people who struggle with dependency don’t have any discernible genetic predisposition. In fact, the NCADD, as well as other organizations tend to downplay the role a person’s genes play in their susceptibility to drug addiction. Former acting director of the National Institute on Drug Abuse (NIDA) Glen Hanson notes:

> …just because you are vulnerable, doesn’t mean its inevitable. Just because you are prone to addiction doesn’t mean you’re going to become addicted during your life… It just says that if circumstances are right the chances are that you’ll get into difficulty are greater than most people.

Part of this message is certainly rooted in fighting a defeatist attitude among recovering addicts, but part of it is rooted in neuroscience and genetics. The laundry list of possible genetic sources for drug dependency insinuates that drug addiction may not be hard written *into* our DNA, but instead may be hard wired *onto* our DNA in the form of epigenetics.

Genetics vs. Epigenetics

Epigenetics and genetics are very intimately entwined, but have distinctly different mechanisms for affecting a person’s phenotype — their observable traits. The genetic component of phenotype comes from genes in the form of strands of DNA that are inherited from mom and dad. The epigenetic component comes from how the DNA is packed in a cell, which drives the activity of a gene. While a person’s genome, outside of the occasional mutations, comes entirely from inheritance, a person’s epigenome is heavily influenced by both a person’s environment and probably also has some degree of inheritance.

Epigenetic changes are physical alterations to the DNA that don’t change the sequence of a gene and scientists have found that in response to addictive substances, these changes are profound and can happen rapidly. One of the leaders in epigenetic and drug addiction research, Dr. Eric Nestler MD, PhD describes epigenetic changes in response to drugs as “scars”:

> [In our research] we are looking at how drugs change the brain to cause lifelong

> abnormalities… It still has to be proven, but we think that taking a drug changes certain nerve cells to make a person continue to want the drug. These epigenetic changes actually 'scar' the cell to make it respond differently…

These epigenetic 'scars' have been detected postmortem in drug users by researchers at the Icahn School of Medicine at Mount Sinai. They found significant changes related to glutamate — a neurotransmitter — pathways in the striatum, a part of the brain involved in the reward system. The changes were also in a dose-dependent manner, meaning alterations were most pronounced in long-term users.

While it may seem intuitive that these changes occur during exposure to the drug, studies have actually found that they actually may occur during withdrawal — a period of abrupt discontinuation of the drug. Methylation — one of the main mechanisms of epigenetics — is a process by which a cell adds a methyl group (a small molecule composed of a carbon and a few hydrogens) to a gene or a region of the genome with the result normally being the shutting off of a gene.

In a study published in the *Journal of Neuroscience* researchers found that hundreds of genes underwent methylation while a drug-addicted subject underwent withdrawal. Many of the genes that were methylated were also genes that have been implicated previous in drug addiction. Interestingly, subjects that received, during the withdrawal state, a drug that inhibits methylation reversed the addictive behavior.

Epigenetics and Genetics

Dr. Nestler's lab has actually been able to show how epigenetic regulation of just one gene can influence drug addicition. In a publications from October of 2014 in *Nature Neuroscience,* his team found that epigenetic regulation in the nucleus accumbens, a brain reward region, of just one gene, was sufficient to control drug dependency. The gene they focused on was *FosB* which has been previously implicated as vital for neural plasticity and has been associated with extensively with drug addiction. The results showed that when that using histone acetylation, an epigenetic activating mechanism, *FosB* was sufficient to enhance the sensitizing effects of cocaine on the brain, while methylating the gene produced the reverse affect.

But despite his own work which has extensively shown a strong connection between epigenetics and drug addiction, Dr. Nestler believes that both epigenetics and genetics play important roles in drug addiction, stating that:

> A person's DNA sequence provides a baseline sensitivity, and then their lifetime experience and drug exposures either cause scars or protective factors.

This sounds similar to Hanson's belief that certain genes doesn't make drug addiction inevitable, but 'the right circumstances', i.e. environment and epigenetics, creates addiction. For example, different versions of a gene could increase or decrease a person's sensitivity to a particular drug, while epigenetic changes (possibly during withdrawal) could create the cellular underpinnings of an addiction. This relationship lends credence to the idea that we need to look at the effects of both genetics and epigenetics

when researching the cellular mechanism of drug addiction. But on the other hand, data has supported the notion that targeting the epigenetic scars offers a real possibility to treat drug addiction. So while they both may matter for establishing addiction, one seems to be more promising in reversing it.

Nicholas Staropoli is the associate director of GLP and director of the Epigenetics Literacy Project. He has an M.A. in biology from DePaul University and a B.S. in biomedical sciences from Marist College. Follow him on twitter @NickfrmBoston.