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Genetics and Epigenetics of Addiction

Genetics: the Blueprint of Health and Disease

Why do some people become addicted while others don't? Family studies that include identical twins, fraternal twins, adoptees, and siblings suggest that as much as half of a person's risk of becoming addicted to nicotine, alcohol, or other drugs depends on his or her genetic makeup. Pinning down the biological basis for this risk is an important avenue of research for scientists trying to solve the problem of drug addiction.

Genes—functional units of DNA that make up the human genome—provide the information that directs a body's basic cellular activities. Research on the human genome has shown that, on average, the DNA sequences of any two people are 99.9 percent the same. However, that 0.1 percent variation is profoundly important—it's still 3 million differences in the nearly 3 billion base pairs of DNA sequence! These differences contribute to visible variations, like height and hair color, and invisible traits, such as increased risk for or protection from certain diseases such as heart attack, stroke, diabetes, and addiction.

Some diseases, such as sickle cell anemia or cystic fibrosis, are caused by an error, known as a *mutation*, in a single gene. Some mutations, like the BRCA 1 and 2 mutations that are linked to a much higher risk of breast and ovarian cancer, have become critical medical tools in evaluating a patient's risk for serious diseases. Medical researchers have had striking success at unraveling the genetics of these single-gene disorders, though finding treatments or cures has not been as simple. Most diseases, including addiction, are complex, and variations in many different genes contribute to a person's overall level of risk or protection. The good news is that scientists are actively pursuing many more paths to treatment and prevention of these more complex illnesses.



Purified DNA fluorescing orange under UV light

Photo by Mike Mitchell, NCI Visuals Online/
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Linking Genes to Health: Genome-Wide Association Studies

Recent advances in DNA analysis are helping researchers untangle complex genetic interactions by examining a person's entire genome all at once. Technologies such as genome-wide association studies (GWAS), whole genome sequencing, and exome sequencing (looking at just the protein-coding genes) identify subtle variations in DNA sequence called *single-nucleotide polymorphisms* (SNPs). SNPs are differences in just a single letter of the genetic code from one person to another. If a SNP appears more often in people with a disease than those without, it is thought to either directly affect susceptibility to that disease or be a marker for another variation that does.

GWAS and sequencing are extremely powerful tools because they can find a connection between a known gene or genes and a disorder, and can identify genes that may have been overlooked or were previously unknown.

Through these methods, scientists can gather more evidence from affected families or use animal models and biochemical experiments to verify and understand the link between a gene and the risk of addiction. These findings would then be the basis for developing new treatment and intervention approaches.

Research Advance: Genetic Variation May Increase Risk for Nicotine Addiction and Lung Cancer

NIDA-sponsored research has led to an understanding of how certain gene variants are linked to nicotine dependence.¹⁻⁵ This major breakthrough has paved the way for analysis in animal models, revealing the importance of these variants in the brain's response to nicotine, including withdrawal and nicotine aversion—the body's resistance to nicotine addiction.⁶⁻¹¹ In addition, some genetic variants are associated with a two- to threefold increase in risk for lung cancer, which may be even higher among those who smoke fewer than 20 cigarettes a day.¹² These discoveries have inspired investigators to develop new medications¹³ and other ways that affect how agents bind to brain receptors.¹⁴ Gene variants in these nicotinic receptors as well as enzymes that metabolize nicotine are also beginning to provide clinically useful markers to guide treatment decisions.¹⁵⁻¹⁹

The Role of the Environment in Diseases like Addiction



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That old saying "nature or nurture" might be better phrased "nature *and* nurture" because research shows that a person's health is the result of dynamic interactions between genes and the environment. For example, both genetics and lifestyle factors—such as diet, physical activity, and stress—affect high blood pressure risk. NIDA research has led to discoveries about how a person's surroundings affect drug use in particular.

For example, a community that provides healthy after-school activities has been shown to reduce vulnerability to drug addiction, and recent data show that access to exercise can discourage drug-seeking behavior, an effect that is more pronounced in males than in females.²⁰⁻²²

In addition, studies suggest that an animal's drug use can be affected by that of its cage mate,^{23, 24} showing that some social influences can enhance risk or protection. In addition, exposure to drugs or stress in a person's social or cultural environment can alter both gene expression and gene function, which, in some cases, may persist throughout a person's life. Research also suggests that genes can play a part in how a person responds to his or her environment, placing some people at higher risk for disease than others.

The Promise of BIG DATA in Genetics Research

Scientists doing genetics research have collected millions of data points that could be of use to other scientists. However, different software systems and measurement formats have made sharing data sets difficult. NIH has created "Big Data" policies that will enable better sharing of information (<https://gds.nih.gov/03policy2.html>). When the data can be combined and harmonized, a process called data integration, the chances of identifying new genetic information that could give rise to new disease insights is amplified.



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Identical twins are born with the same genetic footprint. Over time, as they are exposed to differences in their environments and make choices of their own, their DNA gets marked with information that can affect their behavior, their risk of addiction, and even their response to treatment. Some of these changes can be passed on to later generations. This is called epigenetics.

Epigenetics: Where Genes Meet the Environment

Epigenetics is the study of functional, and sometimes inherited, changes in the regulation of gene activity and expression that are not dependent on gene sequence.²⁵ "Epi-" itself means "above" or "in addition to." Environmental exposures or choices people make can actually "mark"—or remodel—the structure of DNA at the cell level or even at the level of the whole organism. So, although each cell type in the human body effectively contains the same genetic information, epigenetic regulatory systems enable the development of different cell types (e.g., skin, liver, or nerve cells) in response to the environment. These epigenetic marks can affect health and even the expression of the traits passed to children. For example, when a person uses cocaine, it can mark the DNA, increasing the production of proteins common in addiction. Increased levels of these altered proteins correspond with drug-seeking behaviors in animals.

Histones, as another example, are like protein spools that provide an organizational structure for genes. Genes coil around histones, tightening or loosening to control gene expression. Drug exposure can affect specific histones, modifying gene expression in localized brain regions.²⁶ Science has shown that manipulation of histone-modifying enzymes and binding proteins may have promise in treating substance use disorders.²⁷⁻²⁹

The development of multidimensional data sets that include and integrate genetic and epigenetic information provide unique insights into the molecular genetic processes underlying the causes and consequences of drug addiction. Studying and using these data types to identify biological factors involved in substance abuse is increasingly important because technologic advances have improved the ability of researchers to single out individual genes or brain processes that may inform new prevention and treatment interventions.

Genetics and Precision Medicine

Clinicians often find substantial variability in how individual patients respond to treatment. Part of that variability is due to genetics. Genes influence the numbers and types of receptors in peoples' brains, how quickly their bodies metabolize drugs, and how well they respond to different medications. Learning more about the genetic, epigenetic, and neurobiological bases of addiction will eventually advance the science of addiction.

Scientists will be able to translate this knowledge into new treatments directed at specific targets in the brain or to treatment approaches that can be customized for each patient—called *pharmacogenomics*. This emerging science, often called precision medicine, promises to harness the power of genomic information to improve treatments for addiction by tailoring the treatment to the person's specific genetic makeup. By knowing a person's genomic information, health care providers will be better equipped to match patients with the most suitable treatments and medication dosages, and to avoid or minimize adverse reactions.

Research Advance: Genetics and Smoking Cessation

To determine the best course of smoking cessation treatment, our ultimate goal is for clinicians to combine knowledge of a person's genetic data; how fast the person's body metabolizes nicotine; the person's age, sex, and race; and the number of cigarettes smoked per day to provide the best treatment regimen. Current research suggests that smokers with high-risk genotypes are more likely to receive greater benefits from certain medications. Also, the rate of nicotine metabolism can help inform treatment decisions. One study found that "normal" nicotine metabolizers did better with the help of the drug varenicline (Chantix®) while "slow" metabolizers did better with the nicotine patch.¹⁹ Helping people quit smoking by understanding the underlying genetic factors underscores its enormous clinical and public health potential related to long-term smoking.¹⁸

NIDA's Genetics Research Program

The mission of the Division of Neuroscience and Behavior (DNB) is to advance the science of drug abuse and addiction through basic and clinical biomedical neuroscience and behavioral research. The Genetics, Epigenetics, and Developmental Neuroscience Branch supports research on the genetics, epigenetics, and developmental mechanisms that underlie substance abuse and addiction.

The DNB accomplishes its mission by developing and supporting an extramural research program that provides an understanding of the neurobiological and behavioral mechanisms of drugs of abuse and its consequences. The research supported by DNB provides important fundamental information to prevent and/or intervene in drug abuse and addiction.

Learn More

For more information about genetics and drug abuse, visit:

www.drugabuse.gov/about-nida/organization/divisions/division-basic-neuroscience-behavioral-research-dbnbr/genetics-molecular-neurobiology-research-branch-gmnrp

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