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## Genes and Addiction

“Meth became the most important thing in my life. Everything I did, I did to get more meth, to stay high. I didn't know what else to do...I went to work high and I was tired because I hadn't slept in days... I changed my values so they matched my behavior; it was "right" if it got me high.... Before I used that first line, I did have a choice. After that, I was in the grip of a disease more powerful than myself. I lived to use and used to live. There was no choice, I had to get high. I did anything to get more meth.”

–Abby Betsinger (2006), DrugFree.org

Addiction is a powerful motivator: first starting as an experiment, subsequent usage of drugs may cause many curious people to fall prey to the ravages of addiction. Continual need for the drug causes many to disregard all aspects of life, like in Abby's case, resulting in health issues, making poor choices for the sake of obtaining drugs, and alienating all friends and family to experience the next transient moment of euphoria. These are not issues relegated to a small number of the population however: in fact, there are 1.3 billion smokers, 2 billion alcohol users, and 185 million illicit drug users worldwide (Li and Burmeister, 2009). By the sheer proportions alone, addiction is a problematic disease that must be examined and addressed for the promotion of a healthy world.

But what causes this drastic downturn in behavior? The psychological mechanisms of addiction can be elucidated through the brain's reward system. Drugs of abuse such as heroin, cocaine, methamphetamine, alcohol, and cigarettes increase the activity of dopamine on the brain; for example, cocaine blocks the transporter that reuptakes dopamine into the presynaptic bouton thereby prolonging the generated pleasurable feelings. This euphoria stimulates the user in their reward seeking behavior to again recreate those feelings. The value that is placed on these drugs thus increases linearly without a point at which the value of the drug caps (McClure, 2008). Drug abusers continually seek out their next "hit" to experience the same extent of pleasure they had before; but already their bodies are producing CREB, a transcription factor activated by cyclic AMP. CREB activates genes to produce the protein dynorphin which inhibits dopamine release and the brain's reward system. More dopamine is needed to overcome CREB's effects resulting in continued usage and classic addiction (Madras, 2006, p. 5).

Addiction through mere sustained usage is not the complete story however. Twin and family studies suggest that genetics plays a significant role in increasing the probability of continued use. In one particular study, it was found that the genetic influence for lifetime smoking, 46% for women and 57% for men, was similar for twins segregated by age group and country (Finland, Sweden and Australia) (Madden, 2004, p. 82-97). This probability of increased drug dependence from 40-60% has been recreated in multiple studies. The heritability of addiction to various substances points to several genes affecting how the abused drugs are received in the body. To name a few, FAAH or fatty acid amide hydroxylase, NRXN1 or Neurexin1, CHRNAB3 or cholinergic nicotinic receptor gene, and CYP2A6 or cytochrome P450 are all purported factors that lead to increased probability of

addiction. These genes were discovered in genome wide association studies or other forms of genetic analysis.

In one study conducted in 2002 at the Scripps Research Institute, the homozygous form of the single nucleotide polymorphism of fatty acid amide hydroxylase (FAAH) results in addictive illicit and nonillicit drug and alcohol use (Sipe, Chiang, Gerber, Beutler, & Cravatt, 2002). FAAH's primary mode of action is the hydrolysis of endogenous fatty acid amides—a class of substances in the body called endocannabinoids that activate cannabinoid receptors—thereby terminating their activity. The SNP's missense mutation from cytosine to adenine causes a proline residue (which is conserved across mammals such as humans, rats, mice, pigs, and bovine) to convert into threonine; this produces an FAAH enzyme that is normal catalytically but degrades much more easily to proteases. Since less FAAH is present due to ease of degradation, the endocannabinoids can activate a greater amount of cannabinoid receptors. In turn, the body's internal cannabinoid signaling system is abnormal deriving a greater effect when external forms of cannabinoids are abused.

In addition to FAAH, the genes Neurexin1 (NRXN1) and the B3 cholinergic receptor (CHRN3) were determined as genes involved in nicotine dependence in a particular genome-wide association study (Bierut, et al., 2006). Since addiction is an imbalance between excitatory and inhibitory neurotransmission, NRXN1 contributes to the differential decision for a postsynaptic neuron to become inhibitory or excitatory through the stimulation of GABA or glutamate. (Bierut) If NRXN1 decides to induce many postsynaptic neurons to become excitatory, then under the effects of a stimulant such as cocaine or methamphetamines, there is the classic great surge of euphoria. In the case of

CHRN3 which are ligand-gated ion channels, nicotine is the agonist which causes fast signaling at the synapse for the release of dopamine.

Apart from genes that cause an increased propensity for sustained usage, Pianezza et al. showed that the cytochrome p450 gene enabled protection against a smoker becoming tobacco-dependent (Pianezza, Sellers, & Tyndale, 1998). CYP2A6 normally aids in the oxidation of nicotine to cotinine in the human liver; but with a mutant CYP2A6 gene, the nicotine does not fully metabolize. The smokers with these null alleles do not become tobacco-dependent and therefore smoke a fewer amount of cigarettes than those who have normal, functional CYP2A6 genes. It was also found that the CYP2A6-null alleles offer some defense against cancer as the nitrosamines in cigarettes are not as efficiently activated to carcinogens. However, follow-up studies attempting to replicate these results by Pianezza et al. were not able to obtain these exact results in such strong association: Sabol and Hamer (Sabol & Hamer, 1999) did not find any smoking association with CYP2A6, and Gambier et al. (Gambier, Marie, Pfister, & Visvikis-Siest, 2005) only found that individuals with different variants of CYP2A6 had significantly different levels of cigarette consumption.

Current treatment for addiction has no panacea but involves treatment plans individual for each drug user's detoxification. Frequently, the drug user enrolls in a rehabilitation clinic where he or she engages in counseling programs which identify the problematic behaviors leading to their addiction. Additionally, medications such as methadone and buprenorphine are available that alleviate the initial withdrawal effects; affecting the same area as heroin and morphine, they act on the brain in a more controlled fashion due to slow onset and longer persistence of the stimulating effect (Abuse, 2008).

Thus, there is an absence of the highly addictive burst of euphoria associated with abused drugs as well as an absence of intense, debilitating withdrawal effects. The most important facet for all present treatment of addiction is the prevention of relapse through continual care for addiction.

As more and more is being learned about the mechanisms and genetics behind addiction, the future of drug and alcohol addiction treatment offers promising alternative to current treatments. Pharmacogenomics, which is the usage of genes or SNPs to maximize the efficacy of drug therapies, could be part of the solution: drug treatment is tailored to the individual's genes that modulate how the drug is received in relation to their addictive behavior. Already at the University of Colorado at Boulder, participants of a study were found to be differentially affected by naltrexone which reduces the effects of alcohol in terms of stimulation, enjoyment, positive mood, and craving: those with the G allele in the mu-opioid receptor gene (OPRM1) were found to derive a greater effect from the naltrexone than those without the allele (Ray & Hutchison, 2007). Further as reported by Dr. Nora D. Volkow, director of the National Institute on Drug Abuse, vaccines are being developed against addiction and relapse (Volkow, 2008). These vaccines would spur the body to produce antibodies which upon binding with the drug molecules forms a compound too large to cross the blood-brain barrier. Specifically, Nabi Biopharmaceuticals is currently developing the NicVAX nicotine vaccine: preliminary research has resulted in 16% of NicVAX recipients' cessation of smoking compared to the 6% of those receiving placebos who quit smoking.

As was demonstrated, there are many genes purported to genetically predispose a person to addiction such as FAAH, NRXN1, CHRN3, and CYP2A6 (in addition to all of the

genes that were not discussed in this paper). These genes and all those genes lending to the major problem that controlling addiction is offers hope in new avenues of technology for those in the addictive grasp of drugs or alcohol. Addiction is a complex disease: not only does heredity factor into addictive behavior but the environment plays a major role as well. The question arises then how much of the addiction is really genetics and how much of it is an individual's choice: genes such as FAAH increase the probability of sustained smoking, but the decision of whether or not to take that first hit or sip is almost entirely up to the individual. The mistake must not be made of falling into the genetic trap by automatically accepting these genes as explanations for addiction; it is not so clear what the role of some of these genes discovered in studies is. As discussed previously, it was difficult to duplicate the results of the proposed CYP2A6 addiction gene. Much more research is needed to determine unwaveringly the specific roles of genes in addiction. But this is not to belittle the contribution of the genes discovered so far as they lend to progress for understanding addiction's nature.

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