

Chapter 2

The Genetic Basis of Addiction

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Introduction

Addiction is a complex disease influenced by genetic, environmental, developmental, and social factors. Once viewed as a moral weakness in character, substance use disorders are now defined as maladaptive patterns of substance use leading to inability to control use despite significant consequences in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1]. Family, adoption, and twin studies support the importance of biologic factors and prompted the search for an inherited link. Because addiction is a heterogeneous and complex disorder without a clear Mendelian pattern, identification of specific genes has proved challenging.

This chapter reviews the role of genetic factors, molecular mechanisms, and related imaging of the addicted brain. Although drug dependency is commonly associated with illegal substances (e.g., opioids, cocaine, marijuana, and methamphetamine), legal substances such as alcohol and nicotine must also be considered. Because there is a preponderance of data on alcohol and tobacco use, these drugs are emphasized throughout the chapter though the concepts are, in many cases, applicable to other substances.

Genetic Factors in Substance Abuse

Two primary strategies exist for identifying genetic factors in substance abuse. The first is the candidate gene approach in which techniques are developed to target

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specific genes that may determine susceptibility to addiction. The details of these techniques are beyond the scope of this chapter but involve dissection of deoxyribonucleic acid (DNA) into specific nucleotide patterns called markers [2]. These markers are then examined to determine if there is a linkage (when the marker is transmitted along with the disease in families) or an association (when a marker allele is seen more commonly among diseased individuals in a population). The second approach is the genome-wide linkage approach in which the whole genome is studied blindly to determine points of integration among addicted phenotypes.

Candidate Genes

Candidate genes thought to influence the pathogenesis of dependence and addiction have been postulated to include genes that act on neural mechanisms involved in reward and behavior (e.g., dopamine receptor and catechol-O-methyltransferase) and genes that encode enzymes involved in alcohol metabolism (alcohol dehydrogenase and aldehyde dehydrogenase).

The first report of an “alcoholism gene” occurred in 1990. Blum et al. [3] identified a gene for the D₂ dopamine receptor (DRD2) that was thought to be associated with risk for developing alcoholism. Dopamine’s role in the mesolimbic reward circuit had been clearly established at this point; so, Blum’s idea was widely received. Since then, the role of DRD2 has been the subject of much debate and remains controversial [4, 5]. Gamma-aminobutyric acid (GABA) is the major central inhibitory neurotransmitter and the genes for its receptor are also implicated in alcoholism. Studies have determined that GABA receptors play an important role in the depressant effects of alcoholism [6]. It appears that two GABA_A receptor genes are related to the risk of developing alcoholism [7]. In addition to the dopaminergic and GABAergic systems, the serotonergic system also appears to be a source of genetic variation favoring addiction. Various genes that encode serotonin receptors and transporters have also been implicated in the development of addiction [8, 9].

Catechol-O-methyltransferase (COMT) is one of several enzymes responsible for metabolizing and inactivating the catecholamine neurotransmitters, including dopamine and norepinephrine. The COMT protein is coded by gene *COMT* in which G to A polymorphisms are common at codon position 158 resulting in the amino acids valine (Val158) or methionine (Met158), respectively. The allelic variant, Val158, is well studied and is known to result in a fourfold increase in enzyme activity [10]. The prefrontal cortex, known to be closely linked to a person’s personality and executive function, is highly dependent on COMT for regulation of dopamine activity as there are few dopamine transporters [11]. The Val158 allele results in lower dopamine concentrations in the prefrontal cortex and is associated with inefficient frontal lobe function and behavior disinhibition leading to impulsive behavior

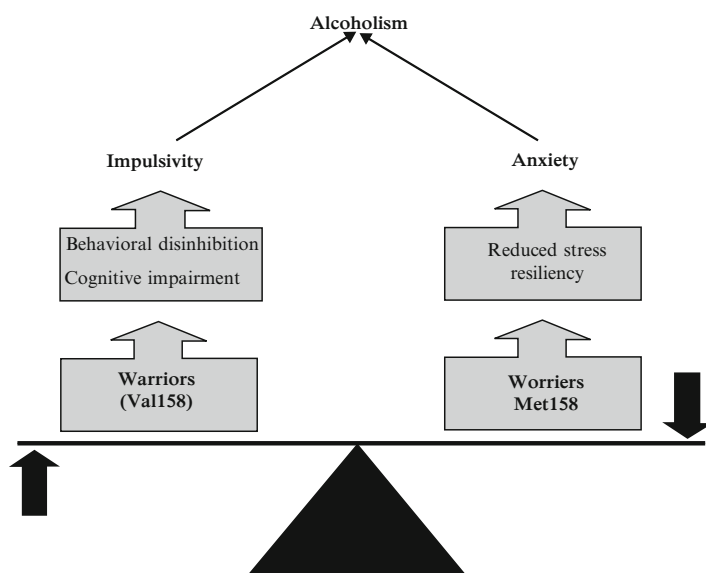


Fig. 2.1 Catechol-O-Methyltransferase (COMT): the warrior (Val158) versus worrier (Met158) model (From Ducci F. Genetic approaches to addiction: genes and alcohol. *Addiction*. 2008;103:1414–1428)

[12, 13]. The Met158 allele is associated with better cognitive performance but less stress resiliency, increased levels of anxiety [14], and increased reactivity of the amygdala to unpleasant stimuli [15]. For any given individual, a balance exists between “warriors” (Val158) and ‘worriers’ (Met158) (Fig. 2.1) and though Val158 is most commonly associated with addiction there are subpopulations in which risk appears to be associated with Met158 [16]. Numerous studies have examined the potential association of COMT with personality traits and psychiatric disorders, including obsessive–compulsive disorder, bipolar disorder, and drug dependence with somewhat inconsistent results [17].

Polymorphisms of alcohol metabolizing-enzyme genes have consistently demonstrated an association with alcohol susceptibility and include alcohol dehydrogenase IB (*ADH1B*) and aldehyde dehydrogenase (*ALDH2*). Ethanol is metabolized by the enzyme alcohol dehydrogenase to a toxic intermediate, acetaldehyde. Acetaldehyde is then metabolized by the enzyme aldehyde dehydrogenase to acetate. Acetaldehyde accumulation occurs with high activity of *ADH1B* or low activity of *ALDH2* which results in flushing reaction with hypotension, palpitations, and tachycardia. These disulfiram [ANTIBUSE]-like reaction seems to confer protection against the development of alcoholism. Slower-metabolizing forms *ADH1B* and faster-metabolizing forms of *ALDH2* appear to confer an increased risk of alcoholism and drug dependence [18].

Genome-Wide Scans

To detect genetic differentiation among populations, genome linkage and genome association studies are performed to identify chromosomal regions and genes implicated in addiction. Genome-wide linkage studies attempt to identify risk loci from a panel of polymorphisms in family-based samples. These studies identify chromosomal regions for risk-influencing loci that are shared within the family. To be complete, these studies employ markers that map throughout the entire genome. Genome-wide association studies are performed in very large data sets using panels of more than 500,000 polymorphisms. These association studies have increased power for detecting smaller chromosomal areas compared to the family-based linkage studies [16].

In response to the positive genetic correlations evidenced by twin, family, and adoption studies, the National Institute on Alcohol Abuse and Alcoholism funded the Collaborative Studies on Genetics of Alcoholism (COGA) [19]. Since 1989, the COGA investigators have been performing genetic linkage studies to identify genes that affect the risk for alcoholism in over 300 densely affected families. The COGA has successfully detected at least three genes within linked chromosomal regions (*GABRA2*, *CHRM2*, and *ADH4*) that contribute to predisposition to alcoholism and related disorders [20].

It is most likely that most of the genetic risk associated with drug dependency is not attributed to individual alleles. Genome-wide studies, once thought to hold all the answers, are also somewhat problematic. Association studies are complicated by other co-morbid traits such as bipolar affective disorder and schizophrenia, and appear to be falling short of the definitive results. In addition, a strong genetic association is sometimes difficult to identify in linkage studies [21]. This is most likely explained by the heterogeneity of addiction, population variation, and random variation.

Heritability

It is thought that genetics account for at least 50% of alcohol addiction, although the biologic effects of genetic factors are less well understood [22]. Early twin adoption studies reveal a 54% risk of an identical twin developing alcoholism if the other twin is alcoholic. [23] More recent research confirms the heritability of alcoholism, especially in men [24]. Although not as strong as alcoholism, similar twin studies indicate a genetic predisposition toward cocaine and opiate addictions [25]. Some work has been done on the genetics of opiate addiction, and although the genetic component plays a role, a single causative gene has not been isolated [26]. Other research finds genetic neuroelectric brain-wave differences in sons of alcoholics, who are not alcoholics, which are identical to that in the alcoholic fathers. These brain-wave alterations were not seen in the nonalcoholic control population [27].

Studies to date highlight at least three important points regarding the genetic influence on addiction [2]. First, a family history of addiction is a strong predictor of risk regardless of socioeconomic status. Second, factors that may trigger addictive behavior are diverse and differ from individual to individual. For example, social isolation may trigger addictive behavior in some, while large social gatherings serve as a trigger in others. Third, there is likely no one gene that confers the risk of addiction but rather an interaction of multiple genes along with other environmental factors.

Shared Etiology

Addiction frequently occurs with other disorders in the same patient. The comorbidities may include co-addiction (tobacco, alcohol, illicit drugs, eating, gambling, or even sex) or other mental disorders. There appear to be genetic factors in common between nicotine and alcohol abuse that may partially explain why the two substances are often used concurrently [28, 29]. Persons with mental illness are about twice as likely to smoke as compared to controls [30] and the prevalence of nicotine dependence is 5–6 times higher in persons with psychiatric disorders as compared to the general population [31]. Persons with mental illness are about twice as likely to smoke as compared to controls [30] and the prevalence of nicotine dependence is 5–6 times higher in persons with psychiatric disorders as compared to the general population [31]. Twin studies support a shared genetic vulnerability to and significant genetic correlation between alcohol and tobacco use [28].

Up to 60% of persons diagnosed with alcoholism have evidence of other preexisting psychiatric disorders [32]. Borderline personality disorder [33] and major depression [34] have been associated with a high rate of nicotine dependence. In addition, twin studies reveal a genetic link between alcoholism and externalizing disorders, such as attention-deficit and hyperactivity disorder and antisocial personality disorder [35]. Like addiction, these other psychiatric disorders share a high heritability, suggesting that the genes responsible are likely pleiotropic (i.e., a single gene determining multiple phenotypes) and stress the importance of integrating the study of addiction with other psychiatric illnesses.

Brain-Reward Mechanisms

The most popular theories of addiction involve activation of the brain reinforcement circuit (Fig. 2.2), which is naturally activated by behaviors involving food and sex. Although drugs of abuse produce effects through many receptor systems in the brain, their effect on the mesolimbic dopaminergic system (Fig. 2.3) is critical and most often implicated in producing the rewarding effects. Dysfunction of this system contributes to several pathologic conditions including schizophrenia, attention-deficit and hyperactivity disorder, and Parkinson's disease and is thought to be critical to the

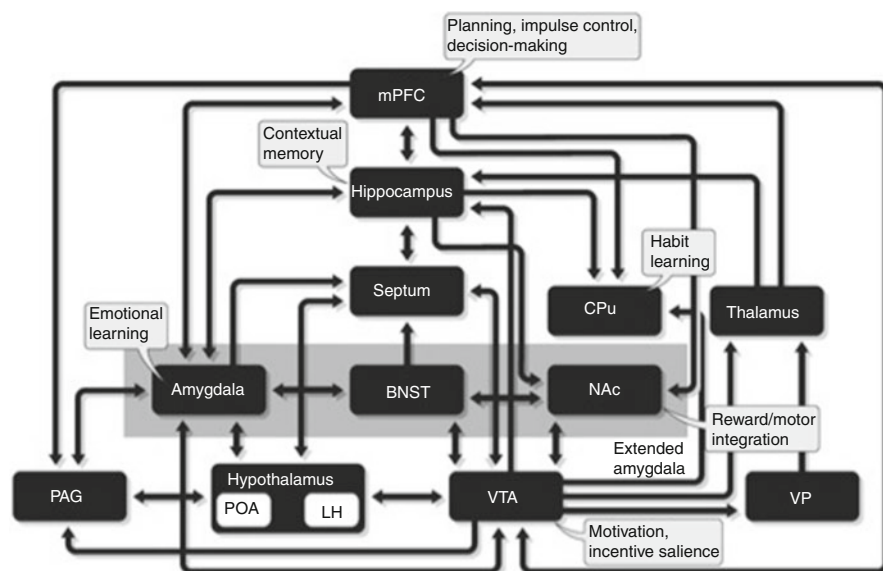


Fig. 2.2 Schematic representation of the brain reinforcement circuit. Brain sites of reinforcement are integrated in a circuit based on their connectivity and putative functional roles. *BNST* bed nucleus of the stria terminalis, *CPu* caudate putamen, *LH* lateral hypothalamus, *mPFC* medial prefrontal cortex, *NAc* nucleus accumbens, *PAG* periaqueductal gray, *POA* preoptic area, *VP* ventral pallidum, *VTA* ventral tegmental area (Reprinted from Le Merrer J, Becker JAJ, Befort K, Kieffer BL. Reward Processing by the opioid system in the brain. *Physiol Review*. 2009;89:1383)

addictive properties of abused substances [36]. Drugs of abuse increase extracellular dopamine concentration overriding the control of motivated and goal-directed behavior, contributing to compulsive drug seeking and taking [37]. Cocaine is known to alter dopamine release and reuptake which, with chronic use, alters the reward system in a way that leads to addiction and, possibly, relapse [38, 39].

The opioid system is also thought to play a key role in brain reinforcement circuits [40]. Brain opioid receptors are expressed primarily in the limbic system, cortex, and brain stem and are central in the mediation of nociception as well as other physiologic functions, including stress, endocrine function, and immune function. In recent years, the role of the brain opioid system in modulating mood and addictive behaviors has also become apparent [41, 42]. Pharmacologic activation or blockade of opioid receptors at several sites has demonstrated the role of these receptors in both the “pleasure” natural reward system and the reinforcing properties of abused drugs [40]. Brain sites where opioid agonists or antagonists modulate drug reinforcement include the ventral tegmental area (VTA) and nucleus accumbens (NAc). Mu and delta receptors found in the VTA and NAc modulate positive reinforcement for both opioid and nonopioid drugs of abuse, including ethanol [43], cocaine, and nicotine. In addition, mu and delta receptor blockade leads to a decreased response when drugs of abuse are administered [44].

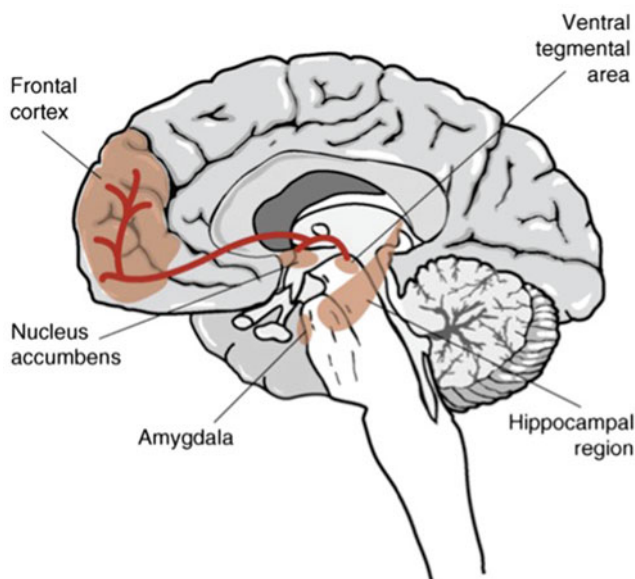


Fig. 2.3 The mesolimbic dopamine (reward) pathway in the brain. The dopamine pathway originates in the ventral tegmental area (VTA) and projects into the nucleus accumbens (NAC) and the prefrontal cortex (PFT). The VTA consists of dopaminergic neurons, which respond to glutamate, whereas the NAC consists primarily of medium spiny neurons, which are GABA-ergic neurons. The hippocampus is involved in learning and memory (From Kalsi G, Prescott CA, Kendler KS, Riley BP. Unraveling the molecular mechanisms of alcohol dependence. *Trends Genet.* 2008;25(1):50)

In addition to dopamine and opioids, other neurotransmitters, including glutamate, serotonin, and acetylcholine, are involved in the experience and progression of drug use [45, 46]. It is clear that these neurotransmitters share a neurobiologic interconnectiveness but further investigations are needed to investigate the full scope of relevance.

Imaging the Addicted Brain

The imaging of genetically different brains is fairly new, but may play a larger role in the future as genetic research expands. In the area of addiction, investigators have focused on genes that modulate dopamine in the reward system. This type of research may help determine whether addiction causes neuroplasticity or the genetic differences lead to the neuroplasticity associated with addiction.

Dopamine₂ (D₂) receptor polymorphism affects reward system processing. The presence of an A1 variant allele on post-synaptic D₂ receptor results in less expression of D₂ receptors in areas of the ventral striatum and putamen. These receptors are also

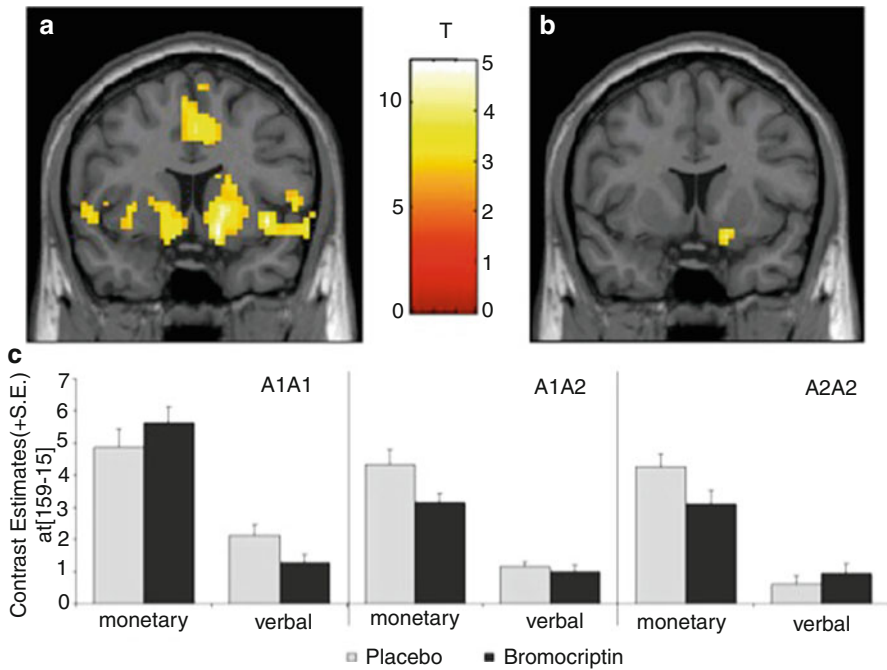


Fig. 2.4 Increased striatal activation during the anticipation of reward varies by genotype. (a) Main affect in all groups. (b) Stronger activation to bromocriptine in the NAc varied by genotype, with greatest activation by A1 genotype. (c) Response to anticipated monetary reward greatest with A1 allele after bromocriptine administration (Reprinted from Kirsch P, Reuter M, et al. Imaging gene-substance interactions: the effect of the DRD2 TaqIA polymorphism and the dopamine agonist bromocriptine on the brain activation during the anticipation of reward. *Neurosci Lett.* 2006;405:199, with permission)

associated with less dopamine binding. It is thought that decreased numbers of receptors and less dopamine binding lead to reduced dopamine release in the nucleus accumbens. In addicts, this reduced sensitivity to dopamine causes an urge to increase dopamine levels with their substance of choice; hence, craving results. In a sense, this allele rewards substances that increase dopamine levels. Kirsch et al. have demonstrated differences in blood oxygen level-dependent (BOLD) activation in functional magnetic resonance imaging (fMRI) of the nucleus accumbens between those with the A1 gene and those without [47]. This difference was in response to the anticipation of a monetary reward after the administration of a dopamine agonist. Initially, participants with the A1 allele performed worse on a monetary reward task than the non-A1 participants ($P < 0.05$), supporting genetically altered reward system processing. After administration of a dopamine agonist, the A1 participants significantly increased their ability to obtain monetary rewards as well as activation of the striatum in response to reward anticipation ($P < 0.05$) (Fig. 2.4) [48]. This genetic difference may help explain the overinflated anticipation associated with addiction.

On the other hand, the described work of van Eimeren et al. demonstrated that increased dopamine activity in the lateral orbitofrontal and ventral striatum altered

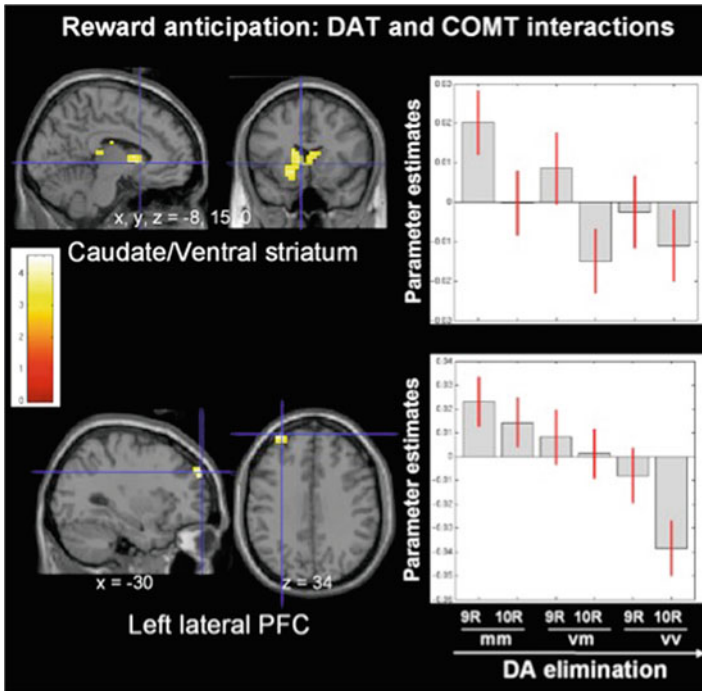


Fig. 2.5 Interaction between COMT and DAT1 genotypes with COMT and DAT variant showing those (left) augmented neural response in the caudate, ventral striatum, and prefrontal cortex and (right) reduced elimination of dopamine in anticipation of an uncertain reward in those with the variants (Reprinted from Dreher JC, Kohn P, Kolachana B, et al. Variation in dopamine genes influences responsivity of the human reward system. *Proc Natl Acad Sci USA*. 2009;106:619)

reward processing [49]. This phenomenon could have a genetic basis. Genetic influences on the reward system may also involve the modulation by the enzymes responsible for catabolism of synaptic dopamine and its re-uptake into the presynaptic membrane in the prefrontal cortex and ventral striatum [48]. Synaptic dopamine levels are maintained by (COMT), which catabolizes synaptic dopamine, and the dopamine transporter enzyme (DAT1), which transports synaptic dopamine back into the presynaptic vesicle. COMT is very active in the prefrontal cortex, where little DAT1 is found and vice versa, although COMT likely plays some role in modulating dopamine in the ventral striatum via downstream neural connections. Specific variants of either of these genes cause reduced expression and activity of these enzymes, ultimately resulting in increased synaptic dopamine and increased activity in the prefrontal cortex and ventral striatum [48]. A genetic difference was demonstrated in brain activity with BOLD activation on an fMRI in response to uncertain reward anticipation and reward outcome. Participants with the COMT variant had a significant increase in activity of the lateral prefrontal in anticipation of uncertain reward ($P < 0.001$, uncorrected) and orbitofrontal cortex in response to reward ($P < 0.005$) and reduced dopamine elimination in these areas (Fig. 2.5) [48]. Those with the DAT1 variant had increased activity in the caudate nucleus and the

striatum. An interaction effect was also noted between the COMT and DAT1 genotypes in the ventral striatum, caudate nucleus, and lateral prefrontal cortex ($P < 0.01$). This interaction resulted in a hyper-responsivity of reward system (Fig. 2.6) [48]. These results support van Emerein and colleague's work that revealed increased dopamine via administration of a dopamine agonist in the ventral striatum and lateral orbitofrontal cortex was associated with increased risk-taking behaviors. It should be noted that neither of studies looked specifically at the addicted brain; however, these results provide a foundation for understanding how genetics play a role in brain reinforcement circuits and risk-taking behavior associated with addiction.

Summary

Substance abuse and addiction are heritable disorders often found concurrently with psychiatric comorbidities. The causes are complex and multifactorial but recent studies suggest multiple genetic influences. Linkage studies have identified genes likely involved in the pathogenesis, but only a fraction of the entire genetic risk has been accounted for. Newer methodologies including genome-wide scans will assist in identifying more rare risk variants.

Activation of the brain reinforcement circuit is integral to the addictive process and drug-seeking behavior. Recent advances in imaging have greatly contributed to our understanding of addictive behavior, the genetic influence, and underlying mechanisms.

Spotlight on the Role of the Opiate System in Addiction

Michelle M. Jacobs, PhD

The μ -opioid receptor (OPRM1) is the primary receptor target for both endogenous opioid peptides and exogenous opioid analgesics. There is individual variability for response to opioid analgesics as well as a likelihood to become tolerant and/or dependent on these agents. As such, it is important to understand the genetic and biological basis for individual differences that may guide better pain management with reduced side effects.

The OPRM1 gene is a large, highly complex gene located on chromosome 6q24–25. Currently, there are over 800 single nucleotide polymorphisms (SNPs) associated with this gene. However, the most frequently studied SNP has been the A118G SNP located within exon 1 that results in a substitution of asparagine for aspartate at position 40 in the receptor's extracellular domain

(N40D). This SNP is relatively common in individuals of European (10–15%) and Asian ancestry (36–50%), but much less frequent in African American (0–4%) populations. In vitro studies have produced conflicting results as to the functional relevance of this substitution. Initial studies indicated that the human G118 variant had an increased binding affinity for β -endorphin and enhanced activation of G-protein coupled potassium channels [50], suggesting a gain of function as a result of A118G mutation. Other studies have failed to replicate the original findings [51]. Additional studies performed in postmortem brain tissue have supported a loss of function role for the mutation with G118 subjects demonstrating a 1.5-fold reduction in mRNA expression [52].

A118G in Substance Abuse

Various human genetic studies have highlighted the importance of the A118G SNP in substance abuse. It has been associated with opioid dependence in several different ethnic populations including Han Chinese [53], Indian [54, 55] and European Caucasian [56, 57]. Several studies have also found a role for A118G and alcohol abuse across many populations including Korean [58–60], Japanese [61] and Caucasian [62–64]. In addition to substance abuse, individual differences have also been reported for responses to pain. Individuals carrying the 118G allele report an elevated pain response as well as decreased pain threshold [65, 66]. Chronic pain patients and those who have undergone surgery who are 118G carriers consume more morphine or other opioids as compared to A118A homozygote subjects [67, 68]. Of interest, 118G individuals often have reduced side effects such as lower levels of nausea and respiratory depression [66, 69].

Treatment for Substance Abuse and Relevance of A118G

Two main classes of drugs are available to treat opioid addiction; opioid receptor antagonists including naloxone and naltrexone, and opioid receptor agonists or partial agonists such as methadone, levomethadyl acetate (LAAM) and buprenorphine. These drugs act on the μ -opioid receptor and can block the effects of an ingested opioid. However, each of these drugs varies in treatment efficacy as well as adherence rates. Risk of overdose on methadone and LAAM is also a concern as these drugs are full agonists of the μ -opioid receptor and considered highly addictive themselves.

Given the differences and difficulties in treatment efficacy and adherence and the known functional role of A118G in OPRM1, recent studies have questioned if individual genetic variability at A118G can predict therapeutic outcomes to opioid receptor agonists and antagonists. One of the best characterized examples of this theory is the response to naltrexone in alcohol dependent subjects. 118G subjects reported more sensitivity to alcohol while naltrexone blocked this alcohol-induced “high” [70, 72]. Numerous clinical trials have

reported A118G's effects on responses to naltrexone [60, 70–73]. 118G subjects were more likely to respond to naltrexone than A118A subjects and most importantly, 118G subjects had longer rates of relapse [71]. In addition, cue-induced craving is also greater in 118G-carrying individuals. Clearly, these studies have highlighted the importance of including individual genetic analysis when determining optimal therapy for addiction and the need for additional studies for opioid antagonists/agonists.

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