Pharmacogenetics of Drug Dependence: Role of Gene Variations in Susceptibility and Treatment

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Key Words

addiction, dopamine, smoking, alcohol, therapy, pharmacogenomics

Abstract

Drug dependency is a highly prevalent mental health disorder that imposes a significant burden on those directly affected, health care systems, and society in general. There is substantial heritability in the susceptibility to drug addiction, which indicates that there are genetic risk factors. Variation in the human genome is abundant and can directly affect drug dependency phenotypes, for example, by altering the function of a gene product or by altering gene expression. Pharmacogenetic studies can assess the effects of genetic variation on the risk for a particular phenotype (e.g., being an alcoholic). In addition, pharmacogenetic variability in treatment efficacy and adverse reactions can be investigated to identify particular genetic variants associated with altered responses. This review highlights examples of genetic variations that are important in the development and maintenance of specific drug dependencies as well as those that affect the response to treatment.

INTRODUCTION

Single nucleotide polymorphism (SNP): a single base pair difference in DNA sequence, which can alter the structure, function, or expression of the gene product

Variable number tandem repeat (VNTR): a DNA variant containing a variable number of short tandem-repeated DNA sequences at a locus

Genome-wide association study: an approach that investigates variation throughout the entire genome with the goal of identifying SNPs uniquely present in patients with disease (cases) relative to those without disease (control)

Drug dependency is a complex disorder of interacting genetic, physiological, environmental, and socio-behavioral factors. Drug addictions result in a significant burden on health care systems and continue to remain highly prevalent in society. In 2007, an estimated 22.3 million people in the U.S. were classified with substance dependency or abuse in the past year (1). A recent study across six U.S. states found that for people with substance abuse disorders, $104 million more was spent on medical care, and $105.5 million more on behavioral health care, compared to patients who did not have an alcohol or drug abuse diagnosis (2). A substantial genetic influence on drug dependency has been determined through family, adoption, and twin studies in which inherited risk estimates that range between 40–60% are observed for differing phenotypes (3, 4). The exact role of individual genes in these complex diseases is not fully characterized, and the contribution of genetics is generally thought to be polygenic, with multiple genes with low impact combining to create the genetic vulnerability (5).

Pharmacogenetics is the study of the influence of genetic variation on the response to drugs. The human genome contains 3.2 billion nucleotides of DNA (5); researchers estimate that more than 11 million single nucleotide polymorphisms (SNPs) occur with frequencies over 1% (6). As a general rule, variations with allelic frequencies less than 1% are considered rare, and those greater than 1% are considered polymorphic. Although SNPs are the most abundant form of variation, genetic variants can also arise from deletions, insertions, and duplications. Variations can also arise in the form of microsatellites or variable number tandem repeats (VNTRs) that consist of specific sequences of DNA, which contain a repeating pattern of two or more nucleotides that are directly adjacent to each other. These genetic variations can directly alter the expression or function of proteins related to drug reward and addiction, resulting in an altered risk to drug dependency. These variations may differ in frequency across ethnic populations.

Family, twin, and linkage studies can provide us with heritability estimates that can tell us about the genetic influence on a phenotype. Genome-wide linkage studies can identify general locations in the genome that associate with specific phenotypes. Genetic variants that might contribute to drug-dependency phenotypes can also be identified through case-control candidate gene-association studies. This is done by selecting genes (e.g., nicotinic receptors) that might be involved in the phenotype (e.g., amount smoked) and associating the prevalence of the genetic variants with the addiction phenotype using statistical approaches. Furthermore, genome-wide scans also aid in the identification of genes involved by extending the analysis over the entire genome. These genome-wide association studies do not select genes of interest a priori. Instead, they test for associations throughout the genome without a specific biological hypothesis. These tools can be used to assess the association of drug-dependency phenotypes with genetic variation to identify genes that can alter either the susceptibility to drug dependency or the response to treatment. Here we provide examples of some genetic factors in the multifactorial aetiology of addictions and their treatments.

Many genes involved in the brain reward pathways play a role in the addiction susceptibility to a variety of drugs, whereas other genes only affect the risk for dependency on specific abused drugs. Some genes that encode for proteins involved in monoaminergic transmission in the brain are important to the shared susceptibility to addictions, and this system interacts with other brain receptor systems such as the opioidergic system to coordinate brain reward and affect and therefore the development, maintenance, and withdrawal of addictive drugs. Genetic variation that affects particular drugs is often identified in genes that are involved in the pharmacodynamic responses to, or the pharmacokinetics of, the drug.

The studies below highlight some of the findings that pertain to the role of pharmacogenetics in the susceptibility to, and the treatment of, drug dependency across a spectrum of abused drugs.

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Due to space limitations, the expansive body of knowledge available on this topic is not covered entirely; for additional information on genetic aspects of drug addiction, see cited reviews (4, 7–10). Notably, there are conflicting association study data for some of the candidate genes reviewed below. Different phenotypic definitions (11) as well as differences in variant allelic frequencies across populations can contribute to the apparent lack of reproducibility of these studies. In addition, the grouping of genotypes, specific SNPs tested within a gene, the size and power to detect associations, and the statistical methods used for analyses are potential sources of variance among studies.

***ANKK1*:** ankyrin repeat and kinase domain containing 1 gene

***DRD2*:** dopamine D2 receptor gene

GENES IN PATHWAYS POTENTIALLY INVOLVED IN RISK FOR DRUG DEPENDENCE COMMON TO MULTIPLE DRUG TYPES

The monoaminergic neurotransmitter system serves as the primary chemical messenger for the reward pathways in the human brain. Monoamines can be further divided into catecholamines (i.e., dopamine and norepinephrine) and serotonin. Dopamine is synthesized from the amino acid tyrosine by tyrosine hydroxylase and 3-hydroxy-tyrosine decarboxylase (12). Upon appropriate signaling, dopamine can be released by presynaptic neurons into the synapse where it proceeds to bind to dopamine receptors on both pre- and postsynaptic receptors. The unbound dopamine is then taken up by dopamine transporters on the presynaptic membrane for reutilization or degradation. Dopaminergic pathways are involved in brain reward, and their disinhibition can activate the reward pathway (13). Genetic variations in genes that encode for proteins involved in this system are associated with the vulnerability to, as well as the acquisition and persistence of, drug dependency.

Dopamine D2 (encoded by the *DRD2* gene) receptors are primarily expressed in the terminal regions of dopaminergic neurons (14, 15). Studies in *DRD2*-null mice suggest that the D2 receptor functions as an autoreceptor on dopamine neurons (16–18). The most well-established polymorphism in the *DRD2* gene is *Taq*1A, a C > T substitution located 10 kb (kilobases) 3′ of the *DRD2* gene in the coding region of the neighboring *ANKK1* gene (19, 20). The *A1* allele results in lower DRD2 receptor density in striatum (21). Subjects with reduced DRD2 content may compensate for this lowered input through the use of drugs that stimulate the dopaminergic system. This *Taq*1*A* polymorphism is associated with an increased risk for multiple types of substance abuse (22), including heroin use (23), cocaine dependency (24), psychostimulant polysubstance abuse (25), and smoking (26–29), as well as a predisposition to alcoholism (30–32), although not all of these findings have been replicated (33). *Taq*1B, another polymorphism in the *DRD2* gene, is located 913 base pairs (bp) upstream of exon 2. This SNP was associated with an earlier initiation of smoking, as well as an increased risk for polysubstance abuse and cocaine dependency (22, 24, 34–36). Genetic variations in other dopamine receptor subtypes have also been positively associated with risk for addiction. For example, polymorphisms in the dopamine receptor D3 gene (*DRD3*) have been shown to contribute to an increased risk for nicotine dependency (37, 38), and the *Bal*I restriction site variant is associated with greater risk for cocaine use (27). The VNTR (longer repeat allele) in the dopamine receptor D4 gene (*DRD4*) was positively associated with smoking persistence in African Americans (39) but not in Caucasians (39). The longer repeat allele was also found to be associated with greater craving and more attention to smoking cues (40), as well as a greater likelihood of smoking and higher nicotine dependency scores (41). A seven-repeat polymorphism in exon 3 of the *DRD4* gene occurred more frequently in methamphetamine users than in control subjects (42).

The *SLC6A3* gene encodes for the dopamine transporter, which is responsible for sequestering dopamine back into presynaptic neurons (43, 44). A 40-bp VNTR in the 3′ end, which results in

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lower expression of the dopamine transporter in the putamen, was shown to affect a variety of smoking behaviors and the risk for cocaine-induced paranoia (45, 46). A 30-bp functional VNTR in intron 8 of the *SLC6A3* gene was also positively associated with cocaine dependency in a Brazilian population (47). Another SNP in 3′UTR of this gene (A allele) was associated with a lower risk of being a smoker (48).

MAO: monoamine oxidase

***SLC6A4*:** serotonin transporter gene

The dopamine β hydroxylase enzyme converts dopamine to norepinephrine (49). The enzyme is stored within synaptic vesicles along with catecholamines and is released during synaptic transmission from neurons. A SNP (1368G>A) in the gene coding for dopamine β hydroxylase (*DβH*) was associated with increased cigarette consumption (50), but this was not replicated in a larger sample (51). In addition, two polymorphisms, 1021C>T and 1603C>T, in the dopamine β hydroxlase gene have been identified, and they have been shown to decrease enzyme activity and account for a large proportion of interindividual variation in this enzyme's activity (52, 53). However, no association studies have been done to assess the effects of these polymorphisms on drug dependency. In addition to dopamine β hydroxylase, monoamine oxidase (MAO) can also metabolize dopamine. A SNP in *MAO*-A gene (1430C>T) was initially associated with a greater amount of cigarette consumption (50), but further studies with larger sample sizes did not replicate these findings (51). Studies of a 30-bp VNTR in the promoter region of *MAO-A* indicate that the 3.5- and 4-repeat alleles have greater transcription efficiencies than the 3- or 5-repeat alleles (54). In a Japanese population, the 4-repeat allele was associated with a greater risk of nicotine dependency in males but not in females (55). On the other hand, the 4-repeat allele was associated with a lower risk of being a smoker among females, but this association was not seen in males (55). *MAO*-A is a sex-linked gene, thus differences in the impact between genders are not necessarily surprising. However, these were not replicated in the same ethnic population (56). There is also some conflicting evidence regarding the association of *MAO*-A variants with alcohol dependency (57–59) with some studies suggesting that polymorphisms within *MAO*-A might modify the associations between *DRD2* and alcohol dependency (58).

The enzyme catechol-*o*-methyl transferase (COMT) is involved in the metabolism of catecholamines, including dopamine (12). Variation in *COMT* may influence dopamine levels in the prefrontal cortex, leading to changes in cognition, affect, and reward processes, and may influence susceptibility to drug dependency (60). The high-activity 1947G allele is associated with an increased risk for methamphetamine abuse (61) and could potentially interact with *DRD4* variant alleles to alter susceptibility to its use (62). The lower expression 1947A variant allele could have protective effects against smoking (63, 64). The low-activity allele has also been associated with an increased likelihood of being alcohol dependent (65, 66).

Serotonin and norepinephrine are two other important monoamines that also play a significant role in the rewarding effects and abuse potential of drugs. Tryptophan hydroxylase is the rate-limiting enzyme in the biosynthesis of serotonin, and individuals with two copies of the variant allele for the C779A SNP in the tryptophan hydroxylase 1 gene (*TPH1*) were shown to be at a greater risk for early smoking initiation (67). The variant allele at this locus was also found at a higher frequency in smokers (68). Multiple variations in *TPH1* and *TPH2* (tryptophan hydroxylase) genes have been associated with a greater likelihood of heroin addiction in Hispanic and African-American populations (69). Polymorphisms within intron 7 of the *TPH1* gene were found to be associated with increased risk for alcohol dependency in different ethnic groups (70, 71). However, studies have consistently reported a lack of association between *TPH2* and alcoholism (72, 73).

The serotonin transporter mediates the reuptake of serotonin and is expressed on presynaptic terminals of serotonergic neurons. The serotonin transporter gene (*SLC6A4*) has a GC-rich 44-bp insertion or deletion in the promoter region (−1.4 kb from the translation start site) referred to as the 5HT transporter gene–linked polymorphic region (5HTTLPR). Short variants result

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in decreased transcriptional efficiency of the serotonin transporter promoter (74). Long variants (insertion) were found at a higher frequency in alcohol-dependent populations (75, 76), whereas others have shown the short variant to be associated with a greater risk for alcohol dependency and relapse (77–81). Individuals with two copies of the short variant were found to be associated with a greater risk for being heroin dependent (82). VNTRs in the second intron have also been associated with a greater likelihood of heroin addiction in a Chinese population (83).

CHRN: nicotinic acetylcholine receptor gene

In addition to genes involved in neurotransmission of reward and affective responses, other genes that play a role in neural processes such as implicit memory, or proteins involved in cell signaling and growth, are also associated with altered risk for drug dependencies. This includes a wide variety of proteins involved in cell adhesion activities, growth, and differentiation pathways; variation in these genes has been associated with a greater risk for substance dependency (4, 84–86).

GENES POTENTIALLY INVOLVED IN RISK FOR DEPENDENCE ON SPECIFIC DRUGS

Pharmacogenetics of Smoking

Cigarette smoking is the single largest cause of preventable deaths worldwide. In 2007, more than 60 million Americans over the age of 12 years were current cigarette smokers, making up 24% of the population in that age range (1). Nicotine is the main reinforcing component of tobacco smoke. It binds and activates the nicotinic acetylcholine receptors in the ventral tegmental area, which facilitates dopamine release in the shell of the nucleus accumbens, thereby activating the mesolimbic brain reward pathway (87).

There is a substantial genetic contribution to various aspects of smoking, including initiation, progression, maintenance, amount smoked, and the ability to quit (88–95). Notably, genetic risk factors only partially overlap between different aspects of cigarette smoking, and there is some variation in the heritability estimates between genders (88, 91).

Similar to other diseases with complex etiologies, each gene probably contributes only part of the genetic susceptibility to nicotine dependency, and interactions between multiple genes ultimately contribute to the risk for smoking. Genes that are involved in nicotine metabolism and nicotine response are biologically plausible risk factors and are discussed here.

In addition to the dopaminergic system, nicotinic acetylcholine receptors have been implicated in nicotine reward and dependency. Two nonsynonymous SNPs on exon 5 (rs1044396/1629G >T and rs1044397/1659G>A) of the gene encoding for the α4 subunit of the nicotinic acetylcholine receptor (*CHRNA4*) were associated with a lower risk of nicotine dependency in Chinese men (96), which was recently replicated in a European population (97). A G>A variant, rs2236196, in the 3′ untranslated region of *CHRNA4*, was associated with greater subjective effects of nicotine (98) and higher risk of nicotine dependency (97). Interestingly, although β2 subunits are essential for developing nicotine self-administration behaviors in animal models (99, 100), several studies have failed to find any associations between genetic variation in this gene and smoking phenotypes (101, 102). There is some evidence, however, that suggests that a SNP in *CHRNB2* was protective against smoking initiation (103). Because the β2 subunit is often expressed with the α4 subunit to form a functional heteropentameric nicotinic acetylcholine receptor, *CHRNB2* was found to have a large effect on nicotine dependency when analyzed with *CHRNA4* (104). Several other genetic variations in nicotinic acetylcholine receptor subunits may also be associated with nicotine dependency. Specifically, variation in the *CHRNA5-CHRNA3-CHRNB4* gene cluster on the long arm of chromosome 15 was associated with a higher risk for lung cancer, smoking a greater number of cigarettes, and nicotine dependency (105–107). It is not clear whether the association

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with lung cancer was a direct or indirect effect mediated by the increase in cigarette consumption. Although some studies suggest this locus is not associated with smoking behaviors (108, 109), recent evidence suggests that multiple SNPs in this gene cluster are associated with a higher number of cigarettes per day and greater nicotine dependency (110). Specifically, the nonsynonymous SNP rs16969968 in *CHRNA5* has been associated repeatedly with higher nicotine dependency (111, 112), and individuals with the variant allele in this SNP had a higher intensity of smoking (113) and greater lung adenocarcinoma risk (114), which suggests that the risk for lung cancer may be related to increased exposure. Further studies are required to clarify the role of variation in α3 and α5 gene clusters in smoking and related illnesses.

CYP: cytochrome P450

Haplotype: a set of closely linked genes or DNA polymorphisms inherited as a unit

In addition to the brain reward pathways, genes that alter the pharmacokinetics of nicotine metabolism are also involved in smoking phenotypes. Most nicotine is metabolized to cotinine primarily by cytochrome P450 2A6 (CYP2A6) (115–117). Cotinine is then metabolized to 3′-hydroxycotinine exclusively by CYP2A6 (118). *CYP2A6* is genetically polymorphic, with over 37 alleles identified for this gene, and this genetic variation influences the metabolism of nicotine (119, 120). Genetic slow metabolizers have longer nicotine half-lives, resulting in prolonged nicotine plasma levels (95). Slow metabolizers smoke fewer cigarettes per day and smoke less intensely as indicated by smaller puff volumes (94, 95). They also have reduced withdrawal symptoms and higher quitting rates (120, 121). Slow metabolizers are at a lower risk for cancer because CYP2A6 can also activate tobacco-specific nitrosamines (122). However, some studies have failed to see associations between *CYP2A6* genotype and smoking or cancer risk (123–125), which may be due, in part, to a variable number of alleles being assessed in different studies and new alleles being identified (**http://www.cypalleles.ki.se/cyp2a6.htm**). Genetic variations in *CYP2B6*, another member of the cytochrome P450 family, can also alter smoking behaviors. Individuals with one or more copies of *CYP2B6*5* allele (1459C>T) were shown to have greater craving and a higher relapse rate (126). Individuals with the *CYP2B6*6* allele were also less likely to quit during attempted smoking cessation (127). The *CYP2B6* genotype does not substantially affect the systemic clearance of nicotine; however, genetic variation in CYP2B6 expressed in the brain might alter local CNS metabolism of nicotine (128).

Pharmacogenetics of Alcohol Dependence

The World Health Organization estimates that approximately 76.3 million people have alcohol use disorders (129), and 18.6 million Americans aged 12 years or older were classified with dependency or abuse in 2007 (1). Alcoholism has heritability estimates that range from 52% to 64% (130). Researchers have identified several genes that predispose individuals to developing alcohol dependency and encode for proteins that play a role in the pharmacokinetics and pharmacodynamics of alcohol; these alter the rewarding effects of alcohol, thereby affecting its abuse liability.

Ethanol produces a wide variety of behavioral and physiological effects, including sedation, euphoria, motor incoordination, and disinhibition. Multiple neurotransmitters are involved in orchestrating ethanol's reward profile including dopamine, γ–aminobutyric acid (GABA), glutamate, and serotonin (131). Ethanol has been shown to enhance the function of γ–aminobutyric acid receptor type A ($GABA_A$), neuronal α2β4 nicotinic acetylcholine, and glycine receptors, and to inhibit *N*-methyl-D-aspartate-type glutamate receptor function (132, 133).

$GABA_A$ receptors are pentameric structures composed of multiple subunits that determine the receptor's properties. A 1236C>T polymorphism in the gene that encodes the α6 subunit of the $GABA_A$ receptor is associated with a low level of response to alcohol, which is a strong predictor of developing alcohol dependency (134, 135). SNPs within a haplotype block spanning

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the central and 3′ region of the gene that encodes the $GABA_A$ α2 subunit have been associated with an increased susceptibility for alcohol dependency (136–138). SNP haplotypes in the gene encoding the α1 subunit have also been detected at higher frequencies in alcohol-dependent individuals (139). The opioidergic transmission system in the brain has also been implicated in alcohol reward and response. The 118A>G SNP in the first exon of the μ opioid receptor gene (*OPRM1*) results in the loss of a putative N-linked glycosylation site, as well as a threefold increase in β-endorphin binding compared to the wild-type allele (140) and accompanying differences in physiological and analgesic responses to morphine (141); the 17C>T SNP variant receptor has a valine instead of alanine in the N-terminal domain of the receptor. Although there is conflicting evidence regarding the role of 118A>G and 17C>T variants of *OPRM1* in alcohol dependency, some studies have shown that these alleles are found at a higher frequency in alcoholics (142). In addition, variants resulting from SNPs in *OPRKI* and *PDYN*, which encode the κ opioid receptor and its dynorphin ligand, have also been associated with an increased risk for alcohol dependency (143–145). An insertion/deletion variant (indel) of *OPRKI* has also been identified, which resulted in a net addition of 830 bp upstream of the translation start site. The presence of the indel decreases transcription of *OPRKI* by 53% in vitro and was found at an increased frequency in alcoholics (146). A group of polymorphisms in the nicotinic acetylcholine receptors *CHRNA5-CHRNA3-CHRNB4* gene cluster have been identified and were associated with a greater risk for alcohol dependency. These variants show low linkage disequilibrium with the SNPs previously reported to be associated with nicotine dependency (147). Several of these variants altered the α5 subunit mRNA expression in the frontal cortex (148). In addition to variation in genes that are involved in the neuromodulation of alcohol's effects, individuals with the 516G allele of the *hTAS2R16* gene, which encodes the taste receptor for bitter β-glucopyranosides, were also shown to have an increased risk for alcohol dependency (149).

***PDYN*:** dynorphin ligand gene

ADH: alcohol dehydrogenase

ALDH: aldehyde dehydrogenase

Alcohol dehydrogenase metabolizes ethanol to acetaldehyde, a toxic intermediate, which is then metabolized to acetate by aldehyde dehydrogenase. Variations in the genes encoding these enzymes can alter alcohol metabolism and result in the accumulation of acetaldehyde during alcohol consumption, which causes a flushing response as well as headache, nausea, and palpitations (150). These unpleasant responses are thought to decrease heavy alcohol consumption and protect against the development of alcohol dependency (151). Functional polymorphisms in multiple alcohol dehydrogenase genes, namely *ADH4*, *ADHIB*, and *ADHIC* as well as the aldehyde dehydrogenase gene *ALDH2*, have been shown to alter the risk for developing alcohol dependency (152–157). Twelve SNPs in and around the *ADH4* gene have been consistently associated with a greater risk for alcohol dependency in a variety of populations (158, 159). In particular, the C-136A polymorphism in the promoter region of the *ADH4* has been extensively studied. The -136A allele has been associated with an increased susceptibility to alcohol dependency (160, 161). Studies have shown that the -136A variant results in greater promoter activity compared to the -136C variant (158, 162). Furthermore, the higher activity -136A allele caused a lower peak blood ethanol level after alcohol ingestion compared to the -136C allele (158). The *ADH1B*2* variant is associated with increased ethanol oxidation to acetaldehyde and has been shown to protect against alcohol dependency in a variety of populations (163). A meta-analysis of 15 studies in Asian populations revealed that possession of one *ADH1B*2* allele is associated with a fourfold reduction in alcohol dependency, and individuals homozygous for the *ADH1B*2* allele have a fivefold reduction (152). Another increased activity variant, *ADH1C*1*, has been associated with reduced alcohol dependency; however, this effect may be attributed to its linkage disequilibrium with the *ADH1B**2 variant (164). The *ALDH2*2* allele results in the production of an inactive ALDH2 enzyme (165). Results from the same meta-analysis indicate that possession of one *ALDH2*2* allele is associated with a fivefold reduction in alcohol dependency, whereas homozygotes have a ninefold

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reduction; documented cases of alcoholics who are *ALDH2*2* homozygotes are rare as a result (152).

Cytochrome P450 2E1 (CYP2E1) also contributes to the metabolism of ethanol. This enzyme metabolizes ethanol to acetaldehyde, and acetaldehyde to acetic acid. CYP2E1 accounts for approximately 20% of ethanol metabolism at low blood concentrations, and its contribution increases to 60% at high concentrations (166). Hepatic CYP2E1 protein levels and activity are induced by chronic ethanol intake (167). CYP2E1 protein levels are also induced in the brain by ethanol, suggesting a greater role for CYP2E1 in the local metabolism of ethanol in the induced state (168). *CYP2E1*1D* has been shown to have increased enzymatic activity and has been associated with alcohol dependency, although inconsistent results have been obtained across studies (169–171). The *CYP2E1*5B* polymorphism has been associated with altered transcriptional activity of the *CYP2E1* gene. *CYP2E1*5B* has been associated with greater ethanol consumption and risk for alcohol dependency (172, 173). However, there are conflicting reports on the impact of this variant on enzymatic activity and on alcohol dependency (174–177).

Pharmacogenetics of Stimulant Abuse

Cocaine had one of the highest levels of past year dependency of all illicit drugs in 2007 with over 1.6 million Americans reporting that they were cocaine dependent (1). Methamphetamines are another form of commonly abused psychostimulants, and their use is on the rise in the United States with an estimated 1.3 million users in 2007 (1). The heritability estimates for psychostimulant use are approximately 60–70% (178, 179). Cocaine is a central nervous system stimulant that acts primarily at the dopamine transporter, preventing dopamine uptake into presynaptic terminals and increasing synaptic dopamine levels. Cocaine also inhibits the reuptake of serotonin and norepinephrine (180). Increased levels of these neurotransmitters mediate the behavioral effects of cocaine, including hyperactivity, euphoria, and analgesia. There is also some evidence that suggests that glutamatergic neurotransmission system may also contribute to tolerance and withdrawal from cocaine (181). Methamphetamine increases brain dopamine levels resulting in euphoria, thereby contributing to its addictive properties (182).

The susceptibility to cocaine dependency has been associated with variations in the genes involved in monoaminergic transmission as discussed in the section above. Homer scaffolding proteins are key components of the excitatory postsynaptic density, which is the network of neurotransmitter receptors, adhesion molecules, scaffolding proteins, and signaling molecules situated on postsynaptic membranes. Homer1 plays a role in the biological response to cocaine by regulating glutamate signaling and subsequently modulating synaptic activity (183). A SNP in the *Homer1* gene, rs6871510, was positively associated with cocaine dependency in a population of African Americans (184). In addition, the C17T variant of *OPRM1* has also been associated with an augmented risk for cocaine dependency in select populations (185). Butyrylcholinesterase contributes to the metabolic inactivation of cocaine. The gene that encodes butyrylcholinesterase is polymorphic, and several variants that result in decreased enzyme activity have been identified (186). Individuals with these variants may metabolize cocaine at a slower rate and are therefore at risk for toxicity or overdose. Butyrylcholinesterase genetic variants may also influence vulnerability to cocaine dependency; however, this has not been investigated yet. An association between an increased risk for methamphetamine abuse and $GABA_A$ receptor $\gamma 2$ subunit gene (*GABRG2*) was also found (187). Gluthatione-*S*-transferase P1 gene (*GSTP1*) encodes for an enzyme that is involved in protection against oxidative stress; a polymorphism 313A>G was found to be associated with a greater likelihood of methamphetamine abuse and psychosis in a Japanese population (188).

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PHARMACOGENETICS OF OPIATE DEPENDENCE

GABA: γ-aminobutyric acid

Opium and its derivatives have been abused for centuries; heroin and noncodeine prescription opioid abuse is on the rise. The 2007 National Survey on Drug Use and Health stated that the number of current (past-month) heroin users in the United States was 153,000 with a prevalence rate of 0.06%. The effects of opioids and opiates are mediated primarily through the endogenous opioid receptor system, which includes μ, δ, and κ subtypes. Stimulation of μ opioid receptors by abused opiates or endogenous ligands (e.g., enkephalins) inhibits transmission through the inhibitory GABA neurotransmitter system, thereby resulting in a disinhibition of the mesolimbic-mesocortical dopamine pathways, which are integral to the reinforcing effects of opiates (189). Codeine is an opiate that is frequently abused, and it is metabolized to morphine, which has higher potency. The decline in codeine use is, in part, due to the increase in popularity of stronger noncodeine prescription opioids. The total genetic variance associated with heroin and other opiate abuse is 40%–50% (179, 190). Many genes have been previously assessed in the context of opiate abuse, and some have been significantly associated with opiate dependency.

Because the μ-opioid receptor is the primary target of opiates, variations in this receptor become an important area of study when assessing the effects of pharmacogenetics on opiate dependency. Studies in mice assessing quantitative trait loci have identified the chromosomal region containing the μ opioid receptor gene as a large contributor to variance in the rewarding properties of morphine (191). Targeted deletion of this gene also helped establish its role in the rewarding effects of morphine (192, 193). Many functional variants have been identified in the μ opioid receptor gene (*OPRM1*), the most common is 118A>G in the coding region with a frequency of 2%–49% among different ethnic groups (194). This variant has also been studied in case-control opiate dependency studies with conflicting results. The 118G allele was associated with a greater risk for opiate addiction in a Swedish population as well as in a population of Han Chinese males (195, 196). In the Swedish population, there was also a substantial attributable risk (18–21%) of heroin addiction contributed by the 118G allele. A study, with a smaller sample size, found that the 118A allele was present at a higher frequency in opioid-dependent cases of Indian ancestry (197); these findings, however, have not been replicated (198), and the role of this variant in susceptibility to opiate addiction remains to be clarified. The second most prevalent variant of the *OPRM1* is the 17C>T SNP in the coding region, and it is found at frequencies that range from 0.5%–21% across different populations (7). This SNP has been associated with a greater risk for opiate dependency (140). Using a haplotyping approach, similar results were reported in which a cluster of 43 variants in this gene was associated with a greater susceptibility to opiate dependency (199).

Because the κ opioid receptor gene (*OPRK1*) has also been implicated in response to opiates, and multiple variants in the gene have been reported (200). Some preliminary evidence suggests that the 36G>T SNP (1–3% frequency) may be associated with an increased risk for opiate addiction (201). Although the primary actions of the δ opioid receptor (*OPRD1*) manifest themselves in nociception, some of its function lies in modulating the actions of μ opioid receptor-directed opiates (202). The 921T>C variant of *OPRD1* was associated with a greater risk for opiate addiction in heroin addicts and controls (203), although others were not able to replicate these results (204, 205). The 80G>T SNP was also significantly associated with a higher likelihood of opioid dependency, and the haplotype that contains both the 80G>T and the 921C>T SNPs had a significant risk effect on opioid dependency (144). Variants in the noncoding regions of all three opioid receptor subtypes and associations with a greater risk for heroin dependency have been found (206), which emphasizes the importance of further study into variation in these genes and their effects on opiate dependency.

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COMT: catechol-o-methyl transferase

In addition to variants in the opioid receptors, a variety of other related and unrelated genes have been identified as contributors to opiate dependency. The preproenkephalin gene (*PENK*) encodes for peptides that modulate pain perception and play roles in reward and addiction (207). The $(CA)_n$ repeat polymorphism in 3′-flanking sequence of the *PENK* gene was associated with increased likelihood of opiate dependency in multiple studies (27, 208). Another gene involved in stress responses is the melanocortin receptor type 2 (*MC2R*); variations in this gene have been associated with both a protective effect and susceptibility to heroin addiction (209).

Uridine diphosphate glucuronosyltransferases (UGTs) glucuronidate morphine to the inactive morphine-3-glucuronide and to the μ opioid receptor agonist morphine-6-glucuronide. A *UGT2B7* promoter region variant (161C>T) was associated with reduced morphine-6-glucuronide/morphine ratios, but its effects on the addiction liability of morphine are not known. Opiates, other than morphine and heroin, are generally metabolized by CYPs; for example, CYP2D6 metabolizes codeine, oxycodone, and hydrocodone. Slow CYP2D6 activators of oral opiates were associated with a lower risk for opiate dependency with an estimated odds ratio of greater than seven (210).

PHARMACOGENETICS OF TREATMENTS FOR DRUG DEPENDENCE

Pharmacotherapies are commonly used to combat drug-dependency disorders. These drugs usually interfere with the receptor response to the drug, or they alter the pharmacokinetics of the abused drug. Variation in genes that affect the susceptibility to drug dependency (mentioned above), and other genes that are specific to the action of the pharmacotherapy, can also affect the response to treatments. The efficacy of most of these therapeutics remains modest, and success rates could potentially be enhanced through the implementation of personalized medicine tailoring the choice/dose of a treatment to an individual's genotype. Here we outline how genetic variation can impact the effectiveness of treatments for drug dependency and how further research into pharmacogenetics can help improve treatment outcomes.

Pharmacogenetics of Smoking Cessation Aids

The therapeutic outcome of some forms of nicotine replacement therapy (NRT) is affected by genetic polymorphisms in the dopamine reward system. The cessation rates from transdermal nicotine patches are higher among females with the *Taq*1*A A1* allele in the *DRD2/ANNK1* gene but not among males with *Taq*1*A A1* (211). However, another study showed that individuals with the *Taq*1*A A1* allele have significantly higher quitting rates using transdermal nicotine patch with no gender differences observed (212). Moreover, individuals with the *DRD2* -141C Del genotype had better smoking cessation rates with the nicotine patch compared to the homozygous *DRD2*–141 C Ins genotype (213). In addition, individuals with the *DRD2* 957C allele are less likely to be abstinent compared to those with the T allele (213) who were using a nicotine patch. Individuals with the variant allele in the 1368G>A SNP in the dopamine β hydroxylase gene were also more likely to quit with nicotine replacement patch treatment (212). Women with low activity variant alleles in the *COMT* gene (1947G>A) also had higher abstinence rates when they used a nicotine patch and nasal spray (63).

In addition to the dopamine reward system, genetic variations in *CYP2A6* can also influence the therapeutic outcomes of NRT treatments. CYP2A6 slow metabolizers have modestly higher nicotine plasma concentrations when using transdermal nicotine patches compared to normal metabolizers; they also have reproducibly higher abstinence rates compared to the normal metabolizers (214, 215). However, this difference was not observed for nasal nicotine spray; this is likely

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due to slow metabolizers titrating the amount of spray they used (95, 214). In the placebo arm of a treatment trial, CYP2A6 slow metabolizers had substantially higher smoking cessation rates, which suggests that slow nicotine clearance while smoking leads to enhanced quit rates, even in the absence of pharmacological support (216).

Bupropion was the first non-nicotinic smoking cessation treatment approved by the U.S. Food and Drug Administration. It inhibits dopamine reuptake, thus causing elevated dopamine levels in the brain, which is believed to alleviate the symptoms associated with nicotine withdrawal (217). Genetic variations in the *DRD2/ANNK1* gene can alter the therapeutic outcomes for bupropion. Specifically, females homozygous for the *Taq*1*A A2* allele were more likely to quit smoking with bupropion (218, 219). This may be caused by the fact that women with the *Taq*1*A A1* allele were more likely to stop taking bupropion due to side effects. Individuals homozygous for the *DRD2−141 C* Ins allele responded better to bupropion compared to individuals with the *DRD2−141 C* Del allele (213). Interestingly, polymorphisms in nicotinic acetylcholine receptor genes can also alter the therapeutic outcomes of bupropion. A SNP in the 3′ UTR of *CHRNB2* affected the abstinence rates for both bupropion and placebo (220).

Bupropion is metabolized by CYP2B6 to three active metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. Genetic variation in *CYP2B6* can alter the therapeutic outcome of bupropion. Males with the variant allele for the *CYP2B6*5* allele (exon 9, 1459C>T) had lower abstinence rates during bupropion treatment. However, individuals of both genders with the variant allele had lower abstinence rates in the placebo group as well (126); these findings were not replicated (219). Bupropion was not more effective, compared to placebo, in *CYP2B6* wild-type individuals. (This group had very high cessation rates on placebo.) However, individuals with the *CYP2B6*6* allele (G516T and A785G) were shown to have an enhanced ability to quit and a notable maintenance of abstinence rates at the 6-month follow up on bupropion compared to placebo (127).

Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist recently approved for smoking cessation treatment. In vitro experiments suggested that varenicline is a substrate for the genetically polymorphic renal cation transporter OCT2; however, although the effect of OCT2 inhibition on varenicline clearance is unlikely to alter circulating varenicline levels in a clinically relevant manner (221), it may alter penetration into the brain via the expression of OCT2 in the blood brain barrier. Because this is a recently approved treatment, little is known about pharmacogenetic influences on treatment outcomes or side effect profiles.

Pharmacogenetics of Alcohol Treatment

Naltrexone is an opioid receptor antagonist used in the treatment of alcohol dependency. Blockade of opioid receptors with naltrexone results in decreased alcohol induced intoxication and pleasure, which consequently decreases cravings and relapse (222). This drug has proven to be an effective treatment for alcohol dependency, but there is great interindividual variability in therapeutic efficacy. Alcoholics with at least one copy of the *OPRM1* 118G allele have better naltrexone response compared to those with the 118A allele. During the treatment period, they showed an increase in percentage of days abstinent and a decrease in percentage of heavy drinking days (223, 224).

Pharmacogenetics of Treatment for Cocaine Addiction

Disulfiram is used to reduce cocaine abuse and relapse (225). It increases brain dopamine levels by inhibiting the dopamine-catabolizing enzyme, dopamine β hydroxylase (226). Polymorphisms in

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the dopamine β hydroxylase gene may have a pharmacogenetic impact on disulfiram treatment, but these polymorphisms have not been studied in the context of disulfiram efficacy.

Pharmacogenetics of Opiate Dependence Treatment

Commonly prescribed medicines for opiate addiction include methadone, levo-α-acetylmethadol, and buprenorphine. Methadone is a synthetic opioid with high oral bioavailability. The efficacy of methadone can be affected by variations in its efflux drug transporter P-glycoprotein, which is encoded by the *ABCB1* gene (MDR1). Pharmacogenetic studies have found that individuals homozygous for the wild-type haplotype of this gene required higher doses of methadone (227).

Conclusions

Herein we reviewed some examples in which genetic variation contributes to the risk for drug addiction or alters the efficacy of treatment. Evidence for the involvement of specific genetic variants has been replicated in some cases, whereas others remain uncertain. One approach to improve replication could be to narrow the phenotypic definitions tested because the impact of specific genetic variants will probably be greater when the phenotype is very specific. Pharmacogenetics has increased our understanding of the underlying mechanisms involved in the risk for drug dependency; it may also help to identify individuals that are at an increased susceptibility for drug dependency and in particular need of prevention strategies. Another goal of pharmacogenetics is the optimization of treatment choice, as well as identifying novel targets for treatment. However, issues such as the ethical use of genetic information and the application of this information into clinical practice need to be addressed so that pharmacogenetic information can be routinely implemented in treatment.

SUMMARY POINTS

1. Pharmacogenetic information can be used to investigate susceptibility to drug dependency and evaluate response to treatments for drug dependency.
2. Variation in genes involved in monoaminergic transmission can alter the risk for multiple types of drug dependencies.
3. Future studies are required to replicate association data and to assess the functional changes that result from the genetic variations identified.

FUTURE ISSUES

1. Replication of association data is required, as well as the need for narrower phenotypic definitions.
2. We need to characterize how genetic variations result in functional changes in the proteins encoded by genes.
3. Pharmacogenetic information will be employed to optimize treatment options to maximize efficacy and minimize the risk for adverse drug reactions.
4. Understanding the roles of these genes in drug dependency and treatment can result in the discovery of novel drug targets.

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DISCLOSURE STATEMENT

Dr. Rachel F. Tyndale holds shares in Nicogen Research Inc., a company that is focused on novel smoking cessation treatment approaches, and plays an active role in the scientific leadership of Nicogen. Dr. Tyndale also consults for pharmaceutical companies.

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Identified that the OPRM1 gene status was associated with response to naltrexone response, which was subsequently replicated suggesting it could be used as a predictor of naltrexone response.

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Errata

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