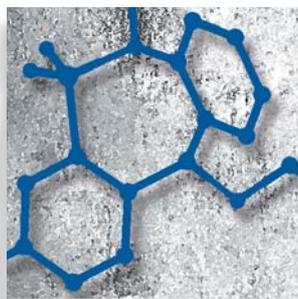


Pharmacogenetic aspects of addictive behaviors

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Addictions are illnesses of complex causation, including inheritance and a role for gene-environment interactions. Functional alleles influencing pharmacodynamic (tissue response) and pharmacokinetic (absorption, distribution, and metabolism) play a role, but these interact with diverse environmental factors including early life stress, underage drug exposure, availability of addictive agents, and response to clinical interventions including pharmacotherapies. Identification of genetic factors in addiction thus plays an important role in the understanding of processes of addiction and origins of differential vulnerabilities and treatment responses.

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Addictions are among the world's major health problems, both in terms of cost, and in terms of morbidity and mortality.¹ Addictions frequently are of early onset, and are associated with many other psychiatric and other medical conditions, both as cause and consequence. According to the 2005 national survey on drug and alcohol by the Substance Abuse and Mental Health Administration (SAMHSA), first-time users of alcohol, illicit drugs, and tobacco over the age of 12 years numbered 4.3 million, 2.9 million, and, 2.3 million, respectively.² The relapsing/remitting nature of addictive disorders, and the high frequency of suicide in addiction, are notable features of these often lifelong disorders. Pharmacogenetic factors modify both the vulnerability to addiction and response to treatment, making it vital to identify specific pharmacogenetic factors to design better treatment and prevention strategies, and to better target those interventions (*Figure 1*).

Inheritance

Heritability accounts for 40% to 80% of the variation in vulnerability to a range of addictive disorders.³ These heritability estimates are primarily based on a series of large studies comparing concordance of monozygotic (identical) and dizygotic (fraternal) twins (*Figure 2*). It is important to note that heritability has been estimated from epidemiologically sampled twins and in age cohorts within national or state populations. The heritabilities computed from these studies are thus likely to reflect the average action of genes on addiction within a population, but not across populations or across time, where there are additional sources of environmental variance.³ In the US, heritability accounts for approximately 50% of the interindividual variation in vulnerability to alcohol dependence, as

Pharmacological aspects

shown by meta-analysis of large methodologically sound, epidemiologically based twin studies augmented by family and adoption studies. Although alcoholism and other addictions are probably influenced by variation at many genes, alcoholism resembles other addictions in that the concordance ratios for risk in vulnerability are approximately 2:1 for monozygotic (MZ):dizygotic (DZ) twins, a finding that indicates the possibility for major gene effects and additive actions of alleles, rather than more complex epistatic interactions that are more likely to occur in diseases with high MZ:DZ concordance ratios.³ In the addictions, sex interactions in vulnerability are frequently seen. Often, as for alcoholism and nicotine addiction, men are at higher risk than women. However the male-to-female ratios vary substantially worldwide, and have decreased in many countries as women have gained access to substances, or have actually been targeted by advertising, as in advertising campaigns for cigarettes.^{4,5} For example, alcoholism is an addiction whose prevalence varies across culture, and has varied across time, and many drugs of abuse (eg, nicotine, cocaine, amphetamines) have been introduced in only the past several centuries, or even more recently.³ The heritability of dependencies to substances with higher addictive potential tends to be higher; for example, opioids have high addictive potential and opioid addiction is highly heritable—approximately 65%, as shown by large twin studies such as the Vietnam and World War II veterans' studies.⁶

Although much is known about the heritability of addictive agents, the heritabilities of dependency to many

addictive agents that are important on a worldwide basis are unknown. Heritability studies have predominantly been carried out in Western countries, and on substance dependencies that are common in these countries. In many countries, other agents play a more important role. In several instances, the active agent is similar or identical, but delivered to the body by chewing. For example, khat leaves harvested from the tree *Catha edulis* are chewed for their euphoric properties in East Africa and Yemen.^{7,8} The heritability of khat addiction may be low or the genetics may be that of protective alleles, since in certain regions such as Yemen 90% to 95% of males and an increasing number of females are addicted. While the heritability of cigarette smoking is well understood—nicotine dependence heritability is approximately 60%⁵—tobacco is often chewed in the rural US and in other parts of the world. In Andean countries, the coca leaf is chewed. Finally, on a worldwide basis, young people are being exposed to video games, some Internet-based, that frequently lead to addictive use, and the heritability of this addiction is unknown.

Cross-inheritance

Twin and family studies reveal that addictions are cross-inherited as well as influenced by substance-specific factors. Several cross-transmission studies in the Vietnam Veterans, World War II Veterans, and Virginia Adoption study all revealed a common vulnerability factor, of varying magnitude, shared by nicotine and alcohol addiction. In these studies, the risk of the second disorder was higher in the co-twin of the proband with the first disorder.

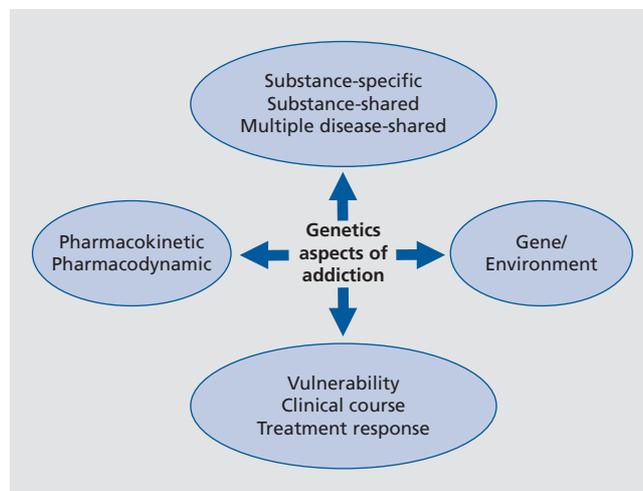


Figure 1. Genetic aspects of addiction: four nonorthogonal axes of gene action.

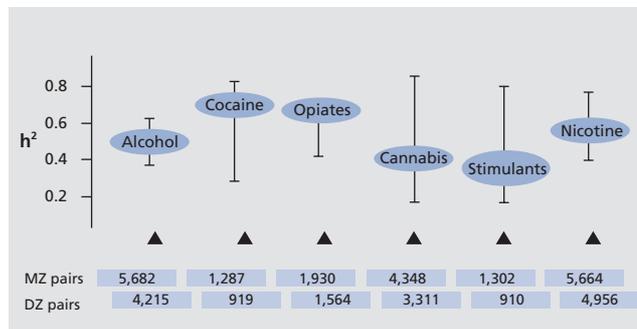


Figure 2. Heritabilities (h^2) of six addictive disorders. The heritabilities are weighted means estimated by Goldman et al³ from large twin studies.

Adapted from ref 3: Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. *Nat Rev Genetics*. 2005;6:521-532. Copyright © Nature Publishing Group 2005.

der, indicating a common underlying vulnerability factor. The cross-inheritance explains, in part, the tendency for certain addictions to be comorbid (to co-occur) at higher frequencies than expected randomly. For example, it has been reported that nearly 80% of alcoholics are heavy smokers.⁴ Comorbidity of cocaine dependence and opioid addiction frequently occurs, and both are frequently comorbid with nicotine dependence. The use of cocaine, opiates, and amphetamine is 10 times higher in alcoholics as compared with nonalcoholics.⁹⁻¹² Addictions also tend to be comorbid with other psychiatric diseases, and cross-inheritance again provides part of the explanation.¹³ Both internalizing disorders—depression, anxiety—and externalizing disorders—antisocial personality disorder—show excess comorbidity and some evidence of cross-inheritance. The sharing of inheritance presumably reflects the effects of the same genes on mechanisms common to different addictions and diseases.³

A potential role for the muscarinic acetylcholine M2 receptor gene (*CHRM2*) in comorbid vulnerability to alcoholism and other drug dependencies was identified in families with alcohol addiction in the large Collaborative Study on the Genetics of Alcoholism which comprises samples collected from families with alcoholism from across six states nationwide. In a family-based study, Schuckit et al examined the role of the muscarinic acetylcholine receptor (*CHRM2*) among individuals with alcohol dependence alone and in those with alcohol dependence and comorbid drug dependence. Samples were collected from 2282 individuals in 262 COGA families. A total of 477 individuals had alcohol dependence with comorbid drug dependence, and 433 individuals had alcohol dependence without comorbid drug use. The association of *CHRM2* originated entirely in alcoholics with comorbid drug dependence. In the alcohol-dependent group without drug dependence there was no evidence of association to *CHRM2*.¹²

Studies in mice indicate that the 5HT1B receptor gene, which encodes the terminal auto receptor regulating serotonin release, is involved in cocaine and alcohol addiction. Mice lacking the 5HT1B receptor show heightened response to cocaine and alcohol and augmented cocaine and alcohol self-administration, and mice knocked out for the HTR1B receptor were more aggressive and drank more alcohol.^{14,15} In humans, HTR1B was associated with antisocial alcoholism (alcoholism comorbid with antisocial personality disorder) in two populations,¹⁶ and depression and anxiety.¹⁷ One of the earliest

observations of cross-inheritance in addictions was the tendency of fathers with antisocial personality disorder to have children with alcoholism, whether or not the child was adopted out to a family without pathology.¹⁸

Pharmacokinetic and pharmacodynamic variation

Pharmacokinetic variation refers to variation in drug absorption, distribution in the body, metabolism, and excretion. *Pharmacodynamic* variation refers to the response of the body and encompasses dose effects, ascending and descending limb variation, sensitization and tolerance, developmental and age effects, and genetic variation.

The classic and well-known examples of pharmacokinetic variation in addiction are the functional polymorphisms of alcohol dehydrogenase 1B (*ADH1B*-His47Arg) which metabolizes alcohol to acetaldehyde and aldehyde dehydrogenase 2 (*ALDH* -Glu487Lys) which metabolizes acetaldehyde to acetate. Following alcohol consumption, both the Arg47 and Lys487 alleles, alone or together, can lead to the accumulation of acetaldehyde, producing aversive flushing, nausea, and headache.^{19,20} People of Southeast Asian ancestry are especially likely to carry the *ADH1B* Arg47 and *ALDH2* Lys487 alleles, but individuals of Jewish ancestry also often carry the Arg47 allele.²¹ Both the Arg47 and Lys487 alleles lead to a reduction in risk of alcoholism, with a protective effect of fourfold to tenfold in carriers, and an additive protective effect when both alleles are carried by the same person. The *ADH1B* alleles are codominant in action but *ALDH2* Lys487 is semidominant, such that heterozygous carriers have very low levels of *ALDH2* enzyme activity. However, *ALDH2* Lys487/Lys487 homozygotes are nearly completely protected from alcoholism. The action of these two genetic variants has an interesting pharmacologic parallel. Disulfiram, which inhibits ALDH, is one of several drugs in use for treatment of alcoholism. Metronidazole and certain other antiprotozoal drugs also inhibit ALDH, and also lead to the aversive flushing reaction following ethanol ingestion.¹⁹⁻²² In addition, the Lys487 allele has been shown to be associated with higher risk of gastrointestinal cancer after alcohol consumption, and probably through the carcinogenic action of acetaldehyde.²²

Less clear is the pharmacogenetic role of enzymes such as catalase and cytochrome P450 2E1 (*CYP2E1*) that

Pharmacological aspects

also play a role in the metabolism of ethanol and acetaldehyde, albeit a quantitatively more minor role.²⁴ Many proteins and their genes are targets for pharmacodynamic variation in vulnerability to alcohol dependence. In a prospective study of young, relatively alcohol-naïve male college students, low response to alcohol was shown to be a predictor of alcoholism, and has been used as a heritable intermediate phenotype, both for candidate gene studies and for genome linkage scans.²⁵

Dopamine β hydroxylase (D β H) is the enzyme that converts dopamine to norepinephrine. *DBH* exhibits inherited functional variation that has been linked to various psychiatric disorders including depression and alcoholism. The *DBH* variant -1021 C>T predicts reduced plasma D β H enzyme activity. *DBH* linkage studies to nicotine are so far inconclusive.²⁶⁻²⁹ However, Freier et al found that individuals with the *DBH* -1021T allele smoked less than -1021C/-1021C homozygotes. Equivocal linkage data are also reported for the *DRD2* dopamine receptor, which is thought to be integral for dopamine-mediated reinforcement.²⁶ A “gatekeeper” for nicotine’s central nervous system actions is the nicotine receptor. The $\alpha 4\beta 2$ heteromer is essential for nicotine’s rewarding actions, as shown by studies in knockout mice.²⁷ In the future more information is likely to be developed on the role of functional nicotine receptor variants, which may be rare or uncommon.

Alcohol exerts its sedative and rewarding actions in part through stimulation of GABAA receptors and inhibition of NMDA glutamate receptors, and key signaling proteins include protein kinase C enzymes, as revealed by a variety of studies including electrophysiology studies of receptors and investigations on mice knocked out for these genes. Some of these “gatekeeper” molecules have been implicated by linkage and association studies. Genetic linkage studies implicating *GABAA* subunit genes include a series of mouse ethanol-related quantitative loci (for behaviors such as alcohol preference and sensitivity to the sedating actions of ethanol) and, in the human, whole genome scans and linkage disequilibrium studies linking the Chromosome 4 *GABAA* receptor subunit gene complex and the *GABAA* $\alpha 2$ gene. The Chromosome 5 *GABAA* receptor subunit complex and the *GABAA* $\alpha 6$ gene therein at the *GABAA* $\alpha 6$ gene is the Ser385 allele, which may correlate with LR, and a higher risk of alcoholism and variation in response to benzodiazepines.³⁰⁻³⁴ The *GABRG1* haplotype markers showing greater allelic, genotypic, and haplotypic associ-

ation with alcohol dependence compared with those of haplotype block may act in a dominant manner in relation to risk of alcohol dependence.³⁵

The μ -opioid receptor gene *OPRM1* is the most extensively studied of the opioid receptor genes because of its important role in reward mediated by endogenous opioids. The functional *OPRM1* Asn40Asp variant of the μ -opioid receptor gene has been shown in some studies to be associated with opioid addiction.^{36,37,38} For example, association of this *OPRM1* variant to polysubstance abuse including opioids, cocaine, and alcohol was reported by Kranzler et al.³⁶ Berrettini and colleagues reported that the major opioid preference quantitative trait loci in mice mapped to the location of the murine μ opioid receptor gene.³⁹ *OPRM1* Asn40Asp has also been variably linked to alcoholism,^{29,30} and perhaps most intriguingly, appears to alter opioid-mediated release of cortisol, this effect on the hypothalamic-pituitary-adrenal axis potentially revealing its action on stress activations important in addiction.⁴⁰ A delta opioid receptor, *OPRD1*, variant has also been reported to be associated with substance dependence.⁴¹ The endogenous opioid system is also critical to the reinforcing effects of nonopioid drugs including nicotine, alcohol, cocaine, and cannabinoids.^{37,42}

Gene-environment interactions in addiction

Addiction is a complex disease involving the interaction of genes and environment. The vulnerability to abuse of addictive agents is in part determined by genetic variation and in part by environmental factors including exposure to addictive agents, but also such nonspecific factors as stress exposure early in life.

Several of the interacting genes found so far are stress-related, modulating resiliency and vulnerability. Early life stress exposures such as childhood sexual abuse play a powerful but apparently nonspecific role, because such stress also increases vulnerability to other psychiatric diseases. In the rat preferring/nonpreferring (P/NP) model of alcohol consumption, a major quantitative locus for ethanol preference is at the site of the gene for neuropeptide Y, an anxiolytic neuropeptide. In the human, genetic variants of neuropeptide Y have sometimes, but not always, been linked to alcoholism as well as other behaviors, including obesity.^{43,44} A catechol-O-methyltransferase polymorphism that predicts anxiety and cognitive function has been associated with alcoholism and

polysubstance abuse.⁴⁵ Another stress-related gene is the serotonin transporter, which contains the functional *HTTLPR* locus. In the rhesus macaque monkey, the reduction of function allele of the orthologous *rh-HTTLPR* locus predicts enhanced alcohol consumption, but only in the context of early life stress exposure.⁴⁶ In humans with cocaine addiction, the already high rate of suicide attempts is greatly increased in carriers of the reduction of function *HTTLPR* allele who had a history of childhood abuse or neglect.⁴⁷ Childhood trauma is in general associated with depression and suicide in individuals with the 5-*HTTLPR* reduction of function allele.⁴⁸ A functional polymorphism in the promoter region of monoamine oxidase A gene (*MAOA*) resulting in a low expressing genotype has been found to interact with childhood sexual abuse to increase risk of alcoholism, and especially antisocial personality disorder (ASPD) occurring in the context of Alcohol Use Disorders in women.⁴⁹ Other environmental factors influencing vulnerability include price, availability, early life stress exposures, and underage drinking.⁵⁰ For example, alcohol prohibition from 1920 to 1933 in the US led to a large decrease in alcoholism and associated cirrhosis. Also, onset of drinking in the early adolescent or preadolescent years is a strong risk factor. However, the interactions of such factors with gene effects are even less well understood.

The pharmacogenetics of pharmacotherapy

Treatment of addiction encompasses two main phases: acute detoxification and maintenance. Maintenance treatment is aimed at maintaining abstinence, or harm reduction. Supportive therapy plays a vital role and this may include cognitive therapy and self-help groups. Categories of pharmacotherapeutics include:

- Detoxification (eg, benzodiazepines in alcoholism and clonidine in opiate withdrawal)
- Agonist (eg, methadone, levo-alpha-acetyl-methadol (LAAM))
- Partial agonist (eg, buprenorphine for opioid addiction)
- Antagonist (eg, naltrexone in alcoholism)
- Anticraving (eg, bupropion and homotaurine in alcoholism)
- Aversive (eg, disulfiram).

Because each of these drugs targets specific proteins and small molecules, there is considerable potential for specific pharmacogenetics of treatment response. Each of

these drugs is also subject to metabolism, leading to a role for pharmacogenetic variation such as the cytochrome p450 2,6 which predicted response to bupropion in nicotine dependence.⁵¹ The *OPRM1* Asn40Asp polymorphism has, in addition to its disease associations, also been associated with naltrexone treatment response in alcoholism and as recently replicated in a large clinical trial, the COMBINE study.⁵² The role of *OPRM1* in smoking has been studied in relation to nicotine replacement therapy. Nicotine increases the release of β -endorphins indirectly releasing dopamine and leading to pleasurable sensations associated with smoking, as shown by several studies both in rats and humans. In a randomized study, 320 smokers of European ancestry were treated with a nicotine transdermal patch or nasal spray over a 6-month period and 41% of Asp40 carriers remained abstinent at the end of 6 months as compared with 30% of Asn40/Asn40 homozygotes.⁵³ However, the effect of genotype disappeared after treatment cessation. Another gene that may predict nicotine treatment response is cytochrome P450 2B6 (*CYP2B6*) which predicted treatment response with bupropion, which is metabolized by this enzyme. In a study of 426 smokers of European ancestry, participants with the low activity allele reported increased craving and higher relapse rate. This effect may also be attributable to slower nicotine metabolism.⁵¹

Finally, there are genetic factors that are likely to act across different drugs used in treatment and even different diseases, to predict treatment response. These may include genes that influence anxiety and stress response such as *COMT*, *NPY*, and *5-HTTLPR*, as discussed above. They may also include genes altering cognitive function, such as *COMT* which predicts executive cognition.^{54,55} One such functional polymorphism is the Met66Val polymorphism of the brain-derived neurotrophic factor gene (*BDNF*), which predicts hippocampal volumes and episodic memory function.⁵⁶ At present, none of the genetic markers available has found application in clinical practice. The *OPRM1* Asn40Asp polymorphism presently has potential for immediate utility in both alcoholism and nicotine addiction treatment.^{52,57,58}

Concerning methadone treatment, human genetic variation may offer an advantage to this treatment modality for opioid addictions, many identified variants of *CYP2D6*, which metabolizes codeine, have been shown to alter levels of active codeine metabolites such as oxycodone and hydrocodone, potentially altering risk of

Pharmacological aspects

codeine usage. On the other hand, *CYP3A4*, which metabolizes methadone, buprenorphine, and LAAM, has not been found to have functional variants to affect metabolism of these opiates.³⁸

The role of CB1 cannabinoid receptors role in the reward system make them a treatment target for drugs of abuse such as cannabinoids, opiates, and nicotine, and recently rimonabant has been utilized, but the role of genetic variation is unknown. Since the modes of action of certain drugs used or proposed for use in treatment including acamprosate⁵⁹ and topiramate⁶⁰ is unknown, the pharmacogenetic gene targets are also unclear. However, in certain instances, treatment suitability may be defined by general clinical features and the genes influencing these

features. For example, serotonergic abnormalities are thought to be important in early-onset alcoholics, and ondansetron, which targets 5-HT (serotonin)₃ receptors, selectively reduced craving in early onset alcoholics as compared with late-onset alcoholics. Finally, variation is being uncovered in genes, such as *BDNF*, that mediate neuronal signaling and plasticity, and functional loci such as *BDNF* Met66Val may potentially be critical to long-term recovery. In the future, genetic tools are likely to become increasingly useful to increase specificity of diagnosis and to develop and better target treatments. □

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Aspectos farmacogenéticos de las conductas adictivas

Las adicciones son enfermedades de compleja causalidad en que se incluyen la herencia y el papel de las interacciones entre los genes y el ambiente. Los alelos funcionales que afectan la farmacodinámica (respuesta tisular) y la farmacocinética (absorción, distribución y metabolismo) también tienen un papel, pero estos interactúan con diversos factores ambientales como situaciones de estrés de vida precoces, exposición a drogas de los menores de edad, disponibilidad de sustancias adictivas y respuesta a intervenciones clínicas (incluyendo las terapias farmacológicas). La identificación de factores genéticos en la adicción juega un papel importante para la comprensión de los procesos adictivos y de los orígenes de las vulnerabilidades y respuestas al tratamiento individuales.

Aspects pharmacogénétiques des comportements addictifs

Les addictions sont des maladies aux causes complexes, dont font partie l'hérédité et les interactions gène/environnement. Les allèles fonctionnels influant sur la pharmacodynamique (réponse tissulaire) et la pharmacocinétique (absorption, distribution et métabolisme) jouent un rôle mais ils interagissent avec divers facteurs environnementaux comme les stress de vie précoces, l'exposition des mineurs aux médicaments, la disponibilité des produits addictogènes et la réponse aux interventions cliniques y compris les pharmacothérapies. L'identification des facteurs génétiques dans l'addiction joue donc un rôle important dans la compréhension du processus d'addiction et des origines des différences de vulnérabilité et de réponse thérapeutique.

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Pharmacological aspects

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